

## ANTIDIABETIC AND ANTIHYPELIPIDAEMIC ACTIVITY OF RANDIA DUMETORUM

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### ABSTRACT

Problems. The present study was undertaken to evaluate the antihyperglycemic and antihyperlipidemic activity of *Randia dumetorum* fruit extract in experimental animals using Nicotinamide (NA) and Streptozotocin (STZ) induced diabetic rats.

Experimental approach. The first group of male wistar rats was normal control, second group was used as diabetic control group. The diabetic rats of third and fourth group were treated orally with *Randia dumetorum* Fruit extract (200mg/kg b.w. & 400mg/kg b.w.) for 28 days, fifth group was treated orally with 25mg/kg b.w. Gliclazide.

Major findings. The diabetic rats treated with the extract and Gliclazide shows significantly decreased glucose level, as compared to diabetic control group. In case of OGTT the extract OD, extract BD and Gliclazide treated groups, glucose level nonsignificantly decreases at 60 and 120 min giving the indication regarding the supportive action of the extract and also with STZ&NA induced rats significant blood glucose and lipid lowering was found with the same extract.

Conclusion. These new data indicates that *Randia dumetorum* fruit extract represents an effective antihyperglycemic, and a potential source of discovery of new therapeutic agent.

**Keywords:** Diabetes mellitus; *Randia dumetorum*; streptozotocin; albino rats

### INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder affecting approximately 4% population worldwide and is expected to increase by 5.4% in 2025<sup>1</sup>. It is characterized by abnormalities in carbohydrate, lipid and lipoprotein metabolism, which not only leads to hyperglycemia but also cause many complications such as hyperlipidemia, hyperinsulinemia, hypertension and atherosclerosis<sup>[2][3]</sup> which results in decreased ability of insulin to stimulate glucose uptake in peripheral tissues, insulin resistance, and the inability of the pancreatic  $\beta$ -cells to secrete

insulin adequately which ultimately leads to  $\beta$ -cell failure caused by a combination of genetic and environmental factors. The major sites of insulin resistance in type-2 diabetes are the liver, skeletal muscle and adipose tissue<sup>1</sup>. *Randia dumetorum* commonly known as indigo berry (family Rubiaceae, Hindi name; Mainphal, Madan) is one such ayurvedic remedy that has been mentioned in many Indian medical literatures for the treatment of many diseases including its role as antioxidant and liver protectant. The fruit of the drug is said to be emetic, expectorant, diaphoretic, nauseant, anthelmintic, abortifacient and

antispasmodic. Its fruits are considered to be tonic, alterative, demulcent, diuretic and restorative and are claimed as a medical cure for piles, antidysentric agent, asthma, jaundice, diarrhea, emetic and gonorrhoea<sup>4</sup>. In the Ayurvedic texts, *R. dumetorum* is classified as a drug having properties similar to rasayanas<sup>5</sup>.

Oleonic acid 3-glucoside, isolated from the seed, exhibited this property as found from the previous studies. The present study was undertaken to evaluate the antihyperglycemic and antihyperlipidemic activity of *randia dumetorum* fruit extract in experimental animals using Nicotinamide (NA) and Streptozotocin (STZ) induced diabetic rats.

## MATERIALS AND METHODS

**Animals** Male adult albino rats (200–225 g) bred in the animal house of the institute were used. A group of six animals in a cage were kept in controlled conditions, temperature 25–26°C, relative humidity 60–80% and 12/12 h light/dark cycle (light from 08:00 a.m. to 08:00 p.m.). The identification of animals has been done by cage card and corresponding colour body markings using picric acid. The animals were kept in polypropylene cages with stainless steel grill top, facilities for feed and water bottle and bedding of clean paddy husk, fed on standard pellet diet and U.V. purified and filtered water will be provided ad libitum in polypropylene bottles with stainless steel sipper tubes. The standard pellet diet (Protein: 20.12%, Total Oil: 4.38%, Dietary Fiber: 3.65%, Moisture: 8.0%) was supplied by Rayan's biotechnologies Pvt. Ltd, Hyderabad, India. The Institutional Animal Ethical Committee has approved the experimental protocol (Approval No.29) prior to carry out the animal experimentation. The study design was in compliance with guidelines of Institutional Animal Ethical Committee (IAEC Regd No: 926/ab/06/CPCSEA).

## Preparation of extracts

The fruit was obtained from the village area of college of pharmaceutical sciences Mohuda. The plant was authenticated at department of Botany, khaliakote govt college Berhampur by taxonomist Prof. B. Mohanty. A voucher specimen was kept at Roland Institute of Pharmaceutical sciences for reference. The seeds were dried under normal environmental condition and grinded into Powder, the powder was subjected to successive soxhlet extraction with the solvents with increasing order of polarity i.e. petroleum ether (50°C), chloroform (50°C) and methanol (60°C).

## Acute Toxicity studies

Wistar rats weighing 150-175 g of either sex, maintained under standard husbandry conditions, were used for all sets of experiments in groups of six animals. The ethanolic extract was administered to different groups of rats in doses ranging from 100-2000 mg/kg. There is no lethality in any of the groups. One tenth of the maximum dose of the extract and its double dose, tested for acute toxicity, was selected for evaluation of antidiabetic, i.e., 200 mg/kg & 400 mg/kg b.w. and antihyperlipidaemic study. The experiments were performed after the experimental protocols had been approved by the Institutional Animal Ethics Committee, Roland institute of pharmaceutical sciences, Berhampur.

## Chemicals

Streptozotocin (STZ; Himedia Laboratories Pvt. Ltd. Mumbai), nicotinamide (NA; Himedia laboratories Pvt. Ltd. Mumbai), Glucalid (Chemical Products, Mumbai), EDTA (Qualigens, Mumbai, India), Glucose (Nice chemicals Pvt. Ltd. Cochin), Citric acid (Nice chemicals Pvt. Ltd. Cochin), Sodium citrate 2-hydrate (Merk Specialities Pvt. Ltd. Mumbai).

## Biochemical kits

All the kits were obtained from Crest Biosystems, a division of Coral Clinical Systems, Goa. The kits like Glucose, Triglycerides, Cholesterol, etc were used in Auto analyzer (3000 Evolution, BSI, Italy).

## Experimental

### Induction of type II diabetes mellitus

Type II diabetes mellitus was induced by a single intraperitoneal injection of 120 mg/kg of nicotinamide (NA) followed by STZ 50 mg/kg<sup>06</sup> intravenously 15 min afterwards. STZ was dissolved in citrate buffer (pH 4.5) and NA<sup>06</sup> was dissolved in normal saline<sup>07</sup>. The animals were made to fast for 12h before induction. The animals were allowed to drink 5% glucose solution overnight to overcome the drug-induced hyperglycemia. Diabetes was confirmed by the elevated glucose levels in the plasma of the rats, determined after 3 days of the induction. The threshold value of the fasting plasma glucose to diagnose diabetes, was taken as >200 mg/dl. Only those rats that were found to have plasma glucose level >200 mg/dl were used in the study.

### Determination of plasma glucose and other biochemical parameters

Animals were fasted overnight. Blood (0.5 ml) was withdrawn from the sublingual vein under

ether anesthesia and was collected in micro tubes previously filled with 10% EDTA solution (20 µl of 10% EDTA/ ml of blood). The micro tubes were centrifuged at 4000 rpm at 4°C for 20 min to obtain clear plasma. The plasma was then analyzed for glucose in the auto analyser (3000 Evolution, BSI Italy) using commercially available biochemical kits.

#### Grouping of Animals in STZ&NA model for blood glucose estimation

They were divided into 4 experimental groups, each group containing six animals in it. Twenty four rats of body weight range 150-200g were selected from the stock of animal house. Six animals were not treated with NA and STZ and kept as non-diabetic control. Diabetes was induced in rest of 18 rats. Rats that showed blood glucose level more than 200mg/dl were selected for further grouping. The experimental groups are

##### Group 1

Non-diabetic control, treated with normal saline daily.

##### Group 2

Diabetic control (STZ+ NA), treated with normal saline.

##### Group 3

Diabetic (STZ+ NA), treated with *Randia dumetorum* (200 mg/kg b.w.) once a day.

##### Group 4

Diabetic (STZ+ NA), treated with *Randia dumetorum* (400 mg/kg b.w.) once a day.

##### Group 5

Diabetic (STZ+ NA), treated with 25mg/kg b.w. of Gliclazide.

#### Oral glucose tolerance test<sup>8</sup>

Oral glucose tolerance test (OGTT) was carried out in overnight fasted rats, which were equally divided into four groups of six rats each. Group of normal control (Gr II & positive control) received only vehicle (1 ml of 0.3% CMC; p.o.) and standard group (111) received 1 ml of reference drug (Gliclazide 25mg/kg b.w.)<sup>09</sup> Suspended in the vehicle while group IV and V were administered with *paederia foetida* extract (200 & 400mg/kg, p.o.) respectively. Thereafter, following 30 min post extract, all the animals were administered with glucose (2 g/kg). Blood samples were collected from sublingual vein prior to dosing and then at 30, 60 and 120 min after glucose administration. The fasting blood glucose level was analyzed using auto analyzer using sugar testing kits.

#### Statistical analysis

The data obtained in the studies were subjected to one way analysis of variance (ANOVA) for determining the significant difference. The intergroup significance was analyzed using Dunnett's t test. P values <0.05 were considered to be significant. All the values were expressed as mean ± SEM.

#### Results

##### Body weight

Body weight of non diabetic rats was significantly increased week by week. Diabetic rats was shown significantly (p<0.01) reduction in body weight as compared to non diabetic group. While the *Randia dumetorum* and Gliclazide treated rats showed significantly (p<0.01) increase in body weight as compared to diabetic control group. The result of body weight is given in Table No1 and figNo1.

##### Serum lipid profile

The effect of the *randia dumetorum* and gliclazide, in the untreated diabetic rats serum levels of Cholesterol and TG were significantly increased (TableNo2 and 3) and (Fig No2 and 3). These complications of diabetes were attenuated with the administration of *Randia dumetorum*. The effects of standard drug gliclazide on serum TG and cholesterol in the diabetic rats were comparable to those of *randia dumetorum*. Total cholesterol and TG were significantly elevated in diabetic group in comparison to control group. Administration of *Randia dumetorum* for 28 days significantly reduced the serum levels of cholesterol and TG in comparison to diabetic control rats.

##### Blood glucose level (STZ&NA model)

In STZ induced diabetic rats, the blood glucose levels were in the range of 234-296 mg/dl, which were considered as severe diabetes. In the gliclazide (50mg/kg) and *paederia foetida* extract (200mg/kg & 400mg/kg b.w) groups, the peak values of blood sugar significantly decreased from 198±10.89 to 145±3.43 in case of Gliclazide, 238.5±3.50 to 193.3±3.2mg/dl in case of *randia* extract OD and from 243.16±6.81 to 168.66±2.25mg/dl in case of *randia* extract BD on the 28<sup>th</sup> day, respectively (Table-4 & Fig-4). Hence, *Randia dumetorum* fruit extract (OD &BD) reduced the blood glucose levels in diabetic rats but values did not return to those of normal controls. Therefore, *Randia dumetorum* fruit extract possess statistically significant (P<0.01) antidiabetic activity, when compared with diabetic control. There was a marked reduction in blood glucose level (28days) in STZ –diabetic animals.

### Oral glucose tolerance test

The effects of *Randia* fruit extract (200mg/kg & 400mg/kg b.w) groups, at different time points revealed no significant difference among the groups at 0 min & 30 min. However, at 60 min & 120 min, significant difference was observed between the groups (Table-5 & Fig-5). Hence, gliclazide (50mg/kg) and *Randia* extract (200mg/kg & 400mg/kg b.w) groups, the peak values of blood sugar significantly decreased from  $88.5 \pm 6.86$  to  $74.16 \pm 4.02$  in case of Gliclazide between 60 min to 120 min, from  $121.5 \pm 1.97$  to  $112.16 \pm 3.65$  mg/dl in case of *Randia* extract OD and from  $106.16 \pm 7.8$  mg/dl to  $87.5 \pm 5.00$  in case of *Randia* extract BD, and so possess statistically significant ( $P < 0.01$ ) antidiabetic activity, when compared with diabetic control. Hence, *Randia dumetorum* methanolic extract (OD & BD) reduced the blood glucose levels in diabetic rats as found in oral glucose tolerance test but values did not return to those of normal control.

### DISCUSSION

Type II diabetes was induced by administration of NA followed by STZ. STZ produces the chronic diabetic condition in which function of many organs is altered. In type II diabetes, blood glucose level and lipid profile are significantly altered. In our study, after treating with *Paederia foetida* aerial part extract, the biochemical abnormalities were significantly improved and extract decreased the blood glucose level. Action of STZ in  $\beta$ -cells is accompanied by characteristic alterations in blood insulin and glucose concentrations. Two hours after injection, hyperglycemia was observed with a concomitant drop in blood insulin<sup>[10]</sup>. STZ damages pancreatic  $\beta$ -cells, possibly by generating excess reactive oxygen species, and thus widely used for the induction of experimental diabetes mellitus<sup>[11]</sup>. Recent experiments have proved that the main reason for the STZ-induced  $\beta$ -cell death is alkylation of DNA. The alkylating activity of STZ is related to its nitrosourea moiety, especially at the O<sub>6</sub> position of guanine. Since STZ is a nitric oxide (NO) donor and NO was found to bring about the destruction of pancreatic islet cells, it was proposed that this molecule contributes to STZ-induced DNA damage. It can be stated that potent alkylating properties of STZ are the main reason of its toxicity. However, the synergistic action of both NO and reactive oxygen species may also contribute to DNA fragmentation and other deleterious changes caused by STZ. NO and reactive oxygen species can act separately or

form the highly toxic peroxynitrate. Therefore, intracellular antioxidants or NO scavengers substantially attenuate STZ toxicity. STZ-induced DNA damage activates poly ADP ribosylation. This process leads to depletion of cellular NAD<sup>+</sup>, further reduction of the ATP content and subsequent inhibition of insulin synthesis and secretion<sup>[10]</sup>. The rats administered with NA 15 min before STZ has been shown to develop moderate and stable non-fasting hyperglycaemia without any significant change in plasma insulin level. As NA is an antioxidant which exerts protective effect on the cytotoxic action of STZ by scavenging free radicals and causes only minor damage to pancreatic beta cell mass producing type II diabetes<sup>[12]</sup>.

### Blood glucose level

The fundamental mechanism underlying hyperglycemia in diabetes mellitus involves overproduction (excessive hepatic glycogenolysis and gluconeogenesis) and decreased utilization of glucose by the tissues<sup>[13]</sup>. Diabetic rats showed high glucose level (200-300 mg/dl) throughout the experiment compared to non diabetic rats. The diabetic rats treated with *Randia* extract and gliclazide showed significantly decreased glucose level as compared to diabetic control group. The possible mechanism by which *Randia dumetorum* fruit extract brings about its antihyperglycemic action is due to the elevated plasma insulin level.<sup>[13]</sup>

### Biochemical parameters

Diabetic rats showed high cholesterol and triglyceride level. Increased levels of serum triglycerides and cholesterol observed in streptozotocin-induced diabetic rats were in accord with other studies. The abnormal high concentrations of serum lipids in diabetic animals are due mainly to an increase in the mobilization of free fatty acids from the peripheral fat depots, since insulin inhibits the hormone-sensitive lipase. Excess fatty acids in the serum of diabetic rats are converted into phospholipids and cholesterol in the liver. These two substances along with excess triglycerides formed at the same time in the liver may be discharged into the blood in the form of lipoproteins. *Randia* extract and gliclazide treated rats showed non significant decrease in plasma cholesterol and triglyceride level as compared to diabetic control group.

### OGTT<sup>[14]</sup>

In the OGTT or glucose loaded hyperglycemic model, the *Randia dumetorum* treated methanolic extract tested for

antihyperglycemic activity exhibited significant antihyperglycemic activity at a dose level of 400mg/kgb.w. Excessive amount of glucose in the blood induces the insulin secretion. This secreted insulin will stimulate peripheral glucose consumption and control the production of glucose through different mechanisms. However, from the study (glucose control), it was clear that the secreted insulin requires 2-3 h to bring back the glucose level to normal.<sup>14</sup> In case of the *Randia dumetorum* fruit extract OD, *Randia dumetorum* fruit extract BD and gliclazide treated groups, the glucose levels significantly

decreased at 60 min and at 120 min and reached at the normal level compared to diabetic group giving the indication regarding the supportive action of extract and gliclazide.

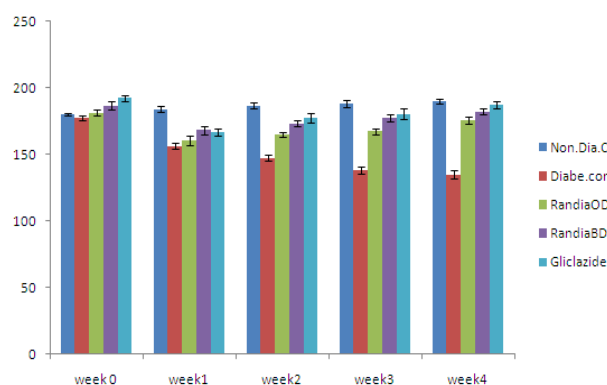
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**Table 1: Effect of *Randia dumetorum* extract on Body weight in STZ-NA induced hyperlipidaemic rats**

	Non-Diabetic control	Diabetic control	<i>Randia dumetorum</i> 200mg/kgb.w.	<i>Randia Dumetorum</i> 400mg/kgb.w	Gliclazide 25mg/kgb.w.
week 0	180.3±0.5	177.5±2.13	181.67±2.1	186.67±3.33	192.5±2.13
week1	184.17±2	156.67±2.1	160.83±3.51	168.33±3.07	166.67±2.78
week2	186.67±24	147.5±2.47	165±2.13	173.33±2.49	177.5±3.81
week3	188.33±24	138.33±2.4	167.5±2.13	177.5±2.49	180.5±3.81
week4	190±1.82	135±2.88	175.83±2.3	182.5±2.13	187.5±2.81

Values are expressed as mean ± SEM, n=6, p ≤ 0.05, Vehicle control Vs Diabetic control, #p ≤ 0.05, Diabetic control Vs Treated groups.



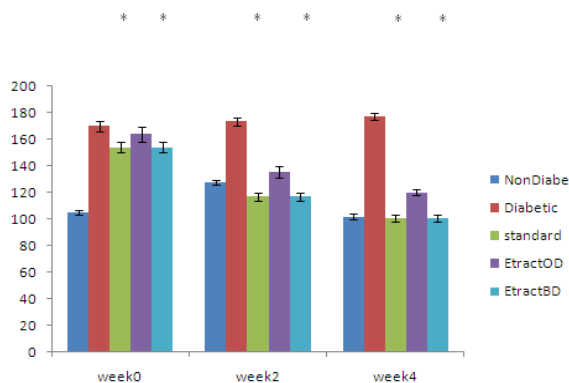
**Fig. 1: Effect of *Randia dumetorum* extract on Body weight in STZ-NA induced hyperlipidaemic rats**

**Table 2: Effect of *Randia dumetorum* extract on Total cholesterol in STZ-NA induced hyperlipidaemic rats**

	Nondiabetic	Diabetic	Standard	Randia	Randia
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	control	control		dumetorum 200mg/kgb.w.	Dumetorum 400mg/kgb.w.
Week 0	105±1.414	170.16±1.722	154.16±3.86*	164±5.65	160.5±7.007*
Week 2	127.6±1.751	173.66±3.98	117±3.09*	135.5± 4.13	128±2.82*
Week 4	102±2.366	177.16±2.04	100.5±2.66*	120.33± 2.42	106.66±2.58*

Values are expressed as mean ± SEM, n=6, p ≤ 0.05, Vehicle control Vs Diabetes control,  
#p ≤ 0.05, Diabetes control Vs Treated groups.

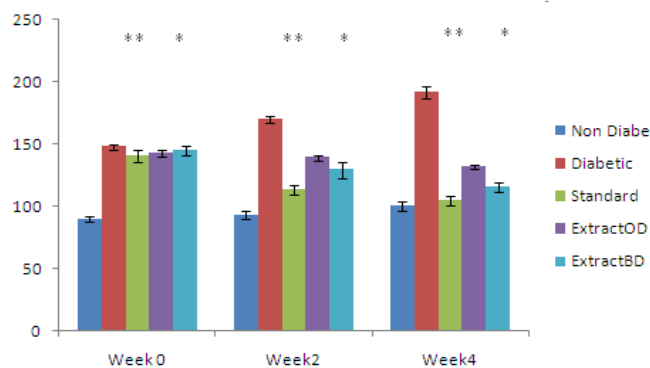


**Fig. 2: Effect of *Randia dumetorum* extract on Total cholesterol in STZ-NA induced hyperlipidaemic rats**

**Table 3: Effect of *Randia dumetorum* extract on Triglyceride level in STZ-NA induced hyperlipidaemic rats**

	Non Diabetic control	Diabetic control	Standard	Randia Dumetorum 200mg/kgb.w.	Randia Dumetorum 400mg/kgb.w.
Week 0	89.5±1.974	147.5±2.07	140±5.05	142.33±2.4	144.83±3.9
Week 2	92.83±2.99	169.33±2.5	113.16±3.6	138.66±2.0	129±6.72
Week 4	100±3.57	191±4.732	104±3.68	131.16±1.8	115±3.577

Values are expressed as mean ± SEM, n=6, p ≤ 0.05, Vehicle control Vs Diabetic control,  
#p ≤ 0.05, Diabetic control Vs Treated groups

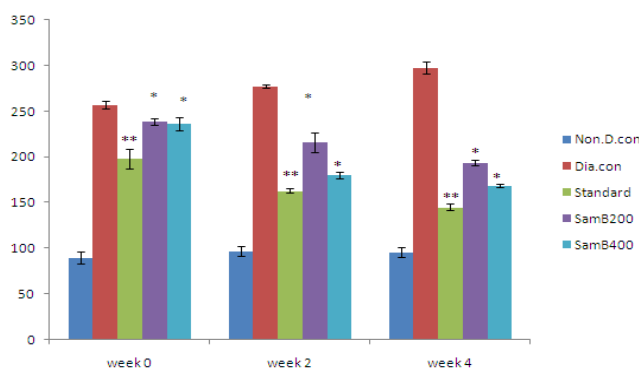


**Fig. 3: Effect of Randia dumetorum extract on Triglyceride level in STZ-NA induced hyperlipidaemic rats**

**Table 4: Effect of randia dumetorum fruit extract on Blood sugar level (STZ&NA MODEL)**

	Nondiabetic control	Diabetic control	Standard	Randia dumetorum (200mg/kgb.w.)	Randia Dumetorum (400mg/kgb.w.)
Week 0	89.66±6.80	257±4.289	198±10.89**	238.5±3.50*	236±6.81**
Week 2	96.5±5.31	277.5±2.16	163±2.33**	215.8±10.7*	180.16±3.8**
Week 4	96.16±5.45	297.5±6.56	145±3.43**	193.3±3.2*	168.6±2.25**

Values are expressed as mean ± SEM, n=6, p ≤ 0.05, Vehicle control Vs Diabetic control, \*p ≤ 0.05, Diabetic control Vs Treated groups.



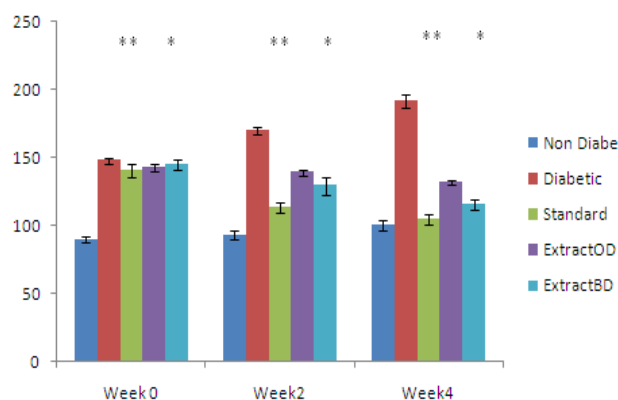
**Fig. 4: Effect of randia dumetorum fruit extract on Blood sugar level (STZ&NA MODEL)**

**Table 5: Effect of randia dumetorum fruit extract on Blood sugar level (STZ&NA MODEL) in oral glucose tolerance test (OGTT)**

	Non Diabetic control	Diabetic control	Standard	Randia dumetorum 200mg/kg b.w.	Randia Dumetorum 400mg/kgb.w.
0 min	75.8±7.11	73.5±7.34	70.33±3.88	79.66±3.14	69.66±5.95
30 min	77.66±6.15	139.5±6.09	85.8±5.11	127.8±4.62	111±5.17
60 min	76.5±4.46	130.3±6.6	88.5±6.86	121.5±1.97	106.16±7.8
120 min	76.33±3.73	127.5±4.23	74.16±4.02	112.1±3.65	87.5±5.00

Values are expressed as mean ± SEM, n=6, p ≤ 0.05, Vehicle control Vs Diabetic control, \*p ≤ 0.05,

Diabetic control Vs Treated groups



**Fig. 5: Effect of *Randia dumetorum* fruit extract on Blood sugar level (STZ&NA MODEL) in oral glucose tolerance test (OGTT)**

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