International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.6, No.5, pp 1468-1475, Sept-Oct 2014

Effect on Liver Enzymes due to Voglibose in Alloxan-Induced Diabetic Rabbits with Type-II Diabetes Mellitus

Manas Ranjan Naik*[1], Ayon Bhattacharya[1], Divya Agrawal[2], Srikant Kumar Dhar[3], Sanjay Kumar[1], Sudhanshu S Mishra[1]

*[1]Dept of Pharmacology, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[2]Dept. of Anatomy, IMS & SUM Hospital, SOA University, Bhubaneswar, India
[3]Dept .of Medicine, IMS& SUM Hospital, SOA University, Bhubaneswar, India

*Corres.author: drmanasnaik@gmail.com
Tel: 9338684500

Abstract: Voglibose has been clinically used as a drug which improves glucose tolerance by inhibiting digestion and absorption of glucose from intestine. Another advantage of voglibose is that it decreases post prandial glucose without inducing hypersecretion of insulin. DM is one of the common causes of liver failure and hepatomegaly. Here we have evaluated the effects of long term voglibose treatment and the changes in liver enzymes like SGOT and SGPT levels.
Aim of the study: Study the effect of voglibose on SGPT and SGOT levels in alloxan induced diabetic rabbits.
Materials and Method: The rabbits were divided into six experimental groups. All 36 rabbits were induced diabetes by administering alloxan IV in the marginal ear vein of rabbits. Rabbits exhibiting fasting blood glucose more than 150 gm/dl after a stabilization period of seven days were considered as diabetic. Rabbits were randomly divided into six groups. Rabbits of group I received 5ml of normal saline as placebo daily and served as control. Rabbits of group II, group III and group IV were treated with voglibose 0.25, 0.5 mg/kg and 1 mg/kg. Rabbits of group V were treated with metformin 50mg/kg and group VI were treated with combination of 50 mg/kg and voglibose1mg/kg body weight daily by gavage method for 24 weeks . FBS and PPBS at 1st hour and 2nd hour were done with help of glucometer (ONE TOUCH, select one, life scan) weekly for 24 weeks. Blood samples were collected from marginal ear vein only thrice throughout 24 weeks: once before induction,on 8th day after induction and on 24th weeks of experiment for estimation of SGOTand SGPT levels by enzymatic test kits.
Results: SGOT increased significantly ($P<0.05$) and it was different from control group. Likewise, SGPT (after 24 weeks of treatment), also increased and was statistically significant.
Conclusion: Voglibose is an α – glucosidase inhibitor used to decrease post prandial hyperglycemia in diabetic patients raise the liver enzymes SGOT, SGPT.
Keywords: Alloxan, voglibose, Acarbose, SGOT, SGPT, Liver enzymes, Liver failure, cholestasis.

Introduction

Diabetes mellitus is a major global health problem and an increasing cause of morbidity and mortality. The term diabetes mellitus describes a metabolic disorder of multiple aetiology, characterized by chronic hyperglycemia with disturbance of carbohydrate,fat and protein metabolism(1). Presently DM is an incurable metabolic disorder which affects about 2.8% of global population. The prevalence is predicted to be double by 2025. Type–II DM is more prevalent than type-l DM. Type-II DM is a progressive disease resulting from either defect in insulin secretion, insulin action or both(2). In recent years many of the metabolic impairments

associated with diabetes mellitus have been traced to defects in insulin action.[3] Indeed, dysfunction of glucose metabolism is closely related to defects in insulin secretion. The plasma glucose level is abnormally elevated as a result of glucose metabolism.[4]The abnormal increase in blood glucose plays a pathogenic role in metabolic disorders.[5][6] Post prandial hyperglycemia otherwise known as Impaired Glucose Tolerance stage (IGT), is a stage of impaired glucose regulation that is present in individuals whose glucose tolerance is above the conventional normal range but lower than the level considered diagnostic of type-II diabetes mellitus. IGT represents transient stage between normal glucose tolerance and type-II DM. Post prandial hyperglycemia or IGT plays a central role in development and progression of diabetic complications particularly cardiovascular diseases. Alfa-glucosidase inhibitors act as competitive inhibitors of internal alfa-glucosidase. Alfa-glucosidase is an enzyme present in the intestinal brush border which is responsible for digestion of oligosaccharide like maltose,maltriose and dextrins and produces monosaccharide like glucose, galactose and fructose which are rapidly absorbed across the wall of small intestine It has been reported that alfa-glucosidase inhibitors like acarbose, voglibose and miglitol inhibits alfa-glucosidase and reduces post prandial hyperglycemia and thereby improves glucose tolerance.[7][8][9]In UKPDS Study[10] and patients receiving alfa-glucosidase inhibitor acarbose[17] had lowered HbA1c over 3 years compared with placebo. Acarbose is the first alfa-glucosidase inhibitor for the treatment of post postprandial hyperglycemia. It showed significant improvement in glycemic control in type-II DM patients.Voglibose a new alfa-glucosidase inhibitor is reported to be 20-30 times more potent than acarbose in inhibiting small intestine disaccharidases[11]. An elevation of liver enzymes has been reported on high doses of acarbose. The increase is always moderate and always returns to normal after cessation of the drug.[12][13]The alkaline phosphatase level in blood is increasing in voglibose treated rats.[14]A case of drug induced hepatitis with severe cholestasis caused by voglibose is also evident.[15] In this study we evaluated the effects of long term vogligose treatment on changes in liver enzymes SGPT and SGOT level.

Objective:

To evaluate the effect of voglibose(alfa-glucosidase inhibitor) on liver enzymes in alloxan induced diabetic rabbits.

Material and Methods:

Thirty six healthy rabbits (New Zealand white) weighing between 1000 to 1800 gm were housed at Central Animal House of IMS and SUM Hospital Bhubaneswar. The study protocol was approved by IAEC (S 'O' A UNIVERSITY, Bhubaneswar) July 2013. The animal were kept in cages under standard laboratory condition (light period 8.00 am to 8.00 pm and at temp 20-24^{o}C), relative humidity 55%,fodder and water available ad libitum). The animals received animal care.[16].

The rabbits were divided into six experimental groups. All 36 rabbits were induced diabetic by administering alloxan IV in the marginal ear vein of rabbits [17] [18] [19]. Doses of alloxan required to induce diabetes were according to key body weight of the rabbits [17] [20]. Rabbits exhibiting fasting blood glucose more than 150 gm/dl after a stabilization period of seven days were considered as diabetic [21]. Rabbits were randomly divided into six groups. Rabbits of group I received 5ml of normal saline as placebo daily and served as control. Rabbits of group II, group III and group IV were treated with voglibose 0.25, 0.5 mg/kg and 1 mg/kg. Rabbits of group V were treated with metformin 50mg/kg and group VI were treated with combination of 50 mg/kg and voglibose body weight daily by gavage method for 24 weeks . FBS and PPBS at 1st hour and 2nd hour were done with help of glucometer (ONE TOUCH, select one, life scan) weekly for 24 weeks. Blood samples were collected from marginal ear vein only thrice throughout 24 weeks: once before induction,on 8th day after induction and on 24th weeks of experiment for estimation of SGOTand SGPT levels by enzymatic test kits.(ROCHE Co)

Results

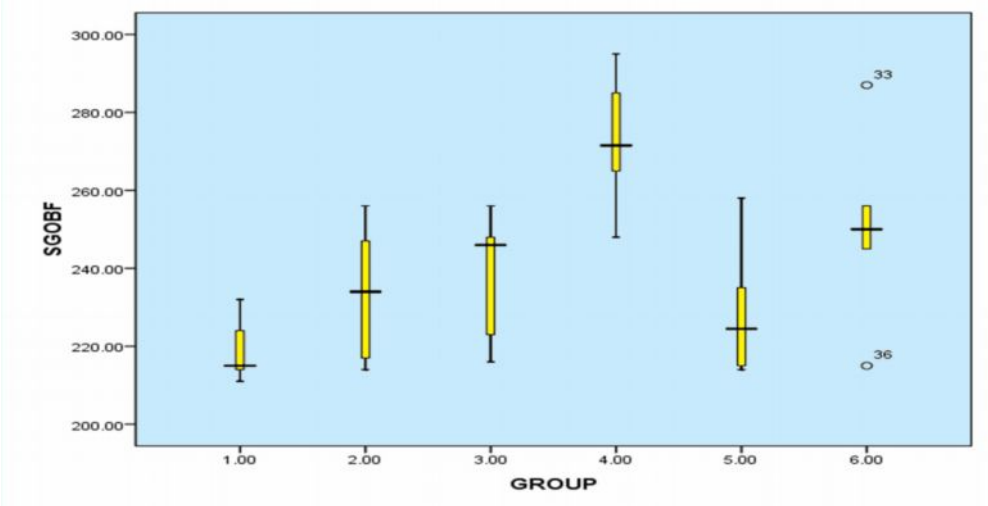
The data pertaining to various characters has been presented in table no…1 and the corresponding ANOVA table has been presented in table no--2. Regarding SGOT (before treatment), it is evident from the mean table that, before treatment of drugs, the six groups were found to be statistically significant and also after treatment the same trend was observed. The DMRT analysis of the all the characters have been presented in tabular form in table no 3 to 6 and also box plot of all the four characters have been depicted in figure no 1 to 4.

Statistical Analysis:

Table 1:Descriptive statistics of various characters

		N	Mean	Std. Deviation	Std. Error
SGOBF	1	6	218.500	7.918	3.233
	2	6	233.667	17.795	7.265
	3	6	239.167	15.842	6.467
	4	6	272.667	16.765	6.844
	5	6	228.500	17.421	7.112
	6	6	250.500	23.175	9.461
	Total	36	240.500	23.681	3.947
SGO24	1	6	248.000	70.595	28.820
	2	6	256.000	21.354	8.718
	3	6	316.167	30.492	12.448
	4	6	360.167	86.654	35.376
	5	6	254.833	74.813	30.542
	6	6	281.167	46.957	19.170
	Total	36	286.056	69.054	11.509
SGPBF	1	6	243.000	18.536	7.567
	2	6	262.000	31.273	12.767
	3	6	252.000	29.237	11.936
	4	6	238.167	22.489	9.181
	5	6	239.667	25.105	10.249
	6	6	244.833	18.368	7.499
	Total	36	246.611	24.295	4.049
SGP24	1	6	263.833	18.999	7.756
	2	6	280.000	23.324	9.522
	3	6	283.333	28.444	11.612
	4	6	312.667	26.815	10.947
	5	6	272.500	10.095	4.121
	6	6	309.667	37.399	15.268
	Total	36	287.000	30.029	5.005

Graph 1: SGOT values before treatment



Graph 2: SGOT after 24 week of treatment

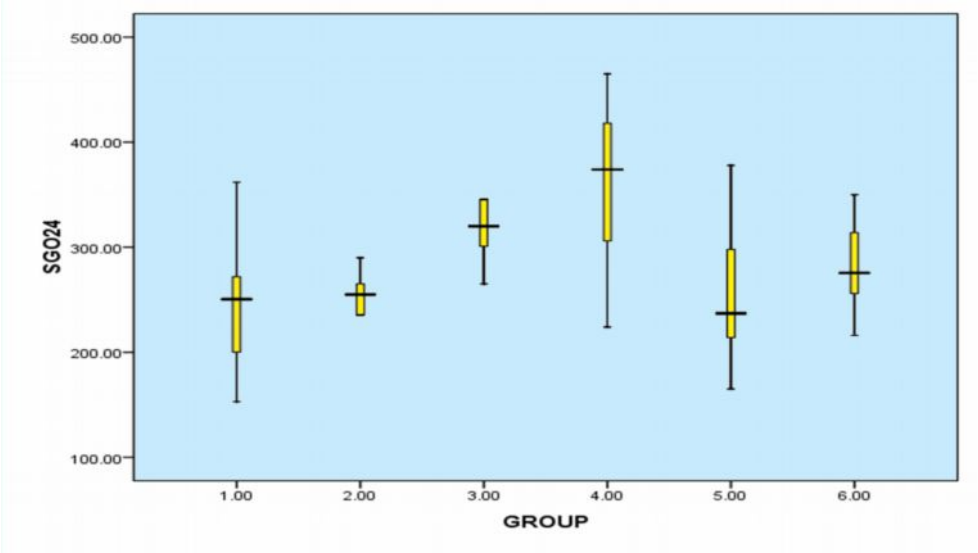
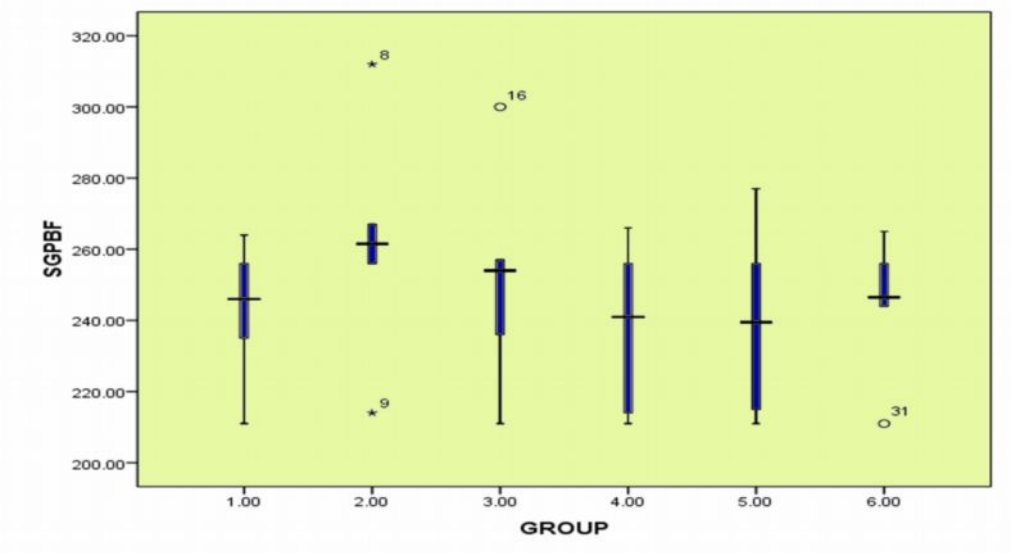


Table 2: ANOVA table of various characters

ANOVA						
		Sum of Squares	df	Mean Square	F	Sig.
SGOBF	Between Groups	10867.000	5	2173.400	7.443**	.000
	Within Groups	8760.000	30	292.000		
	Total	19627.000	35			
SGO24	Between Groups	58496.556	5	11699.311	3.238*	.019
	Within Groups	108401.333	30	3613.378		
	Total	166897.889	35			
SGPBF	Between Groups	2409.556	5	481.911	.792NS	.564
	Within Groups	18249.000	30	608.300		
	Total	20658.556	35			
SGP24	Between Groups	11891.667	5	2378.333	3.628*	.011
	Within Groups	19668.333	30	655.611		
	Total	31560.000	35			

Graph 3: SGPT before treatment



Graph 4: SGPT after 24th week of treatment

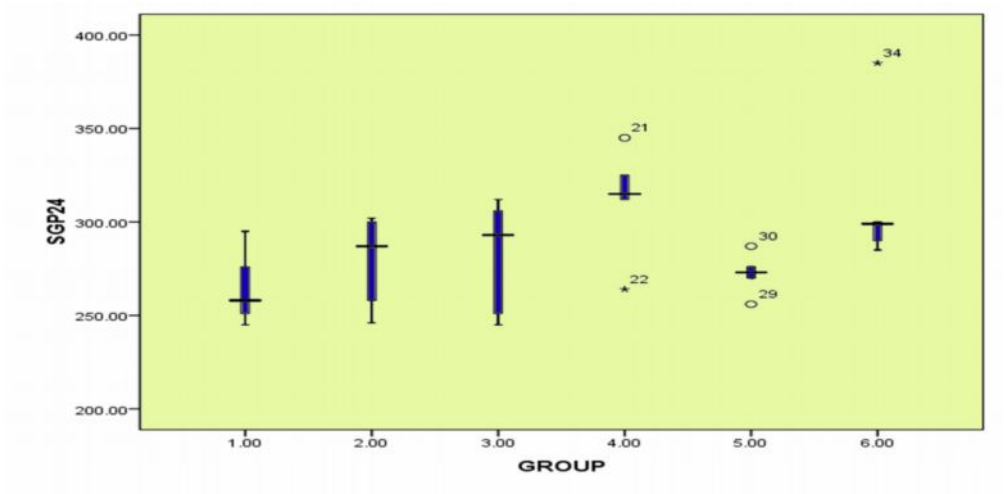


Table 3:DMRT of SGOT values before treatment

SGOT (BEFORE TREATMENT)					
	GROUP	N	Subset for alpha = 0.05		
			1	2	3
Duncan[a]	1	6	2.1850E2		
	5	6	2.2850E2		
	2	6	2.3367E2	2.3367E2	
	3	6	2.3917E2	2.3917E2	
	6	6		2.5050E2	
	4	6			2.7267E2
	Sig.		.063	.117	1.000
Means for groups in homogeneous subsets are displayed.					
a. Uses Harmonic Mean Sample Size = 6.000.					

Table 4:DMRT of SGOT values after 24 weeks of treatment

SGOT (AFTER 24 WEEKS)				
	GROUP	N	Subset for alpha = 0.05	
			1	2
Duncan[a]	1	6	248.0000	
	5	6	254.8333	
	2	6	256.0000	
	6	6	281.1667	
	3	6	316.1667	316.1667
	4	6		360.1667
	Sig.		.088	.215
Means for groups in homogeneous subsets are displayed.				
a. Uses Harmonic Mean Sample Size = 6.000.				

Table 5:DMRT of SGPT before treatment

SGPT (BEFORE TREATMENT)			
	GROUP	N	Subset for alpha = 0.05
			1
Duncan[a]	4	6	238.1667
	5	6	239.6667
	1	6	243.0000
	6	6	244.8333
	3	6	252.0000
	2	6	262.0000
	Sig.		.151
Means for groups in homogeneous subsets are displayed.			
a. Uses Harmonic Mean Sample Size = 6.000.			

Table 6:DMRT of SGPT values after 24 weeks of treatment

SGPT (AFTER 24 WEEKS)				
	GROUP	N	Subset for alpha = 0.05	
			1	2
Duncan[a]	1	6	263.8333	
	5	6	272.5000	
	2	6	280.0000	280.0000
	3	6	283.3333	283.3333
	6	6		309.6667
	4	6		312.6667
	Sig.		.238	.050
Means for groups in homogeneous subsets are displayed.				

The mean along with standard errors of SGOT (before and after 24 weeks treatment) has been presented in table no1. The corresponding ANOVA table of SGOT after 24 week of treatment) revealed that, all the treatment groups were found to statistically significant ($P<0.05$) and significantly different from control group. Likewise, in the SGPT (after 24 weeks of treatment), all the six groups were found to be statistically significant ($P<0.05$) and the DMRT table of the above parameters indicated that group 2, 3 4 and 6 were found to be statistically different from other groups.

Discussion:

DM is one of the common cause of liver failure and hepatomegaly (22). The increased level of SGPT and SGOT in blood indicates liver failure.Our study showed that voglibose increases the liver enzymes after 24 weeks of treatment while the FBS come down to normal in this period of time.An elevation of liver enzymes has been reported in less than 2% of patients on high doses of acarbose (an alpha glucosidase inhibitor);the increase is moderate and always returns to normal after cessation of the drug (12) (13). In the Bayer database on worldwide trials with acarbose of doses of 100mg t.i.d or less ,only 19 cases of transaminase elevation over 500IU/l have been documentated in 500,000 patients (23).In type 2 diabetic patients with liver cirrhosis acarbose (100mg tid) is well tolerated. Thus hepatic reactions are extremely rare ,unpredictable and therefore no specific recommendations to monitor liver enzymes with acarbose.But upto 20% of patients , during therapy with voglibose , show a rise in the liver enzymes (24).one case of hepatitis with severe cholestasis has been reported (15).T.Masumato et al. reported a case of drug induced hepatitis with severe cholestasis caused by voglibose.The patient presented with icterus with pruritus (15).According to this study the patient also developed cholangitis due to MRSA (15).Li Qiang Qin et al. 2005 reported increased levels of both plasma aspartate transaminase(AST) and alanine transaminase (ALT). The glutathione (GSH) content was decreased while malondialdehyde(MDA) increased in the liver after CCl_4 administration(25). Li Qiang Qin et al also

reported that voglibose can potentiate CCl_4 hepatotoxicity in rats. K.Yasuda et al reported that the activities of alkaline phosphatase in voglibose treated rats were higher than in utreated rats (14).From our study it is also seen that treatment with voglibose raises SGOT and SGPT level in alloxan induced diabetic rabbits after 24 weeks of treatment.But the exact mechanism of this rise in liver enzymes due to voglibosecan not be explained satisfactorily.

Conclusion:

Voglibose is an α–glucosidase inhibitor used to decrease post prandial hyperglycemia in diabetic patients raise the liver enzymes SGOT, SGPT. Although clinical concern has not yet been raised,hepatic dysfunction is seen in our study. So there may be chance of drug induced hepatitis with cholestasis caused by voglibose, which should be confirmed after clinical study.But this increase in SGOT and SGPT is whether due to vogliboseor the course of the disease process is subject of interest for future research.

Acknowledgement:

I acknowledge the help provided by Dr B B Nanda, Statistician(former statistician ,Dept of Social and Preventive medicine ,SCB Medical college,Cuttack) and my colleagues of our departments who helped me at every stage.

References:

1. Sacks DB. Implication of revised criteria for diagnosis and clarification of diabetes mellitus.Clinchem. 1997; 43 : 2230-2236.
2. Power A, D' AlessioD.Endrocrine Pancreas and Pharmacotherapy of Diabetes mellitus and Hypoglycemia. In. Laurence brenton(ed). Goodman and Gillman's The Pharmacological basis of Therapeutics. 12th edition 2011;p1238-73.
3. K.Yasudaetla. long therapeutic effects of Voglibose, a potent intestinal alpha glucosidase inhibitor. In spontaneous diabetic G.k.rats.Diabetes research and clinical practice; Vol 59 Feb 2003; PP – 113 – 122.
4. R.A De Fronzo, D.simonson , E. Ferrannini . Hepatic and peripheral Insulin resistance: a common feature of type 2 and type 1 DM. Diabetologia, 23 (1982) ; pp 313-319.
5. R.H Unger, S.Grundy .Hyperglycemia as an inducer as well as a consequence of impaired glet cell function and insulin resistance ; implication for the management of diabetes : Diabetologia, 28(1985); pp 119-121.
6. H.ykiJarvinen .Acute and chronic effects of hyperglyumia on glucose.Diabetologia, 33(1990) ,pp 579-585.
7. B.Goke. C.Hermann. The evolving role of alpha glycosidase inhibitors. Diabetes Metab. Rev, 14(suppl.) (1998); pp 1S31-1S38.
8. J.Hoffmann. M.Spengler. Efficacy of 24 week monothepapy with acarboseglibenclamide or placebo in NIDDM patents. The Essen study. Diabetes Care, 17(1994) pp 561-566.
9. J.L. Chaisson, R.G. Josse, J.A. Hunt etal. The efficacy of acarbose in the treatment of patients withnon insulin dependent diabetes mellitus. A multi centre controlled clinical trial. Ann Intern. Med, 121(1994) pp. 928-935.
10. R.R. Holman, C A. Cull, R.C. Turner. A randomized double blind trial of acarbose in type II DM shows improved glycemic control over 3 years. Diabetes Care,22(1999) pp. 960 – 964.
11. MalsuoT,Odaka.H, LkedaH : Effect of an inhibitor (AO-128) on obesity and diabetes. Am J CimNutr 55(suppl.I) (1992) pp 3145-3175.
12. Buse J,Hart K,Minasi L.The protect study:final results of large post marketing study in patients with type 2 diabetes.Precose Resolution of optimal titration to enhance current therapies.Clin Ther1998; 20:257-69.
13. Hollander P,Pisunyer X,Coniff RF.Acarbose in the treatment of type I diabetes.Diabetes Care 1997; 20:248-53.
14. K.Yasuda et al.Long term therapeutic effects of voglibose, a potent intestinal alphaglucosidase inhibitor, spontaneous diabetic GK rats.Diabetes research and clinical practice 2003;59:113-122.
15. T.Masumato et al.Drug induced hepatitis with severe cholestasis due to voglibose. International Hepatology Communication 1996;5:289-296.

16. M. Ahmad et al.Antidiabetic and hypolipiemic effects of aqueous methanolic extract of Acacia Nilotica pods in alloxan induced diabetic rabbits.Lab animal Sci 2008;vol 35.1.
17. SadiaShazaadAlam, Abdul HameedKhan.Alloxan induced diabetes in rabbits. PJP Vol 22 No-2 July 2005:41-45.
18. TakahasiY. Optic nerve head circulation in alloxan induced diabetic rabbits. Nippon GankaZasshi 1995;99:166.
19. Goldner MG, Gomori. Studies on mechanism of alloxan diabetes endocrinology 1944;35:241-248
20. Akhtar MS et al .Effect of mormordicacharantia on blood glucose levels of alloxan diabetic rabbits 1981.Planta Med;32:103-105.
21. Dunn JS ,McLetche NGB 1943. Experimental alloxan diabetes in rat. Lancet II;384-387
22. Chatila R,ABWest.Hepatomegaly and Liver tests due to glycogenolysis in adults with diabetes. Med Balt 1996;75:327-332.
23. Levobitz H. Alpha glucosidase inhibitors as agents in the treatment of diabetes.Diabetes Rev 1998;6:132-145.
24. Ajay S. Dabhi et al.Voglibose: an alphaglucosidase inhibitor .JCDR 2013;7860:6373-3838.
25. Li Qiang Qin ,Pie Yu Wang et al. Voglibose potentiate hepatotoxicity of CCl_4 and acetaminophen by inducing CYP2E1 rats. Hepatomegaly research 2005;33:50-56.

*****