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REVERSAL OF ROSIGLITAZONE HEPATOTOXICITY BY SILYMARIN ON RATS

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ABSTRACT: The present study was undertaken to investigate the hepatotoxic potential of rosiglitazone- an oral hypoglycemic thiazolidenedione class of drug. The hepatotoxic potential of rosiglitazone was assessed *in-vitro* on isolated rat hepatocytes before subjecting to *in-vivo* studies. The *in-vitro* activity was measured by trypan blue exclusion assay and determination of liver marker enzymes. The hepatotoxic potential of rosiglitazone was measured at 100 to 500 µg/ml concentration and maximum hepatotoxicity was produced at highest concentration tested. *In-vivo* hepatotoxic potential of rosiglitazone was assessed on hyperglycemic rats and protective effect of silymarin a known hepatoprotective agent was also tested. When rosiglitazone was administered at the dose of 2 mg/kg body weight for 21 successive days on rats, has produced marked hepatotoxicity when compared to normal animals. The hepatotoxic potential was evaluated by determination of serum biochemical markers and liver anti-oxidant enzyme studies. Hypoglycemic effect of rosiglitazone in presence of silymarin was also assessed in alloxan induced hyperglycemic rats to rule out any drug interaction. The rosiglitazone has produced significant elevation of serum biomarkers when compared to normal animals and the co-administration of silymarin reversed the toxic potential of rosiglitazone. The liver enzyme studies revealed the hepatotoxic potential of rosiglitazone. The co-administration of silymarin has not shown any interaction and rosiglitazone retains its hypoglycemic activity when it was co-administered with silymarin. The study demonstrates that, rosiglitazone induced hepatotoxicity can be reversed by co-administration of a known hepatoprotective agent silymarin without compromising its hypoglycemic potential.

INTRODUCTION: Drug-induced hepatotoxicity is frequently a major safety issue for an investigational new drug. It may occur as an unexpected idiosyncratic reaction to an otherwise nontoxic drug or it may be an expected consequence of the intrinsic toxicity of a drug, taken in a sufficiently large dose to cause liver injury [1].

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The worldwide prevalence of diabetes is increasing day by day and recent estimation of WHO states more than 180 million people worldwide has diabetes.

The number is likely to be more than double by 2030. Around 3.2 million deaths every year are attributable to complications of diabetes, six deaths every minute [2]. Synthetic hypoglycemic agents can produce serious side effects including hematological, coma, and disturbances of liver and kidney, gastrointestinal disturbances, fluid retention [3]. Recently, a large prospective cohort study was performed to examine whether patients with type 2 diabetes are at an increased risk of developing acute liver failure [4].

Anti-diabetic drugs are having high risk of causing hepatotoxicity. Some of the research works shows that, the oral hypoglycemic agents like sulfonylurea and thiazolidenedione (TZDs) causing hepatotoxicity. Rosiglitazone is a member of the TZDs class of drug acts to enhance sensitivity to insulin in skeletal muscle, adipose tissue and the liver. Troglitazone is the original preparation in this class, has been associated with idiosyncratic hepatotoxicity, sometimes resulting in liver failure and death.

The mechanism of action of these drugs is that it acts on the liver and cause various abnormalities in liver and producing cholestasis and abnormalities in liver enzymes. It has also cause genotoxicity by damaging the DNA on rats. Its first class drug Troglitazone having more reports on producing hepatotoxicity hence it was withdrawn from market[5, 6].

Based on this, in the present study, we have taken rosiglitazone to evaluate its hepatotoxic potential. Moderate to severe acute hepatitis has occurred in several adults who had been taking this drug at the recommended dose for 2-4 weeks.

Plasma Rosiglitazone concentrations may be significantly increased in patients with pre-existing hepatic impairment and very few case reports have implicated that it causes hepatocellular injury, granulomatous hepatitis and severe cholestatic hepatitis [5]. The hepatotoxicity can be minimized by co-administration of various proven hepatoprotective agents [7].

In the present study we studied the hepatotoxic potential of rosiglitazone and protective effect of silymarin by *in-vitro* and *in-vivo* method.

MATERIALS AND METHODS:

Experimental animals: Albino rats of either sex weighing 150-200 gm were used for the study. All animals were kept under standard husbandry conditions for 12hr dark and light cycle respectively in standard propylene cages. The animals were fed with standard food and water *ad libitum*. All the experiments were approved by Institutional Animals Ethics Committee of JSS College of Pharmacy, Mysore (No.033/2009).

***In-vitro* hepatotoxicity study of Rosiglitazone:** Hepatotoxic potential of rosiglitazone was assessed *in-vitro* by using freshly isolated rat hepatocytes at different concentrations. Fasting albino adult rat was used for the study and hepatocytes were isolated using modified method of Kiso *et al* [8]. The animals was disinfected with ethanol and anesthetized by Ketamine (i.p.50mg/kg body weight). Dissection was done under aseptic condition using sterilized instruments.

Midline incision was made on the abdomen of the anaesthetized animal. The portal vein was canulated with needle number 25 connected to a 10 ml disposable syringe. The needle was tied in place and the inferior vena cava was cut below the renal vein. Perfusion of the liver was started immediately with Ca^{2+}-Mg^{2+} free Hanks Balanced Salt Solution (HBSS). When the liver was thoroughly perfused (*i.e.* has turned white), the flow of the HBSS was stopped and the needle was removed.

The liver was transferred to a sterile beaker containing Ca^{2+} - Mg^{2+} free HBSS and minced into small pieces, which were transferred to a sterile conical flask containing 10 ml of 0.075% Collagenase in HBSS. The cell suspension thus obtained was mixed properly and centrifuged at 2000 rpm for 10 minutes. The cells were washed with Dulbecco's Modified Eagle Media (DMEM) 2-3 times and suspended in complete medium and incubated at room temperature for 1.5 hrs possibly to recover from the stress and membrane injury suffered during the isolation of cells. The isolated rat hepatocytes were cultures in DMEM at density of $1X10^6$ cells/ml [9]. Viability of the isolated cells was determined by Trypan blue exclusion assay by counting the number of stained and unstained cells. The cell viability in any case should be more than 90%[10].

The primary rat hepatocytes thus obtained were used for studying the hepatotoxic potential of rosiglitazone. Fixed number of hepatocytes (1×10^6 cells/ml) was incubated with different concentrations (100, 150, 250 and 500 µg/ml) of rosiglitazone in sterile test tubes. The above cell suspension was incubated for 3 hr and after 3hr of incubation the cell viability was determined by the Trypan blue exclusion assay. Afterwards cell suspension was centrifuged at low speed (2000 rpm) for 15 min.

The supernatant solution was used for the estimation of marker enzymes like GOT, GPT and LDH. All determinations were done in Semi Auto analyzer (Micro lab 300) using Mark diagnostic kits [10].

***In-vivo* hepatotoxicity and hypoglycemic studies of Rosiglitazone:** The experimental animals were acclimatized one week for laboratory conditions before the experiments. The animals were divided into four groups and treated as per the **Table 1**. Hyperglycemia was induced by alloxan (45mg/kg i.p) in overnight fasted rats except group I animals. After alloxan administration the animals blood glucose level was checked after 48 hrs to 72 hrs using glucometer, if the blood glucose level was above 140 mg/dl, that animal was consider as hyperglycaemic animals. These hyperglycaemic rats were used for the study [11].

TABLE 1: TREATMENT SCHEDULE FOR THE STUDY OF *IN-VIVO* HEPATOTOXIC POTENTIAL OF ROSIGLITAZONE

GROUPS	TREATMENT
Normal	Normoglycemic animals treated with gum acacia solution (2.5%, 1 ml/kg body weight) orally for 21 successive days.
Hyperglycemic control	Alloxan induced hyperglycemic rats, treated with gum acacia solution (2.5%, 1 ml/kg body weight) orally for 21 successive days.
Rosiglitazone	Alloxan induced hyperglycemic rats, treated with rosiglitazone (2 mg/kg body weight) orally for 21 successive days.
Rosiglitazone + Silymarin	Alloxan induced hyperglycemic rats, treated with rosiglitazone (2 mg/kg body weight) and silymarin (100mg/kg body weight) was administered orally 1 hr after rosiglitazone for 21 successive days

After 24 hrs of last dose administration, all animal were sacrificed, the blood was collected by cardiac puncture, serum was separated by centrifuging at 2500 rpm using cold centrifuge, for estimation of serum enzymes like, serum glutamic oxalotransaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total bilirubin and total proteins by using commercially available kits (manufactured by ERBA diagnostics Mannheim, Germany) using autoanalyzer (Microlab-300).

The liver was removed and washed in cooled 0.9 % saline, kept on ice and subsequently blotted on filter paper, then weighed and homogenized in cold phosphate buffer (0.05 M, pH 7.4). The homogenates were centrifuged at 10000 rpm for 10 min at 4 ºC (MPW-350R, Korea) and supernatant[12] was used for the estimation of lipid peroxidation (LPO) [13]. The supernatant was again centrifuged at 15000 rpm for 1 hr at 4ºC. The supernatant obtained was used for further estimation of superoxide dismutase (SOD) [14], catalase (CAT), glutathione (GSH) [15].

Statistical analysis: Experimental results were given as Mean±SEM and the values were evaluated using the one-way analyses of variance (Tukey multiple comparison test). *P-values < 0.05* were regarded as significant.

RESULTS:

Hepatotoxic potential of rosiglitazone *in-vitro*: The hepatotoxic potential of rosiglitazone *in-vitro* on isolated rat hepatocytes is presented in **Table 2 & 3.** As shown in Table 2, rosiglitazone has demonstrated dose dependent hepatotoxicity on isolated fresh rat hepatocytes; the percentage cell viability was decreased as the dose increases. Maximum decrease in cell viability was found to at 500 µg/ml (50±0.87%) when compared to that of normal hepatocytes (96.41±0.93%). Hepatotoxicity of rosiglitazone was further demonstrated by determining liver biomarker enzymes in the supernatant of isolated rat hepatocytes. GOT, GPT and LDH levels were also elevated dose dependently. The individual enzyme elevation by rosiglitazone treated hepatocytes is presented in Table 3. This study further suppliments the hepatotoxic potential of rosiglitazone on isolated rat hepatocytes by *in-vitro* method.

TABLE 2: *IN-VITRO* HEPATOTOXICITY OF ROSIGLITAZONE ON ISOLATED RAT HEPATOCYTES (% VIABILITY)

Concentration (µg/ml)	% viability
Normal	96.41±0.93
100	84.26±0.54
150	70.13±0.57
250	65.33±0.80
500	52.50±0.87

Values are presented as Mean ± SEM of triplicate values.

TABLE 3: *IN-VITRO* HEPATOTOXICITY OF ROSIGLITAZONE ON ISOLATED RAT HEPATOCYTES (MARKER LIVER ENZYME LEVEL)

Conc. (µg/ml)	GOT	GPT	LDH
Normal	103.33±5.81	783.00±23.62	102.00±8.57
100	197.33±3.48	1675.33±16.75	162.33±10.88
150	198.45±2.64	1729.33±21.07	169.66±12.88
250	239.37±3.75	1785.02±19.62	179.05 ±11.15
500	310.53±2.64	1812.04±20.52	195.78±13.15

Values are Mean ± SEM of triplicates

Hepatotoxic potential of Rosglitazone *in-vivo*: *In-vivo* hepatotoxic potential of rosiglitazone was assessed on albino rats and protective effect silymarin was also assessed and the results are given in **Table 4 & 5.** As shown in Table 4 administration of rosiglitazone was shown to increase liver enzymes as well as biochemical(s) which show the marked injury to the liver by rosiglitazone. The protein level in the rosiglitazone treated animals was less than the normal, which also supports the hepatocytes injury by rosiglitazone administration. The liver injury produced by rosiglitazone was reversed by the co-administration of silymarin, the animal treated with rosiglitazone followed by silymarin have shown the normal level of liver marker enzymes as well as biochemical(s) when compared with normal animals. Even the total protein level also increased as that of normal animals in silymarin treated animals.

The above results clearly demonstrate the hepatotoxic potential of rosiglitazone which is significant in all parameters tested when compared with normal rats. The results suggest that, the silymarin administration has reversed the liver injury induced by rosiglitazone without compromising its hypoglycemic activity (discussed below).

TABLE 4: EFFECT OF SILYMARIN ON ROSIGLITAZONE INDUCED HEPATOTOXICITY IN RATS (SERUM PARAMETER)

Groups	SGPT	SGOT	ALP	Total Protein	Total Bilirubin	LDH
Normal	179.00±7.23	105.00±6.08	445.66±7.62	8.23±0.28	0.60±0.03	167.33±3.44
Rosiglitazone	319.00±3.14[a]	235.00±3.13[a]	728.50±8.50[a]	4.16±0.15[b]	1.17±0.05[a]	292.83±2.74[a]
Rosiglitazone +Silymarin	179.66±2.02[c]	98.33±0.05[c]	466.20±6.85[c]	7.7±0.32[d]	0.78±0.06[c]	175.83±5.42[c]

Values are presented as Mean ± SEM, n=6; [a]P< 0.05 significant increase when compared with normal group; [b]P< 0.05 significant decrease when compared with normal group; [c]P<0.05 significant decrease when compare to rosiglitazone group; [d]P<0.05 significant increase when compare to rosiglitazone group.

To establish the hepatotoxic potential of rosiglitazone and protective effect of silymarin, liver tissue homogenate was assessed for tissue anti-oxidant enzymes and lipid peroxidation (Table 5). The SOD, catalase and GSH level in the rats treated with rosiglitazone alone has shown decreased, which demonstrates the rosiglitazone liver injury. The liver injury of rosiglitazone was significant when compared to normal animals. The rats treated with silymarin along with rosiglitazone have revered the liver injury caused by rosiglitazone. The SOD, catalase and GSH level were returned to normal and significant when compared with rosiglitazone treated animals by silymarin treatment. These results also further demonstrate the hepatotoxic potential of rosiglitazone, which can be reversed by co-administration of well-known hepatoprotective agent.

TABLE 5: EFFECT OF SILYMARIN ON ROSIGLITAZONE INDUCED HEPATOTOXICITY IN RATS (LIVER ANTI-OXIDANT ENZYMES)

Groups	SOD	CAT	GSH	LPO
Normal	10.22±0.62	33.89±0.35	43.07±0.74	26.73±2.23
Rosiglitazone	03.82±0.49[a]	16.68±0.72[a]	23.54±0.74[a]	47.45±1.99[b]
Rosiglitazone+Silymarin	09.81±0.6[c]	31.85±0.31[c]	39.96±0.83[c]	29.62±2.37[d]

Values are presented as mean ± SEM, n=6; [a]P< 0.05 significant decrease when compared with normal group; [b]P< 0.05 significant increase when compared with normal group; [c]P<0.05 significant increase when compare to rosiglitazone group; [d]P<0.05 significant decrease when compare to rosiglitazone group.

Hypoglecemic activity of Rosiglitazone: Hypoglycemic activity of rosiglitazone alone and with silymarin on alloxan induced hyperglycemic rats is shown in **Table 6**. The results showed that, the diabetic control animals treated with vehicle have shown significant ($p<0.05$) increase in blood glucose level (185.51±2.53, 190.62±1.47 and 186.50±2.08 mg/dl) when compared to the vehicle treated normal animals (85.50±0.95, 86.25±2.99 and 85.66±3.91 mg/dl) respectively at the end of 1st, 2nd & 3rd week. This shows that, alloxan administration has produced hyperglycemia in the animals significantly. When rosiglitazone was given for 21 successive days orally at the dose of 2mg/kg, have shown decrease in blood glucose level (140.62±5.83, 111.62±3.7 and 101.85±1.2mg/dl) when compare to the diabetic control animals respectively at the end of 1st, 2nd & 3rd week. The activity was found to be significant at end of 2nd and 3rd week and blood glucose was very much nearer to normoglycemic animals.

Silymarin co-administered with rosiglitazone for 21 successive days has also shown significant ($p<0.05$) hypoglycemic activity (131.37±3.89, 109.62±2.32 and 106.77±1.06 mg/dl) respectively at the end of 1st, 2nd & 3rd week and the activity was found to be significant and very much similar to that of rosiglitazone.

TABLE 6: HYPOGLYCEMIC ACTIVITY OF ROSIGLITAZONE WHEN CO-ADMINISTERED WITH SILYMARIN ON ALLOXAN INDUCED HYPERGLYCEMIC RATS

Groups	Serum glucose level (mg/dl)		
	1st week	2nd week	3rd week
Normal	85.50±0.95	86.25±2.99	85.66±3.91
Diabetic control	185.51±2.53[a]	190.43±1.47[a]	186.50±2.08[a]
Rosiglitazone	140.62±5.83	111.62±3.7[b]	101.85±1.23[b]
Rosiglitazone+ Silymarin	131.37±3.89[b]	109.62±2.32[b]	106.77±1.06[b]

The values are expressed as Mean±SEM (n = 6); [a]P < 0.05 significant increase when compared with the normal group; [b]P < 0.05 significant decrease when compared with the Diabetic control group.

These result demonstrates that, co-administration of silymarin along with rosiglitazone retain the hypoglycemic activity of rosiglitazone. So, silymarin can be used for minimizing the hepatotoxic effects of antidiabetic drugs rosiglitazone without compromising its hypoglycemic activity.

DISCUSSION: Drug-induced liver injury (DILI) are the injuries to liver that are associated with impaired liver function caused by exposure to a drug or another non-infectious agent such as physician-prescribed medications, over-the-counter medications, vitamins, hormones, herbs, illicit ("recreational") drugs and environmental toxins [16]. Many drugs have been withdrawn from the market because of drug induced liver injury.

Recently troglitazone a novel hypoglycemic agent was withdrawn from the market and other drugs of this class may have same degree of liver injury. Based on the above facts, in the current study we have evaluated the hepatotoxic potential of rosiglitazone by *in-vitro* as well as *in-vivo* method and also assessed the protective effects of silymarin. Isolated rat hepatocytes have become a useful model for pharmacological, toxicological, metabolic and transport studies of xenobiotics since the development of techniques for high yield isolation of rat hepatocytes [17]. Freshly isolated rat hepatocytes are also very useful and common tool for study of cytotoxicity and metabolic studies in this area, as they keep enzymatic activity similar to *in vivo* for several hours.

In the present study, we have evaluated the hepatotoxic potential of rosiglitazone by taking into consideration reduction of viability of hepatocytes and leakage of enzymes, which are considered to be the markers of cellular injury. Incubation of rat hepatocytes with rosiglitazone caused significant toxicity at 100, 150, 250 and 500 µM, possibly due to injury of plasma membrane of hepatocytes resulting in the leakage of cellular enzymes and thus leading to increased levels of GOT, GPT and LDH in the cell suspension as shown in **Figure 1**. These studies confirm hepatotoxicity and also indicate satisfactory standardization of hepatotoxicity caused due to rosiglitazone.

Serum Glutamic Oxaloacetic Transferase, Serum Glutamic Pyruvic Transaminase, alkaline phosphatase, total Bilirubin in plasma has been reported to be sensitive indicator of liver injury[18]. The disturbance in the transport function of the hepatocytes as a result of hepatic injury causes the leakage of enzymes from cells due to altered

permeability of membrane. This results in increased levels of SGOT, SGPT, TB and ALP and decreased levels of TP in the serum.

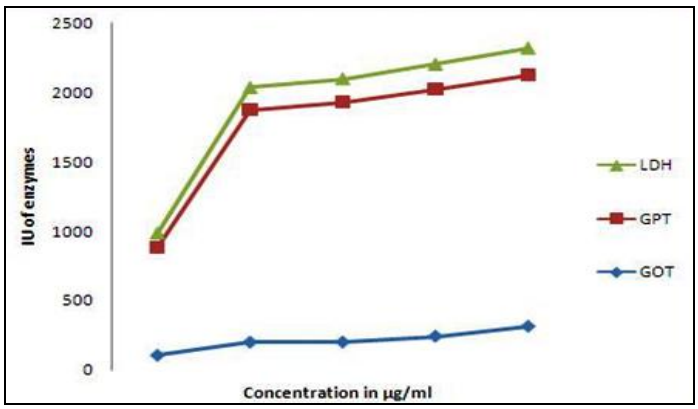

FIGURE 1: HEPATOTOXIC POTENTIAL OF ROSIGLITAZONE ON RAT HEPATOCYTES

Silymarin co-administration significantly decreased the rosiglitazone induced elevated levels of serum marker enzymes, SGOT, SGPT and ALP and total bilirubin and also increased the serum total protein levels which was decreased by rosiglitazone indicating hepatotoxicity of rosiglitazone, which can be reversed by silymarin as shown in **Figure 2**.

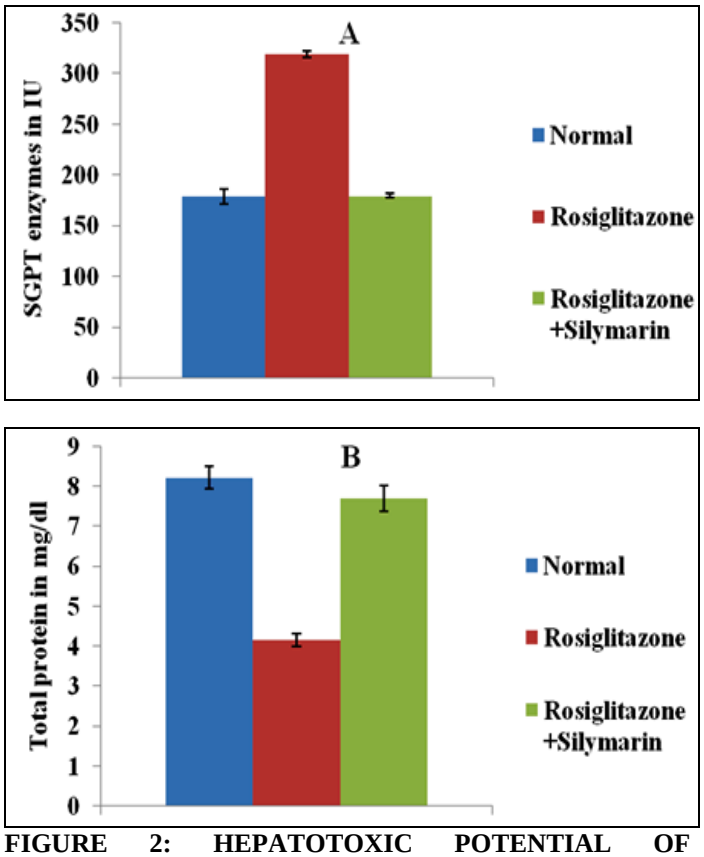

FIGURE 2: HEPATOTOXIC POTENTIAL OF ROSIGLITAZONE ON RATS. (A) SERUM GPT LEVEL (B) SERUM TOTAL PROTEIN LEVEL

Inbuilt antioxidant systems like SOD, CAT, GSH etc. protect the tissues from free radical attack but excessive release of ROS power over this system resulting in organ damage [19].When compared to normal group, rosiglitazone treated rats showed decreased levels of SOD, CAT and GSH in the liver tissue and increase in the levels of TBARS lipid peroxidation indicating improper functioning of the antioxidant system.

Co-administration of silymarin increased the levels of antioxidant enzymes SOD, CAT, GSH and decreased TBARS lipid peroxidation (Table 5) indicating improvement in the functioning of the antioxidant system. Minimizing the hepatotoxic potential of modern drugs without compromising their therapeutic value is challenge for the modern drug development. In the present study we have evaluated the hypoglycemic activity of rosiglitazone in alloxan induced hyperglycemic rats alone and with silymarin co-administration as give in **Figure 3**.

At the end of 1st, 2nd and 3rd week, rosiglitazone decreased the blood glucose level as that of normal animals significantly both when given alone or co-administered with silymarin. These results clearly demonstrate the usefulness of co-administration of silymarin in minimizing the hepatotoxic potential of rosiglitazone without compromising on its hypoglycemic activity.

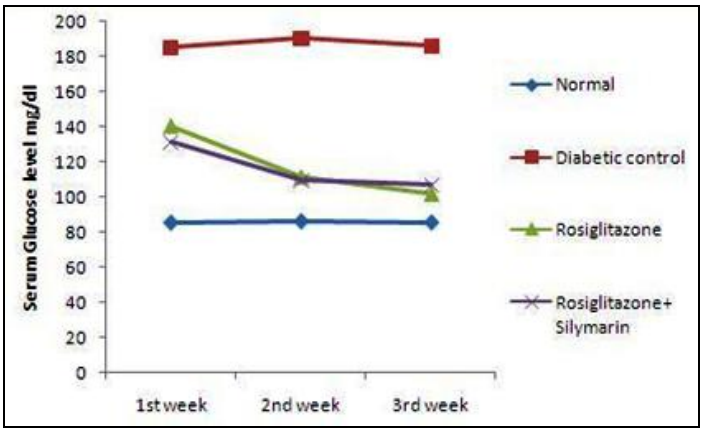

FIGURE 3: HYPOGLYCEMIC ACTIVITY OF ROSIGLITAZONE ON RATS (SERUM GLUCOSE LEVEL IN mg/dl)

CONCLUSION: In conclusion, based on the results obtained, it is evident that, the rosiglitazone has hepatotoxic potential and this can be minimized by co-administration of silymarin. However further research is required to elicit exact mechanism by which rosiglitazone produce hepatotoxicity.

To achieve these objectives further extensive research is required on different animal models. Our study gives a lead for the further extensive research on rosiglitazone for new therapeutic target in the management of hepatotoxicity.

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