# INFLUENCE OF LISINOPRIL ON GLUCOSE LOWERING EFFECT OF GLIPIZIDE IN NORMAL AND DIABETIC RATS

M. A. Khayum[1], T.S. Gouda[1*], N. Venkata Rao[1], Md. Shalam[1], S.M. Shantakumar[2], Richa Verma[1], S. Vijay Kumar[3]

[1]Department of Pharmacology, V.L. College of Pharmacy, Manikprabhu Temple Road, Raichur-584103. Karnataka, India.
[2]Department of Pharmachemistry, V.L. College of Pharmacy, Manikprabhu Temple Road, Raichur-584103, Karnataka, India.
[3]Department of Pharmacognosy, Sri Krishna Chaithanya college of Pharmacy, Madanapalle. Andhra Pradesh, India.

**Summary**

The aim of the present work was to assess the influence of lisinopril on the glipizide action in healthy and streptozotocin induced diabetic albino rats using single and repeated treatments of selected doses (2.5 mg/kg, 5 mg/kg, 10 mg/kg and 12 mg/kg) of lisinopril on the glucose lowering effect of glipizide. The whole study was divided into 3 phases. In the first phase the effect of lisinopril (2.5 mg/kg, 5 mg/kg, 10 mg/kg and 12 mg/kg, p.o) and glipizide (5mg/kg) individually were on the blood glucose levels were established in normal healthy rats. In the second phase the effect of single and repeated treatments (7 days) of lisinopril on the hypoglycemic effect of glipizide in healthy rats were studied. In the third phase the possibility of drug-drug interaction between lisinopril and glipizide in diabetic conditions were explored by the above procedure using STZ induced diabetic rats. Blood samples were collected from tail vein initially at '0' hour and following drug administration at 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0 and 30.0 hours for estimation of blood glucose. Same above experimental protocol was repeated in STZ induced diabetic rats and blood glucose levels were analyzed as mentioned earlier. Lisinopril significantly altered the peak effect and enhanced the hypoglycemic activity in both normal and diabetic rats at single and repeated treatment without any change in onset of action of glipizide. The study suggests that, the dose and frequency of glipizide must be readjusted when it is to be used concomitantly with antihypertensive drug lisinopril in combined hypertension and diabetic conditions to avoid severe hypoglycemia due to lisinopril.

**Key words**: Glipizide; lisinopril; hypoglycemic; antidiabetic; drug- drug interaction.

[*]**Corresponding Author**
T. Shivraj Gouda,
Asst. Professor,
Department of Pharmacology,
V.L. College of Pharmacy,
Raichur-584103.
Cell no. 09341751335
E mail: khayumblack@gmail.com

## Introduction

Hypertension and diabetes mellitus are common chronic conditions which frequently coexist and can significantly affect individual health care needs. The prevalence of hypertension increases with age and is common in both cases of insulin-dependent diabetes mellitus (IDDM) and non insulin-dependent diabetes mellitus (NIDDM) conditions. Hypertension appears to be critically important in diabetes mellitus, not only because of its increased prevalence, but also it accelerates both the microvascular and macrovascular complications of diabetes.

Combination of hypertension and diabetes mellitus produces greater myocardial dysfunction and is associated with significant mortality rates. Hence controlling blood pressure in diabetics is positively more beneficial as far as progressions of diabetic complications are concerned[1]. In such conditions, there is a need for the use of antihypertensive drugs like lisinopril (ACEI) with antidiabetic drugs like glipizide arises. Such combinations may lead to drug-drug interactions, which can be defined as the modifications of the effects of first drug i.e. the object drug by the prior or concomitant administration of second drug i.e. the precipitant or vice versa[2]. Recent studies have suggested that ACE inhibitors may play an important role in the prevention of type II diabetes. This is especially important because many common cardiovascular conditions such as coronary disease, congestive heart failure and hypertension are associated with insulin resistance and increased risk for the development of diabetes[3,4, 5].

The risk of hypoglycemia increases many folds in patients taking insulin or hypoglycemic agent with ACEI (angiotensin converting enzyme inhibitors). Hence it is important to discuss about the occurrence and management of potential drug-drug interactions to bring awareness amongst the health care professionals[6]. Present study was carried with the objective of establishing the effect of lisinopril on glipizide action.

## Materials and Methods

### Animals

Wistar albino rats of either sex (175-250g) were procured from Sri Venkateswara Enterprises, Bangalore, and were maintained under standard husbandry conditions (temperature of 250± $1^0$C; RH 45 to 55% and 12: 12 light/dark cycle). Animals were fasted for 18 hours before commencing the experiment. During this period, they were given water *ad libitum*. The fasting was continued till the completion of the experiment. The experiments were performed after prior approval of the study protocol by the institutional animal ethics committee of V.L. College of pharmacy, Raichur, India. The study was conducted in accordance with the guidelines provided by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA).

### Drugs and Chemicals

Glipizide was obtained as a gift sample from Sun Pharma Ltd., Mumbai and Lisinopril as gift sample from Medreich Sterilab Ltd., Bangalore, Karnatataka, India. Streptozotocin was purchased from Sigma-Aldrich, Bangalore. Kit for biochemical estimation of glucose was procured from Erba Diagnostics Mannheim GmbH, Germany. Estimation was carried by GOD/POD method using semi autoanalyser (ERBA mannheim, CHEM- 5 plus $v_2$).

The percentage reduction in blood glucose levels at time “t” was calculated by using the following equation.

**Percentage of Blood glucose reduction at time‘t’**

$$\frac{A-B}{A} \times 100$$

Where,

A= Initial blood glucose level before drug administration.

B= Blood glucose levels at time “t” after the drug administration.

**Experimental design**

The whole study was divided into 3 phases. In the first phase the effect of lisinopril (2.5 mg/kg, 5 mg/kg, 10 mg/kg and 12 mg/kg p.o) and glipizide (5mg/kg, p.o) were established individually on the blood glucose levels in normal healthy rats. In the second phase effect of single day treatment of lisinopril (2.5 mg/kg, 5 mg/kg, 10 mg/kg and 12 mg/kg, p.o) and repeated treatment of lisinopril (2.5 mg/kg, 5 mg/kg, 10 mg/kg and 12 mg/kg, p.o) for 7 days on the hypoglycemic effect of glipizide (5mg/kg, p.o) in healthy rats were studied.

In the third phase the possibility of drug-drug interaction between lisinopril and glipizide in diabetic conditions were explored by following the above procedure using STZ induced diabetic rats.

'0' hr blood samples were collected for fasting blood glucose levels estimation. Lisinopril (p.o) and Glipizide (p.o) was administered orally to all the rats and the blood samples were collected at prefixed time intervals 0.5, 1.0, 2.0, 4.0, 6.0, 8.0, 12.0, 18.0, 24.0 and 30.0 hrs and were analyzed for glucose levels.

.

**Induction of diabetes**

Rats of either sex weighing (175-200g) were selected and fasted for 18 hours prior to experiment and water supplied ad-libitum. The rats were administered with 65mg/kg of Streptozotocin intraperitoneally which was prepared freshly at the time of administration in citrate buffer (pH 4.4, 0.1M) and was used within 10 minutes of its preparation. After one week, the blood samples were collected and analyzed for blood glucose levels. Rats with blood glucose levels more than 200md/dl were included in the experiment. In our experiment diabetes was characterized by weight loss and hyperglycemia and these animals were used for antidiabetic study.

**Statistical analysis:**

Results are expressed as mean ± SEM. Statistical differences between means were analyzed using one-way ANOVA followed by Bonferroni multiple comparison test and $P< 0.001$ was considered as significant. The statistical analysis was performed using demo version of Instat® software (Graph pad Inc., Santabara, CA).

## Results

Lisinopril when given as a single dose (2.5 mg/kg, 5 mg/kg, 10 mg/kg and 20 mg/kg, p.o) has shown significant alteration in hypoglycemic effect of glipizide in normal animals. However repeated treatment with lisinopril for a period of 7 days at doses of 2.5 mg/kg, 5 mg/kg, 10 mg/kg and 20 mg/kg have significantly ($p<0.001$) altered the hypoglycemic activity of glipizide from 4 to 24 hrs, 4 to 30 hrs, 2 to 30hrs and 1st hour till the end of experiment in normal rats respectively (fig. 1 & 2).

**Fig. 1. PERCENTAGE BLOOD GLUCOSE REDUCTION WITH SINGLE DOSE TREATMENT OF LISINOPRIL (2.5,5,10 &20 mg/kg) + GLIPIZIDE (5mg/kg) IN HEALTHY ALBINO RATS**

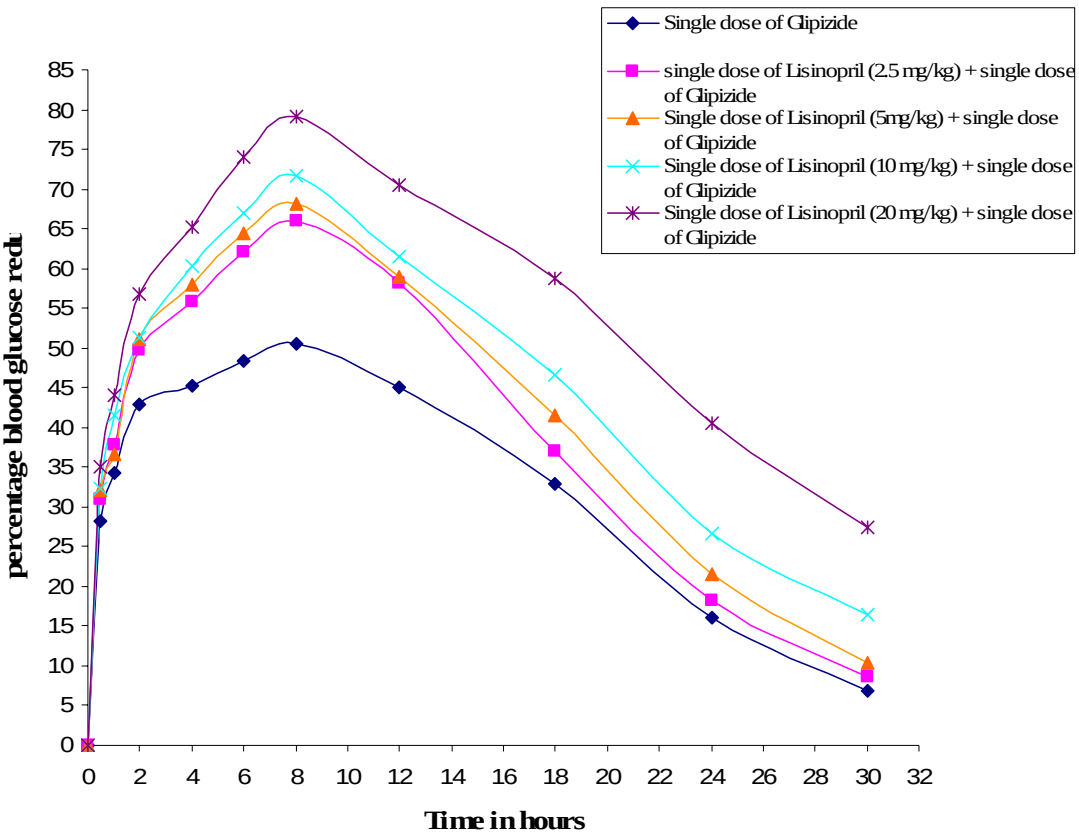
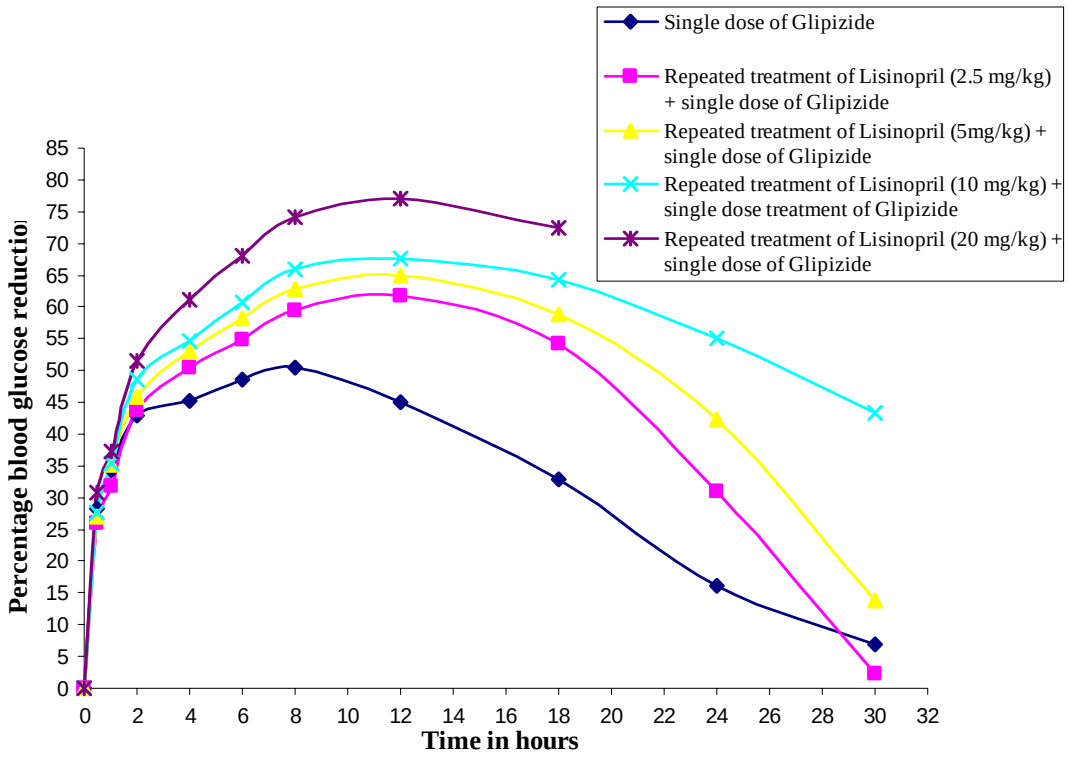


**Fig. 2. PERCENTAGE BLOOD GLUCOSE REDUCTION WITH REPEATED TREATMENT OF LISINOPRIL (2.5, 5, 10 & 20mg/kg) + SINGLE DOSE OF GLIPIZIDE(5mg/kg) IN HEALTHY ALBINO RATS**




Like wise effect of single dose treatment of lisinopril (2.5 mg/kg, 5 mg/kg, 10 mg/kg and 20 mg/kg p.o) on antidiabetic activity of glipizide was studied in streptozotocin induced diabetic rats. No significant alteration in antidiabetic activity of glipizide from 0 to 4 hours was seen with 2.5 mg/kg but there was a significant alteration in hypoglycemic effect from 6 to 24 hours and with doses 5mg//kg, 10mg/kg and 20mg/kg there was significant increase in the antidiabetic effect of glipizide from 1$^{st}$ hour to 30 hours. In case of repeated lisinopril administration it was observed with 2.5mg/kg there was no significant effect up to 4hrs but there was increase in the antidiabetic effect of glipizide from 6 to 24 hours, similarly there was significant increase in the antidiabetic effect of glipizide with 5 and 10mg/kg from 6 to 30 hrs. and with 20 mg/kg there was significant increase in the antidiabetic effect of glipizide from 1$^{st}$ hour till the end of the experiment. (fig. 3 &.4).

**Fig. 3. PERCENTAGE BLOOD GLUCOSE REDUCTION WITH SINGLE DOSE TREATMENT OF LISINOPRIL (2.5, 5, 10 & 20 mg/kg) + SINGLE DOSE OF GLIPIZIDE (5mg/kg) IN DIABETIC ALBINO RATS.**

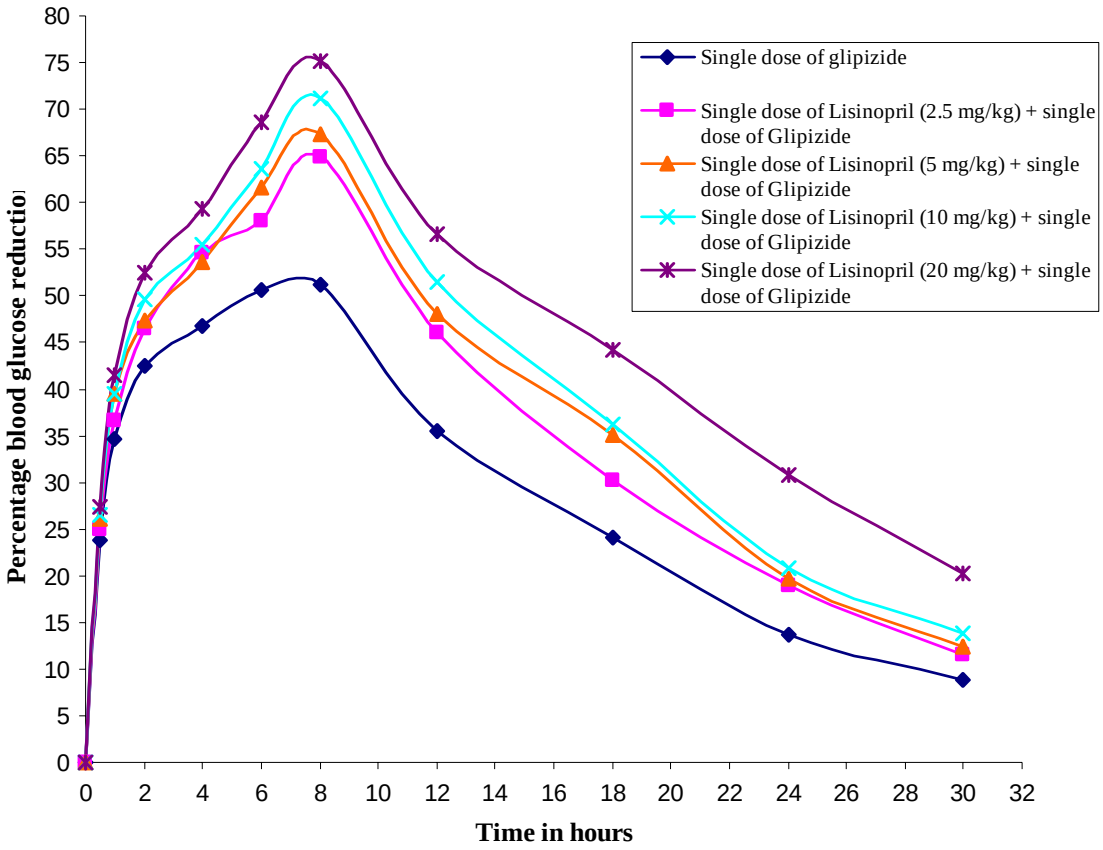
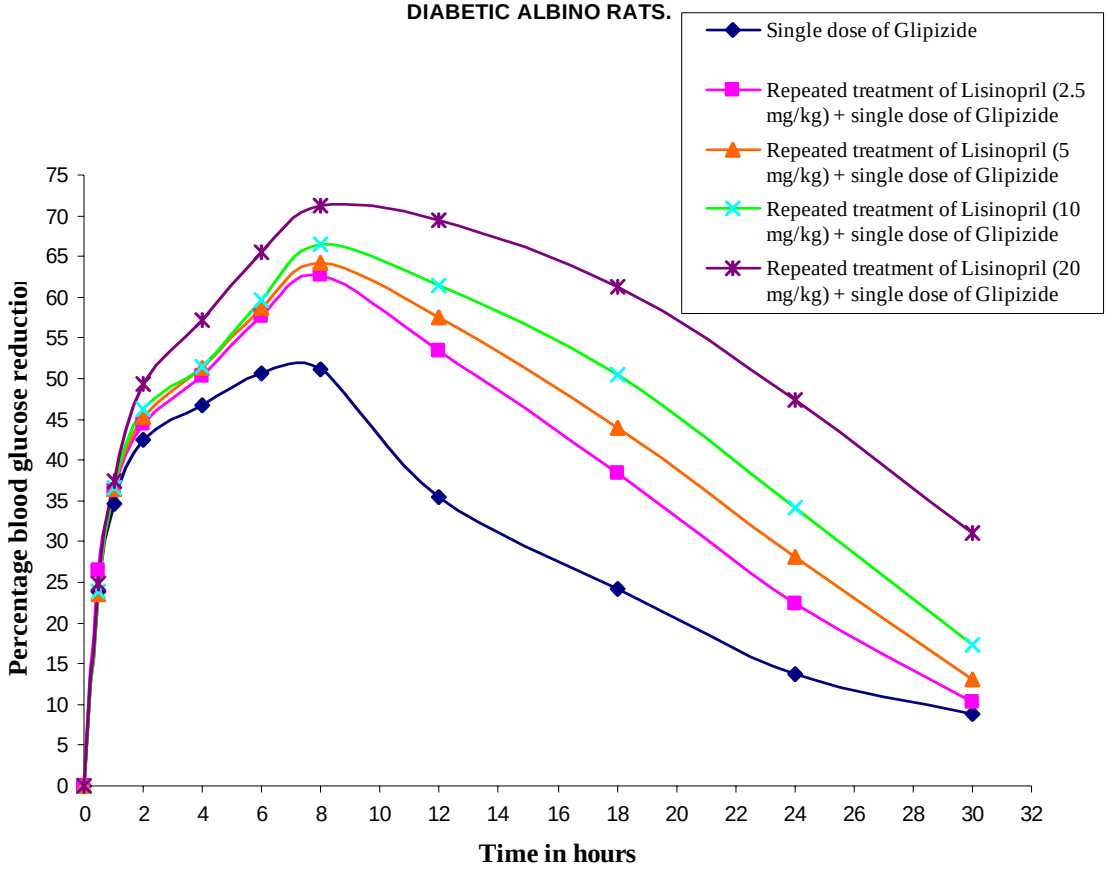


**Fig. 4. PERCENTAGE BLOOD GLUCOSE REDUCTION WITH REPEATED TREATMENT OF LISINOPRIL (2.5, 5, 10 & 20 mg/kg) + SINGLE DOSE OF GLIPIZIDE (5 mg/kg) IN DIABETIC ALBINO RATS.**




## Discussion

The present study was undertaken to verify the possible interaction if any between single and repeated dose treatment of lisinopril on hypoglycaemic and antidiabetic activity of glipizide in both healthy and diabetic rats. Parameters considered for the study were the onset and duration of hypoglycaemic action of glipizide. Single and repeated dose pretreatment of lisinopril have shown significant hypoglycaemia, exhibited by reduced activity (movement), confined to a single place of the case with signs of depression which was further confirmed by significantly enhanced duration of hypoglycaemic activity of glipizide and slight alteration in peak effect.

These results suggest that, during concomitant administration of glipizide and lisinopril, the dose and frequency of glipizide need to be readjusted accordingly. In addition, monitoring of regular blood glucose levels during that period is essential to avoid the unwanted complications like severe hypoglycemia and convulsions.

From the earlier reports it was noted that ACEI has increased the blood glucose levels by decreasing serum potassium levels[7] there by inhibiting insulin release[8,9] and overall inhibition of glucose uptake by peripheral tissues[10] in normal rats and our results are similar with the reports. Several studies have shown that ACE inhibitors and ARBs decrease the incidence of new-onset type 2 diabetes by their possible protective effect on the pancreatic beta cell through inhibiting the vasoconstrictive effect of angiotensin II in the pancreas and increasing islet blood flow, which could improve insulin release by beta cells[11].

Clinically ACE inhibitors are one of the drugs of choice in patients who are diabetic with mild to severe hypertension. Concomitant administration of ACE inhibitors with oral hypoglycemic agents or insulin therapy has been reported. The risk of hypoglycemic was increased several folds in patients taking insulin or hypoglycemic agent with ACE inhibitors. ACE inhibitors could improve the blood circulation in skeletal muscles, thus favoring peripheral insulin action, but also in the pancreas, thus promoting insulin secretion[12, 13]. Hence the alteration of glipizide action by lisinopril may be contributed to its ability to alter potassium levels or its protective effect on pancreatic beta cells. However, the results are yet to be confirmed by understanding pharmacokinetic parameters like AUC, Cmax and tmax of glipizide after treatment with single and repeated doses of lisinopril.

## Conclusion

The present study suggests that during simultaneous treatment for hypertension and diabetes with lisinopril and glipizide the dose and frequency of glipizide has to be readjusted accordingly to avoid severe hypoglycemia.

**Acknowledgements**

The authors wish to thank all management members, AME's V.L. College of Pharmacy, Raichur (Karnataka) for providing the necessary facility to carryout this research work with great ease and precission.

**References**

1. R.K.Goyal. Role of hypertension control in diabetes - mellitus and the agents of choice, Indian Journal of Pharmacology, 1993, 25: 181 – 187.
2. Morales-Olivas FJ Antihypertensive drug-drug interactions Med Clin (Barc). 2005 May 28; 124(20): 782-9.
3. Zavaroni I. Prevalence of hyperinsulinemia in patients with high blood pressure; J Intern Med. 1992, 231: 235-40.
4. Kaplan NM. Treating hypertension in the diabetic patient. Clin Diabet. 1987, 5: 25–34.
5. Tenebanum A. Impaired glucose metabolism in patients with heart failure: pathophysiology and possible treatment strategies; Am J Cardiovasc Drugs. 2004, 4: 269-80.
6. Rohit Singhal. Drug interactions in community pharmacy, Pharma times 2004, 36: 20- 6.
7. Salem HA, Abdel-Rahman MS, Dahab GM.Influence of diltiazem and/or propranolol on rat blood glucose levels in normal and diabetic animals.J.Appl.Toxicol., Mar-Apr 1993; 13(2); 85-9.
8. J.Navarro-Cid, R.Maeso, F.Perez-vizcaino, M.C.Casal, V.Cachorerio,L.M.Ruilope et.Effects of antihypertensive drugs on blood pressure and metabolic alterations in the fructose-induced hypertensive rat.Am.J.Hyertens.July 1996; Vol.9, Issue 7,Pages 669-674.
9. Beer NA, Jakubowicz DJ, Beer RM,Nestler JE. Disparate effects of insulin reduction with diltiazem of serum dehydroepiandrosterone sulfate levels in obese hypertensive men and women. J.Clin.Endocrinol. Metab., 1994 Oct; 79(4):1077-81.

10. Dhar HL, Farzan K.Mechanism of hyperglycemic effect of calcium channel antagonists in rats. Ind.J.Pharmacol., 1994; Vol.26, Issue 3; 222-224.

11. Hussam Abuissa MD Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers for Prevention of Type 2 Diabetes, Journal of the American College of Cardiology, 2005, Vol. 46, No. 5.

12. Morris AD. Hypoglycemic agent (Antidiabetic) drug interactions; 5th Edn (1999), 505.

13. Samy I Mechanisms by which angiotensin- converting enzyme inhibitors prevent Diabetes and Cardiovascular disease. 2003, 91(suppl):30H–37H. 31: 241-242.