Advances in Bioresearch
Adv. Biores., Vol 12 (5) September 2021: 210-218
©2021 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.12.5.210218

Advances in Bioresearch

ORIGINAL ARTICLE

In vivo Anti-Diabetic Study of *Citrullus colocynthis* Schard

***Mohammed Tarique[1,3], Rakesh Jat[2], Ansari Yaasir Ahmed[3], Rahil Khan[3], Band Afzal[3]**
[1]Research Scholar, Shri Jagdishprasad Jhabarmal Tibrewala University, Jhunjhunu, Raj-333001.
[2]Professor, Shri Jagdishprasad Jhabarmal Tibrewala University, Jhunjhunu, Raj-333001.
[3]Jamia College of Pharmacy, Akkalkuwa, Dist: Nandurbar, M.S-425415.
Corresponding Author: Mohammed Tarique, E-mail: tariqanytime@gmail.com

ABSTRACT
Citrullus colocynthis is an important medicinal cucurbit belonging to the family Cucurbitaceae. The present work was carried out to investigate pharmacognostical and pharmacological activity of Citrullus colocynthis schard. The in vivo antidiabetic study of Citrullus colocynthis schard was carried out on healthy wistar pale skinned rodents (rats) somewhere in the range of 150-200 gram were randomly allocated to different groups containing three rats in each group. The antidiabetic studies of Leaf, stem and fruit of C.colocynthis schard were used for study. Effect of Citrullus colocynthis leaf extract was observed on diabetic rodent. Administration of Citrullus colocynthis leaf extract (100 and 200mg/kg body weight) and glibenclamide builds the action of hexokinase and diminishing the exercises of glucose 6-phosphatase and fructose-1, 6-bisphosphatase when contrasted with diabetic rodents. The impact of mix treatment of stem extract of Citrullus colocynthis on blood glucose level in normal and alloxan prompted diabetic rodents is observed. The mix treatment of low portions of C. colocynthis leaf extract demonstrated progressively huge (P<0.001) decrease in blood glucose level contrasted with the individual treatment of C. colocynthis stem extract at high dosages and comparable degree of centrality of standard drug, glibenclamide. Fruit extracts of Citrullus colocynthis200mg/kg and 400mg/kg for a time of 10 days and on the eleventh day the outcomes got were assessed. When Ethanolic extract of C. Colocynthis (200 and 400mg/kg) concentrate treated group was contrasted with diabetic control; there was a decrease in blood glucose levels essentially (p<0.0001). The concentrates of fruit pulp of Citrullus colocynthis treated groups were demonstrated that they brought down blood glucose levels fundamentally.
***Keywords**: Citrullus colocynthis, In Vivo,Anti-Diabetic Study, Leaf, Fruit, Stem.*

Received 06.06.2021 Revised 21.07.2021 Accepted 09.09.2021

How to cite this article:
M Tarique, R Jat, A Y Ahmed, R Khan, B Afzal. *In vivo* Anti-Diabetic Study of *Citrullus colocynthis* Schard. Adv. Biores. Vol 12 [5] September 2021. 210-218

INTRODUCTION

Citrullus colocynthis contained flavone glucosides, terpenoids, alkaloids, anthranol, steroids, cucurbitacins, saponarin, cardicglycoloids, sugar, protein, isolated amino corrosive, tannins, saponins, phenolics, flavanoids, follow components and numerous other substance groups. It had cell reinforcement, Antidiabetic, antimicrobial, anticancer, hostile to inflammatory, pain relieving, gastrointestinal, regenerative and defensive and numerous other pharmacological impacts. It was local to dry territories of North Africa and it has been known in the Mediterranean area since Biblical occasions.
Phytochemical investigation of plant removes uncovered the nearness of sugar, protein, isolated amino acid, tannins, saponins, phenolic, flavanoids, terpenoids, alkaloids, anthranol, steroids, Cucurbitacin A, B, C, D, E (α-elaterin), J, L, caffeic corrosive and cardicglycoloids. The seeds of *Citrullus colocynthis* contained proteins 13.99 ± 0.06%, unrefined filaments, dampness, α-tocopherol, δ-tocopherol and fixed oil with high extent of unsaturated fats, for the most part linoleic corrosive, oleic corrosive, low level of soaked, complete immersed 20.20% and an extremely low n-3 poly-unsaturated FA level. Be that as it may, the seed fat of *Citrullus colocynthis* comprised of palmitic; stearic; arachidic; oleic; linoleic; and linolenic. [1-9]
It is a ceaseless tension issue identified with metabolic aggravation in the midst of portrayed by insufficiency in insulin release or movement of both bringing to hyperglycemia (the raised revolving around glucose levels). The strife was the chief recorded in 1552 B.C. At the point when an Egypt specialist decided a patient to have polyuria (critical signs of diabetes mellitus). For this situation it was

experienced the latest current century study that diabetes mellitus was seen to exist in two critical structures to be explicit DMT1 (insulin dependent) and DMT2 (non-insulin dependent) [10-16].

MATERIAL AND METHODS

Evaluation of antidiabetic activity

Animals

Test rodents were prepared in understanding to Committee with the end goal of Control and Supervision of Experiments on Animals (CPCSEA). Wistar male rodents weighing 150-200 g was utilized for the examination. They were kept up in the creature house for exploratory reason. Rodents were kept up under controlled states of temperature (22 ± 3°C), humidity (30 to 70 %) and 12-h light-dim cycles. All the creatures were acclimatized for seven days before the investigation. The rodents were randomized into test and control groups and housed independently in disinfected polypropylene confines containing sterile paddy husk as bedding. They had free access to standard pellets as basal eating routine and water not obligatory. Rodents were habituated to lab conditions for 48 hours preceding test convention to limit if any of vague pressure.

Antidiabetic activity of leaf extract of *Citrullus colcoynthis* [17]

Experimental induction of diabetes

Diabetes was initiated in male Wistar rodents by intraperitoneal organization of alloxan monohydrate (150 mg/kg body weight) broke down in typical saline. Since alloxan is fit for creating lethal hypoglycemia because of monstrous pancreatic insulin discharge, rodents were treated with 30 percent glucose arrangement orally at various time interims following six hours of alloxan enlistment, and 5 percent glucose solution was kept in bottles in their pens for the following 24 hr to forestall hypoglycemia. Hyperglycemia was affirmed by the raised glucose levels (250 to 375 mg/dl) in plasma, decided at 72 h and afterward on day 7 after infusion. The rodents found with lasting diabetes were utilized for the antidiabetic study. [17]

Experimental design [17]

Rodents were partitioned into six groupss of six rodents each. The concentrate was administered for 60 days. Feed and water were given not indispensable to the rodents:

Group I: typical control rodents controlled drinking water day by day for 60 days
Group II: typical rodents administered *Citrullus colocynthis* leaf separate (250 mg/kg)
Group III: ordinary rodents regulated *Citrullus colocynthis* leaf extricate (500 mg/kg)
Group IV: diabetic control rodents managed drinking water day by day for 60 days
Group V: diabetic rodents administered *Citrullus colocynthis* leaf extricate (250 mg/kg)
Group VI: diabetic rodents administered *Citrullus colocynthis* leaf extricate (500 mg/kg)
Group VII: diabetic rodents regulated (Positive control) glibenclamide (0.25 mg/kg)

The impacts of administration of *Citrullus colocynthis* leaf concentrate to ordinary and diabetic rodents were dictated by estimating fasting blood glucose level and glycosylated hemoglobin were assessed. Day 7 of acceptance was assigned as day 1 for extricate administration in diabetic rodents. Fasting plasma glucose was evaluated on days 1, 5 and 12 of extricate administration. Following 60 days of treatment, the rodents were fasted for the time being and relinquished by cervical beheading. The liver was dismembered out and washed with super cold (- 80°C) saline right away. A bit of the tissue was homogenized utilizing a Potter-Elvejham homogenizer, and the concentrate was utilized for the estimations of hexokinase, glucose 6-phosphatase, fructose 1, 6-bisphosphatase, protein, hemoglobin and inorganic phosphorus.

Statistical analysis

Values were spoken to as mean + SD. Information was investigated utilizing examination of change and group means were contrasted and Duncan's multiple range test.

Antidiabetic activity of stem extract of *Citrullus colcoynthis* [18]

Induction of diabetes in wistar rats

Healthy Wistar rodents weighing around 150-200 grams were taken in each group. Rodents are separated into six groups and each group containing 8 rodents. Rodents were denied to nourishment for 16 hour yet permitted free access to water. Diabetes mellitus was incited by intraperitoneal infusion of newly prepared solution of alloxan monohydrate (150 mg/Kg) soluble in physiological saline in overnight fasted rodents. Since alloxan is equipped for creating lethal hypoglycaemia because of huge pancreatic arrival of insulin. Following a time of three days the rodents with a blood glucose levels more prominent than 200 mg/dL were viewed as diabetic and utilized for this examination work. [18]

Experimental design

The alloxan incited diabetic Wistar rodents were arbitrarily alloted into six groups (1-6) of eight rodents (n=8) each as follows, in particular

Group 1-Received typical saline i.p

Group 2-Received alloxan (Diabetic control, 120 mg/Kg, i.p)

Group 3-Received stem concentrate of *Citrullus colocynthis* Group (300 mg/Kg, orallly

Group 4-Received stem concentrate of *Citrullus colocynthis* (250 mg/Kg, orally)

Group 5-Received Glibenclamide Group (5 mg/Kg, i.p)Blood tests were gathered retro orbital plexus of the rodents, for blood glucose assurance at interims of 0, 3, 7 and 15 days. Assurance of the blood glucose level was finished by the Acu-Check glucometer and results were accounted for as mg/dl. [19]

Statistical analysis

Blood glucose levels were expressed in mg/dl as mean ± SD. The information were factually broke down utilizing ANOVA followed by Dunnet's test. The estimations of $p<0.05$ were considered as statically huge.

Antidiabetic activity of fruit extract of *Citrullus coloynthis* [19]

Experimental induction of diabetes

Diabetes was prompted by a solitary intraperitoneal infusion of a newly prepared alloxan solution (Dose: 30-50mg/kg) in citrate cushion 0.1 M, pH 4.5 to expedite fasted rodents. Diabetes was recognized by polydipsia, polyuria and by estimating blood glucose levels 48 h after infusion of alloxan. Rodents that didn't grow in excess of 250 mg/100 ml of blood glucose levels were dismissed. [19]

Experimental design [20]

The rodents were partitioned into fifteen groups of 6 rodents each.

Group I: Normal untreated rodents (Control)

Group II: Diabetic control (alloxan)

Group III: Diabetic rodents given with glibenclamide (50 mg/kg)

Group IV: Normal rodents given with fruit pulp concentrate of *Citrullus colocynthis* (100mg/kg)

Group V: Normal rodents given with fruit pulp concentrate of *Citrullus colocynthis* (200mg/kg)

Group VI: Diabetic rodents given with fruit pulp concentrate of *Citrullus colocynthis* (100mg/kg)

Group VII: Diabetic rodents given with fruit pulp concentrate of *Citrullus colocynthis* (200mg/kg)

Statistical analysis

The aftereffects of the estimation were accounted for as Mean ± SEM. Understudy's t-test was applied when two groups among were thought about. The values were viewed as huge when $p < 0.05$, $p < 0.001$, $p < 0.0001$. Measurable figuring's were finished utilizing Graph Pad Prism.

RESULT AND DISCUSSION

Evaluation of antidiabetic activity

Antidiabetic activity of leaf extract of *Citrullus colocynthis*

Alters in blood glucose and body weight in diabetic and on treatment of diabetic rodents with *Citrullus colocynthis* leaf extract, glibenclamide are introduced in (Table.1).

Table 1. Changes in blood glucose and body weight in control and alloxan diabetic rats treated with *Citrullus colocynthis*leaf extract and glibenclamide.

Groups	Blood Glucose mg/dl		Body weight(g)		Changes body wt (g)
Control	80.5 ± 4.5	84.3 ± 5.2a	185 ± 5.4	215 ± 7.6	+30
Normal+ CLEt(250mg/kg)	81.2 ± 7.5	85.4 ± 6.3a,c	161 ± 13.2	176.3 ± 12.6	+15.3
Normal + CLEt (500mg/kg)	81.5 ± 5.6	91 ± 5.4a,c	165 ± 14.1	181 ± 11.5	+ 16
Diabetic Control	363 ± 18.2	389 ± 12.7b	191 ± 4.2	131 ± 5.2	-60
Diabetic + CLEt (250mg/kg)	375 ± 32.4	126.4±23.5c,d	189 ± 5.6	170 ± 12.4	-19
Diabetic + CLEt (500mg/kg)	381 ± 34	105 ± 35c,d	185 ± 15.3	156.5 ±16.7	-28.5
Diabetic +glybenclamide (0.25mg/kg)(Positivecontrol)	278 ± 28	165 ± 11.3a,d	186.5 ± 16.4	156.5 ± 17.2	-30

A momentous increment in blood glucose and impressive decrease in body weight are seen in diabetic rodents when contrasted and control rodents. (Table 2) clarifies the impacts of *Citrullus colocynthis* leaf extract and glibenclamide on hemoglobin, glycosylated hemoglobin and serum protein, in charge and alloxan-diabetic rodents. There is a huge decrease in hemoglobin and serum protein while glycosylated hemoglobin considerably expanded in diabetic rodents when contrasted and control rodents. Oral administration of *Citrullus colocynthis* leaf extract (100 and 200mg/kg body weight) radically carries the incentive to approach ordinary. Impacts on the administration of *Citrullus colocynthis* leaf extract and glibenclamide on hepatic hexokinase, glucose-6-phosphatase and fructose-1, 6-bisphosphatase of liver are introduced in (Table 3).

Table 2. Effect of *Citullus colocynthis* leaf extract on hemoglobin, glycolylated hemoglobin and protein, in control and alloxan diabetic rats.

Groups	Hemoglobin (g%)	Glycolylated Hemoglobin (mg/g of Hb)	Protein (g/dl)
Control	14.25± 0.7	0.205 ± 0.02a	5.65 ± 0.13a
Normal+ CLEt(100mg/kg)	14.41 ± 0.31	0.208 ± 0.31a	5.72 ± 0.32a
Normal + CLEt (200mg/kg)	14.62 ± 0.52	0.205 ± 0.26a	5.78 ± 0.25a
Diabetic Control	9.12 ± 1.57	0.629 ± 0.06b	4.21 ± 0.41b
Diabetic + CLEt (100mg/kg)	13.72 ± 1.3	0.275 ± 0.02 c	5.16 ± 0.07c
Diabetic + CLEt (200mg/kg)	14.52 ± 0.8	0.281 ± 0.04a	5.42 ± 0.54a
Diabetic +glybenclamide (0.25mg/kg) (Positivecontrol)	12.43 ± 0.7	0.242 ± 0.02a	5.36 ± 0.45a

The action of hepatic hexokinase is apparently diminished while glucose-6-phosphatase and fructose-1, 6-bisphosphatase are essentially raised in allaxon regarded diabetic rodents when contrasted with normal rodents. Administration of *Citrullus colocynthis* leaf extract (100 and 200mg/kg body weight) and glibenclamide builds the action of hexokinase and diminishing the exercises of glucose 6-phosphatase and fructose-1, 6-bisphosphatase when contrasted with diabetic rodents. There was no measurable importance in parameters assessed in normal rats. The antidiabetic action was not seen as dose dependant as there was no critical distinction between the 100 and 200 mg/kg extract treated groups. (Fig. 1-6)

Table 3. Effect of *Citrullus colocynthis* leaf extract on the activities of hepatic enzymes in control and experimental animals

Groups	Hexokinase (Unit a/ mg protein	Glucose6phosphatase (Unit b/mg protein)	Fructose 1,6-bisphosphatase (Unitc/mgprotein)
Control	0.253 ± 0.031a	0.189 ± 0.012a	0.421 ± 0.025a
Normal+ CLEt(100mg/kg)	0.248 ± 0.023b	0.182 ± 0.031a	0.426 ± 0.027a
Normal + CLEt (200mg/kg)	0.241 ± 0.016a	0.176 ± 0.027a	0.433 ± 0.031a
Diabetic Control	0.084 ± 0.007b	0.420 ± 0.025b	0.695 ± 0.056b
Diabetic + CLEt (100mg/kg)	0.235 ± 0.013b	0.240 ± 0.007c	0.475 ± 0.006c
Diabetic + CLEt (200mg/kg)	0.212 ± 0.021a	0.231 ± 0.063a,c	0.486 ± 0.021c
Diabetic +glybenclamide (0.25mg/kg) (Positivecontrol)	0.237 ± 0.031a	0.225 ± 0.025a,c	0.467 ± 0.031a,c

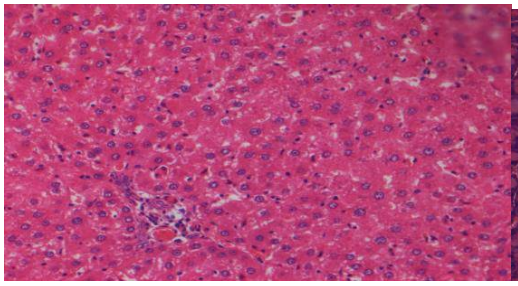

Fig 1.Effect of *C.colocynthis* leaf extract in normal rats on liver

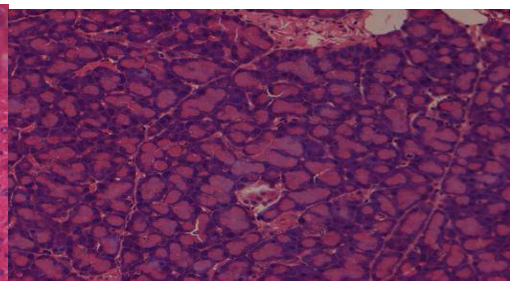

Fig 2. Effect of *C. colocynthis* leaf extract in normal rats on pancreas

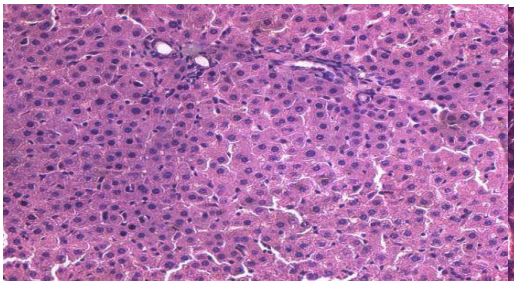

Fig3.Effect of leaf extract of *C.colocynthis* in diabetic rats on liver

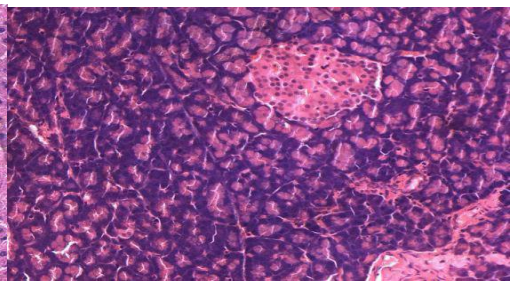

Fig 4. Effect of leaf extract of *C.colocynthis* in diabetic rats on pancreas

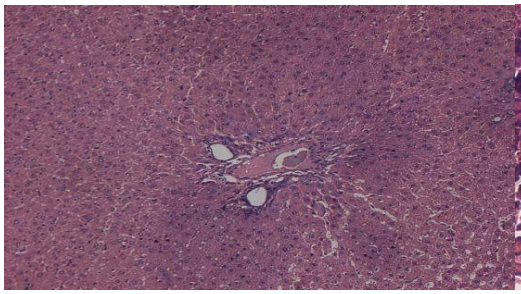

Fig 5.Effect of standard drug glibenclamide diabetic rats on liver

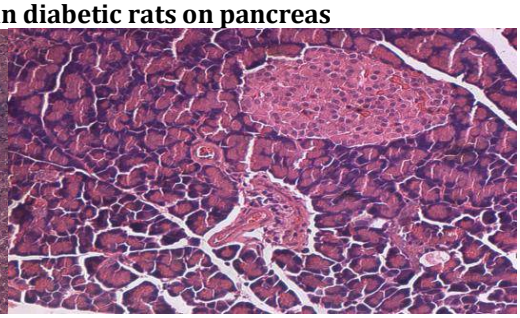

Fig 6. Effect of standard drug glibenclamide in in diabetic rats on pancreas

Antidiabetic activity of stem extract of *Citrullus colocynthis*

The impact of mix treatment on blood glucose level in normal and alloxan prompted diabetic rodents is appeared in Table 4. At 3 days of alloxan administration the peak blood glucose level expanded quickly from introductory value at 0 days and in this way diminished following 7 and 15 days of test drug treatment. The mix treatment of low portions of C. colocynthis leaf extract demonstrated progressively huge ($P<0.001$) decrease in blood glucose level contrasted with the individual treatment of C. colocynthis stem extract at high dosages and comparable degree of centrality of standard drug, glibenclamide.(Fig. 7-10)

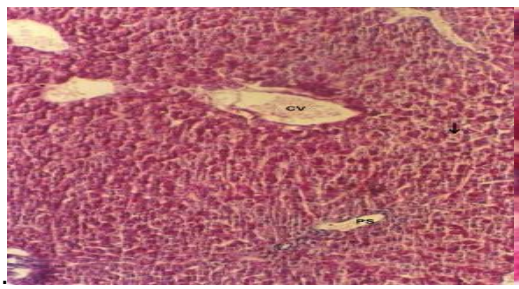

Fig 7.Photomicrograph of the liver of diabetic control wistar rats

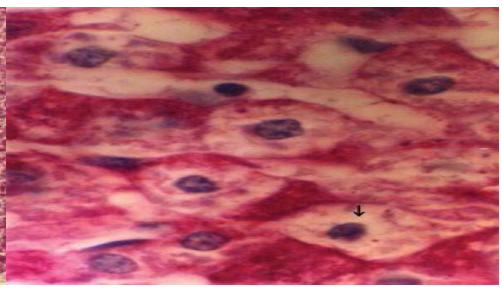

Fig 8. Photomicrograph of liver section of diabetic wistar rat

Table 4. Effect of stem extract *Citrullus colocynthis* on blood glucose level of alloxan-induced diabetic Wistar rats

Treatment	Blood glucose level (mg/dL)			
	0 Days	After 3 Days of Alloxan Administration	After 7 Days of Treatment	After 15 Days of Treatment
Group 1 **Control, (N/Saline)**	95.12±6.578	94.88±7.120	95.75±7.086	95.25±6.861
Group 2 **Diabetic Control**	106.80±2.0	358.2±2.7	356.4±2.2	355.0±1.9
Group 3 ***Citrullus colocynthis* (100 mg/Kg), Orally**	108.50±5.806 *	331.88±9.141a*	119.12±10.063 *	107.62±8.484**
Group 5 ***Citrullus colocynthis* (200 mg/Kg)**	105.75±3.845 *	325.12±14.555	112.50±8.536 *	106.50±15.024**
Group 6 **Glibenclamide (5mg/Kg), i.p**	106.25±4.652	326.88±8.271	115.75±9.407	103.62±10.954

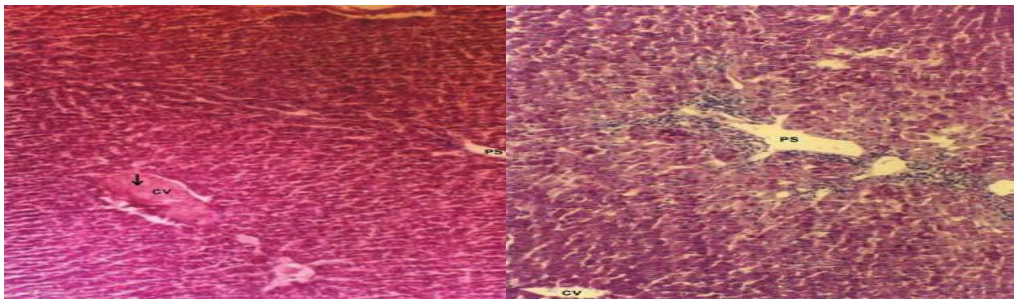

Fig 9. Photo of liver section of diabetic rabbit after treatment with stem extract of C.colocynthis
Fig 10. Photo of pancreatic section of diabetic wistarrat after treatment with stem extract of C.Colocynthis

Antidiabetic activity of fruit extract of *Citrullus colocynthis*

Administration of alloxan (30-50 mg/kg, intra peritoneal) prompted rise of fasting blood glucose levels, which was kept up over a time of 3 weeks. OGTT was acted in all the rodents from group I to group VII. Table 5 shows the consequences of oral glucose tolerance test. All the drug treated groups at 200mg/kg and 400mg/kg portions in diabetic rodents indicated a critical decrease in blood glucose values at 60, 90 and 120 minutes ($p<0.0001$) separately when contrasted with the diabetic control group. Consequences of OGTT of C. colocynthis fruit pulp extract are appeared in table 6.

On administration of various portions of *Citrullus colocynthis* day by day at 200mg/kg and 400mg/kg for a time of 10 days and on the eleventh day the outcomes got were assessed. Simultaneously hypoglcemic impact of ethanolic fruit pulp concentrate of *Citrullus colocynthis* were additionally concentrated in ordinary rodents. Assessment of hypoglycemic action of watery and ethanolic fruit pulp concentrates of *C. colocynthis* in groups was contrasted with typical rodents and saw that there is no critical lessening in blood glucose levels and was likewise seen that there was no distinction in glucose levels in all groups, the values were nearly to be pretty much same. Hypoglycemic action of various concentrates of *C.colocynthis* fruit pulp was assessed, the concentrate treated diabetic groups were contrasted with diabetic control group.

Table 5.Effect of *Citrullus colocynthis* fruit pulp extract on Oral Glucose Tolerance Test in normal and diabetic rats.

Groups	O mins	30 mins	60 mins	90 mins	120 mins
Group I	81.0 ±0.763	102.6 ±2.036	96.51 ±1.46	91.6 ±1.46	80.71 ±1.59
Group II	a296.83 ±4.43	a273.40 ±2.98	a296.7 ±3.35	a294.35 ±2.04	a270.08 ±1.54
Group III	a283.91 ±2.36	a262.63 ±2.30	a245.34 ±3.23	a171.76 ±2.53	a129.41 ±2.72
Group IV	81.15 ±2.57	79.97 ±0.871	78.26 ±1.801	77.94 ±1.221	78.33 ±1.51
Group V	82.98 ±0.846	80.54 ±0.55	82.68 ±0.68	78.44 ±0.933	71.47 ±0.801
Group VI	^{NS}290.06 ±2.72	^{NS}276.59 ±1.168	^{b}267.43 ±1.55	^{b}182.62 ±2.05	^{b}167.76 ±1.109
Group VII	^{NS}283.16 ±0.95	^{NS}277.73 ±3.36	^{b}199.78 ±2.69	^{b}177.66 ±2.38	^{b}157.78 ±1.437

Table 6. Blood glucose levels in normal, aqueous and ethanolic extracts of *Citrullus colocynthis* fruit pulp treated experimental groups

Groups	0 hr	1 hr	2 hr	4 hr	6 hr	8 hr
Group I	95.3 ±2.3	86.31 ±2.11	97.62 ±3.11	84.31 ±0.02	85.12 ±1.61	82.02 ±1.32
Group II	a250 ±1.60	a 267.8 ±2.4	a291.76 ±3.01	a 300 ±2.10	a 301 ±2.02	a 305 ±1.60
Group III	a291.7 ±2.08	a261 ±0.32	a155 ±3.62	a140 ±2.16	a135 ±1.36	a127 ±1.02
Group IV	98 ±1.32	85 ±1.26	80 ±1.67	77 ±0.07	75 ±0.06	73 ±2.08
Group V	99.87 ±1.32	85.09 1.26±	80.54 ±1.67	77.83 ±0.07	75.04 ±0.06	80.13 ±2.12
Group VI	298.87 ±0.62	a284.21 ±1.31	a260.98 ±1.02	a251.75 ±2.08	a248.87 ±2.07	a232.16 ±3.02
Group VII	295.30 ±0.82	a280.64 ±1.61	a200.05 ±1.08	a182.65 ±3.61	a173.35 ±2.31	a152.23 ±0.08

When EECC (200 and 400mg/kg) concentrate treated group was contrasted with diabetic control; there was a decrease in blood glucose levels essentially ($p<0.0001$). The concentrate treated diabetic groups were likewise contrasted with standard medication treated group. Day by day treatment with different concentration of C.colocynthis fruit pulp extract prompted a lessening in blood glucose levels. The serum glucose levels of the C.colocynthis fruit pulp extract treated groups were essentially decreased ($p<0.0001$) particularly from the 1hrs forward when contrasted with the diabetic control group. The concentrate of fruit pulp of *Citrullus colocynthis* treated groups were demonstrated that they brought down blood glucose levels fundamentally. (Fig. 11-14)

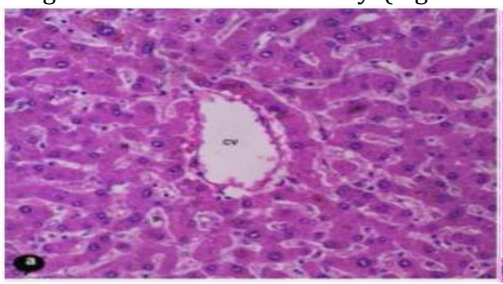

Fig 11. Photomicrographs of the liver of control wistar rat

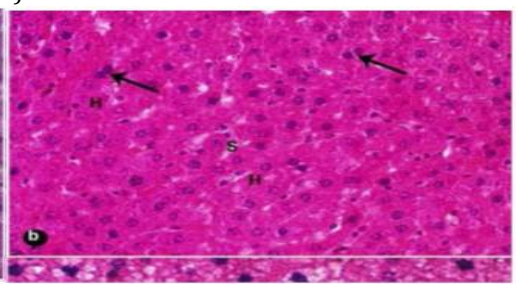

Fig 12. Photo of the Liver of *C.colocynthis* fruit pulp extract treated wistar rats

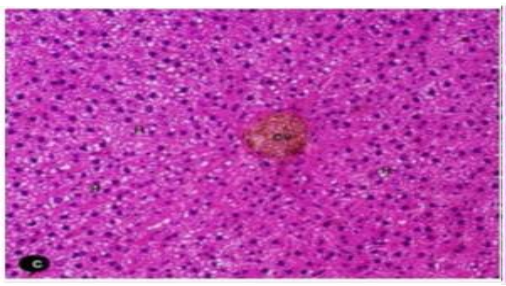

Fig 13. Photo of the Liver of diabetic wistar rats

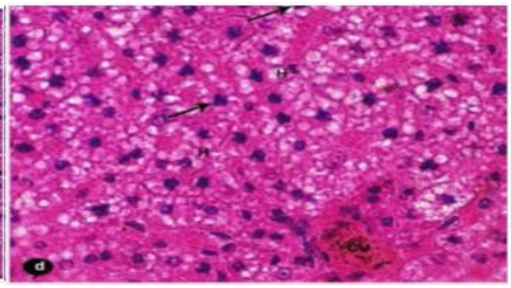

Fig 14. Photo of Liver of diabetic rats treated with *C.colocynthis* fruit extract recovered hepatocytes with less cytoplasmic vacuolization compared with diabetic animals

CONCLUSION

The impact of mix treatment on blood glucose level in normal and alloxan prompted diabetic rodents is observed. The mix treatment of low portions of C. colocynthis leaf extract demonstrated progressively huge (P<0.001) decrease in blood glucose level contrasted with the individual treatment of *C. colocynthis* stem extract at high dosages and comparable degree of centrality of standard drug, glibenclamide.

On administration of various portions of *Citrullus colocynthis* day by day at 200mg/kg and 400mg/kg for a time of 10 days and on the eleventh day the outcomes got were assessed. When Ethanolic extract of *C. colocynthis* (200 and 400mg/kg) concentrate treated group was contrasted with diabetic control; there was a decrease in blood glucose levels essentially (p<0.0001). The concentrates of fruit pulp of *Citrullus colocynthis* treated groups were demonstrated that they brought down blood glucose levels fundamentally.

CONFLICT OF INTEREST

Authors having no any conflict of interest.

ACKNOWLEDGEMENT

Authors are thankful to Maulana Gulam MdVastanvi President, J.I.I.U's Jamia College of Pharmacy, Akkalkuwa, and teaching and non-teaching staff of Jamia and Ali Allana College of Pharmacy, Akkalkuwa, Dist: Nandurbar, M.S. for support and motivation during research work.

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