Assessment of Toxicity and Drug-Drug Interaction of Combination Therapy Prescribed by Physicians/Clinicians for Treatment of Diabetes using Experimental Animals

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ABSTRACT

Purpose: The management of diabetes associated with hyperlipidemia is a challenge not only to the physician but also to medical fraternity. Hence most of the physicians prefer to prescribe antihyperglycemic drug along with some lipid lowering agent. The present study is aimed to find out toxicity and drug interaction of combination therapy of hypoglycemic agents (Glimepride, Metformin) withhypolipidemic drugs (Atovastatin + Fenofibrate). **Materials and Methods:** Young healthy adult Albino Wister rats (150-180 g) were used in the study. The experimental animals we reassessed for acute toxicity study and ant diabetic activity. The drug-drug interaction was also evaluated by changes in physiological, hematological parameters and histopathology of different tissues. **Results:** The result of acute toxicity revealed that there was a change in body weight in the animal treated with hypoglycemic agents (Glimepride, Metformin) withhypolipidemic drugs (Atovastatin + Fenofibrate). Water, food consumption has not been varied with greater extent in all groups of animals. Mild changes were marked inhemoglobin, neutrophils, platelet count. **Conclusion:** The combination of drugs showed mild change in the effect of Glimepride + Metformin alone and in combination with Atorvastatin + Fenofibrate. Other factors showed no significant effect which proves that there is no drug interaction.

Key words: Drug interaction, Diabetes, Toxicity, Combination therapy, Metformin, Atorvastatin.

INTRODUCTION

An alteration in the effectiveness or toxicity of one drug due to another simultaneously administered drug is known as drug-drug interaction. A drug interaction may result in adverse effect where in there is a decrease in the effectiveness or an increase in the toxicity of one drug in the presence of another drug. Biological interference with laboratory test may mislead the diagnosis. Beneficial effects, where in there is an increase in the effectiveness or a decrease in the toxicity of one drug in the presence of another. Pharmacokinetic interaction is those in which absorption, distribution, metabolism, excretion of a drug is altered.[1-4]

The drug interaction studies assume much importance, especially for drugs that have a narrow margin of safety and where the drugs are used for a prolonged period of time.[5] Drug-drug interaction can be defined as the modification of the effects of one drug (i.e., the object drug) by the prior or concomitant administration of another drug.[6] Diabetes mellitus often referred to simply as diabetes, is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia). Blood glucose levels are controlled by a complex interaction

of multiple chemicals and hormones in the body, including the hormone insulin made in the beta cells of the pancreas. Diabetes mellitus refers to the group of diseases that lead to high blood glucose levels due to defects in either insulin secretion or insulin action.[7] Diabetes mellitus is a chronic major endocrine disorder and growing health problem in most countries and is characterized by hyperglycemia, hyperlipemia, negative nitrogen balance, oxidative stress and sometimes ketonemia. The terms "Diabetes" and "Mellitus" are derived from Greek. "Diabetes" denotes "a passer through; a siphon" whereas the "Mellitus" denotes "sweet".[8-11]

Type-1 Diabetes is characterized by autoimmune destruction of insulin producing cells in the pancreas by CD4+ and CD8+ T cells and macrophages infiltrating the islets.[12-14] In type-2 diabetes, these mechanisms break down, with the consequence that the two main pathological defects in type-2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β- cell and impaired insulin action through insulin resistance.[15,16]

Insulin plays an important role in the regulation of intermediary lipid metabolism and fluctuations in the degree of diabetic control thus produce variable effects on plasma lipoprotein metabolism. Non-insulin-dependent (Type 2) diabetic patients are obese and obesity may lead to the development of hyperlipidemia.[17,18] The relationship between diabetes and hyperlipidemia is due to the unusually high prevalence of accelerated atherosclerosis in diabetic patients.[19-21] This is usually caused by the accumulation of very low-density lipoprotein (VLDL) and, rarely, chylomicrons in the plasma.[22-25]

The aim of the present study was to evaluate the possible drug interactions in the prescribed combination therapy in a diabetic patient associated with hyperlipidemia using experimental animals (rats) and make researchers aware of them so as to prevent the occurrence/ reoccurrence of clinical adverse events. Another objective of the study is to provide a basic of drug interaction of widely used diabetes drug therapy, to young physicians and researchers.

MATERIALS AND METHODS

Drugs and Chemicals: Glimepride (1mg) and Metformin (500mg) was procured from local chemical suppliers. Atorvastatin (10mg) and Fenofibrate (145mg) combination with were also procured from local chemical suppliers. All other chemicals used were of analytical grade.

Experimental animals

Young and healthy Albino Wistar Rats weight between 150-180 gm of either sex was procured from Institutional animal ethics committee (IAEC) approved by CPCSEA, Columbia Institute of Pharmacy, Raipur (C.G.) approval No - CIP/IAEC/2017/085 and Regd. No.1321/PO/ ReBi/S/10/CPCSEA. The animals were housed in polypropylene cages and allowed to acclimatize to laboratory conditions for at least 7 days. Animals were randomly assigned to various groups. All the animals were maintained under standard husbandry conditions of 12:12 h light: dark cycle at a temperature of 24 ± 2°C and a relative humidity of 30-70% with free access to water and standard laboratory rat pellet diet. All the animal handling and blood with drawl techniques were carried out in accordance with the Committee for the purpose of control and supervision on experimental animals (CPCSEA) guidelines.

Grouping of Animals

The animals (Wistar rats) of either sex (male -female animals) randomly divided into 4 groups. Number of animals in each group = 10 i.e. (Male = 5, Female = 5).

Group I	Control group (Received Vehicle)
Group II	Control* (Administered with Glimepride + Metformin)
Group III	Test group (Administered with Atovastatin + Fenofibrate)
Group IV	Test group* (Combination of Glimepride + Metformin -Atovastatin + Fenofibrate.)

Acute Oral Toxicity Study

The acute toxicity of marketed formulation was evaluated as per OECD Guideline-407. The four groups were selected and ten animals were present in each group. Animals received dose of Glimepride + Metformin - Atorvastatin + Fenofibrate in Wistar rat orally after a short fasting period using oral gavages. The general behavior of the animal was continuously monitored for ½ hr, 1 hr, 2 hr and 3 hr after dosing, periodically during the first 24 hr (with special attention given during the first 4 hr)and the same treatment was followed for 7 days.

Cage-side observations

The detailed cage-side observations were observed including changes in mucous membranes, Tremor, Convulsion, salivation, diarrhea, lethargy, sleep and also motor activity and behavior pattern. All rats were

observed for toxic signs and any pre-terminal deaths daily.

Body weight, food and water intake

Food and water intake was recorded daily and average weekly consumption was calculated. Individual body weight was recorded once in a week.

Histopathology

Liver, Kidney and Heart were fixed immediately in 10% formalin for routine Histopathological examination. The tissues were embedded in paraffin and then sectioned, stained with Haematoxylin and Eosin and were examined under light microscope.

Repeated dose 28 days Oral Dose Toxicity

A repeated toxicity study of the same drug was conducted on male albino wistar rats for a period of 28 days according to the OECD-407 Guideline. The animals were divided into 4 groups (control, control* Test, Test *), each group containing ten animals. While the drug was orally administered using gavage to test groups, the vehicle was administered to the control group for 28 days. All animals were supplied with standard food and water *ad libitum* during the testing periods. All rats were observed daily for toxic manifestations and mortality. Body weight, water and food intake were measured on a daily basis.

Hematology

Blood was collected by Retro orbital plexus from the overnight fasted animals. Investigation of whole blood for following was done: Hemoglobin (Hb), Platelet count, Neutrophils (N), Lymphocytes (L) and lymphocyte.

Therapeutic effect

Combination therapy

The second set of experiment was carried out on animals (wistar rats) to determine therapeutic effectiveness of combination therapy prescribed by register medical practitioner in different clinics. In set of experiment rats either sex are randomly divided into one group containing 6 animals. All the animals were administered Streptozotocin + High fat diet to induce diabetes associate with hyperlipidemia.

Induction of diabetes

Streptozotocin (STZ) induced hyperglycemia has been described as a useful experimental model to study the activity of hypoglycemic agents. After overnight fasting (deprived of food for 16 hrs, had been allowed free access to water), diabetes was induced in rats by intra-peritoneal injection of STZ dissolved in 0.1 M sodium citrate buffer pH 4.5 at a dose of 50 mg/kg body weight. After the injection, free access for food and water was provided. The development of diabetes was confirmed after 48 h of the streptozotocin injection. The animals having fasting blood glucose levels more than 200mg/dL were considered as diabetic rats and used for experimentation.

Study Procedure

Blood samples were collected from the tail vein at time intervals after drug administration and glucose levels were estimated by using glucose oxidase/peroxidase (GOD/POD) method, which was compared with fasting blood sugar level. The individual effect of Glimepride + Metformin - Atovastatin + Fenofibrate on blood sugar level was tested after administration of single dose in animals, whereas the influence of repeated treatment of Atovastatin + Fenofibrate for seven days on the hypo-glycemic effect of Glimepride + Metformin was studied.

Statistical Data Analysis

All values were expressed in mean ± SD. The data were analyzed by one way analysis of variance (ANOVA) using Graph Pad Prism Instat Software (version 6.00, Graph PadSoftware), using one way ANOVA followed by student - *t*- test.

RESULTS AND DISCUSSION

On the basis of findings in the present study we found that the combination of test drugs has proved to be safe as far as the drug-drug interaction is concerned. The test and test both samples did not show any interaction. In behavioral study (Table 1) there were no extra ordinary changes observed. At the same time, effect of test samples on body weight (Table 2, Figure 1) of the exper-

Table 1: Animal Behavioral activities.					
Test	**Sex**	**Control**	**Control***	**Test**	**Test***
Tremor	**M**	+	-	+	-
	F	-	+	-	-
Convulsion	M	Normal	-	+	-
	F	-	-	-	-
Salivation	M	+	-	+	-
	F	-	-	-	+
Diarrhoea	M	+	-	+	-
	F	-	-	+	-
Lethargy	M	+	+	-	-
	F	+	-	-	-
Sleep	M	+	+	-	-
	F	+	-	-	-

Time duration	Sex	Control	Control*	Test	Test*
Table 2: Effect of Glimepride + Metformin and Atovastatin + Fenofibrate on body weight in Albino Wistar Rats.					
0 Days	M	168.8 ± 1.16	172.4 ± 1.99	167.6 ± 2.73	166.4 ± 1.36
	F	178.4 ± 1.21	173.2 ± 1.46	174.6 ± 3.89	177.2 ± 2.29
7 Days	M	170.2 ± 1.02	172.6 ± 1.32	165.3 ± 2.1	164.2 ± 1.2
	F	181.2 ± 1.23	174.2 ± 1.34	170.5 ± 1.5	175.1 ± 1.8
14 Days	M	171.2 ± 1.5	173.6 ± 1.5	163.4 ± 1.7	161.2 ± 2.43
	F	173.5 ± 1.73	176.2 ± 1.34	168.2 ± 1.62	172 ± 2.13
21 Days	M	173 ± 2.02	174.4 ± 1.43	160.2 ± 1.03	157.4 ± 1.68
	F	174.5 ± 1.32	178.3 ± 1.56	166.3 ± 1.21	168.4 ± 1.42
28 Days	M	174.2 ± 1.45	175 ± 1.7	158 ± 1.6	155 ± 1.89
	F	176.5 ± 1.18	180.2 ± 1.2	164.3 ± 2.02	164.3 ± 2.03
35 Days	M	176 ± 1.8	158.6 ± 1.4	160. ± 0.22	176 ± 1.8
	F	181 ± 1.9	166.4 ± 1.78	168.20 ±1.20	181 ± 1.9
42 Days	M	175.2 ± 1.32	162.4 ± 1.82	172.02 ±1.30	175.2 ± 1.32
	F	182.3 ± 1.53	170 ± 1.8	178.40 ±1.42	182.3 ± 1.53

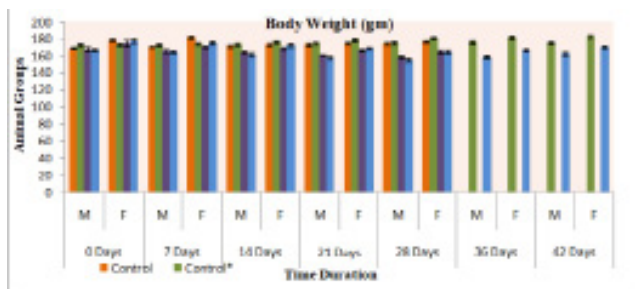All the Values are expressed as mean±SEM. (*n*=5)

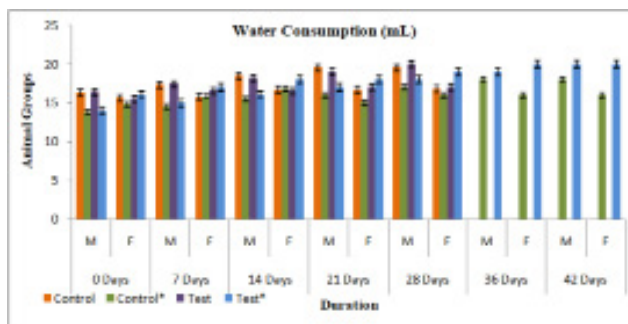**Figure 1: Animals mean body weight during dosing, Number of animals per group=5. All the Values are expressed as mean±SEM (*n*=5).**

Figure 2: Animals mean Water consumption during dosing, Number of animals per group=5. All value are reported as Mean±SEM.

Time duration	Sex	Control	Control*	Test	Test*
Table 3: Effect of Glimepride + Metformin and Atovastatin + Fenofibrate on water consumption in Albino Wistar Rats.					
0 Days	M	16.3 ± 1.64	13.8 ± 1.03	16.4 ± 1.07	14 ± 0.7
	F	15.6 ± 0.3	14.8 ± 1.4	15.5 ± 1.75	16 ± 0.3
7 Days	M	17.3 ± 1.75	14.5 ± 0.25	17.4 ± 0.07	15 ± 0.5
	F	15.8 ± 1.3	15.8 ± 1.07	16.5 ± 0.75	17 ± 1.2
14 Days	M	18.5 ± 1.75	15.5 ± 0.75	18.2 ± 1.65	16 ± 0.5
	F	16.7 ± 0.05	16.8 ± 1.7	16.5 ± 1.5	18 ± 0.1
21 Days	M	19.5 ± 0.25	16 ± 1.5	19.0 ± 0.5	17 ± 0.2
	F	16.7 ± 0.5	15 ± 1.2	17 ± 0.57	18 ± 1.5
28 Days	M	19.5 ± 1.78	17 ± 0.25	20 ± 1.05	18 ± 1.5
	F	16.8 ± 1.4	16 ± 0.5	17 ± 0.25	19 ± 1.35
35 Days	M	17.2 ±0.24	18 ± 0.5	18 ±0.24	19 ± 0.5
	F	18.2 ±0.62	16 ± 1.75	16 ± 1.2	20 ± 1.5
42 Days	M	16.5 ±0.40	18 ± 2.5	16.5 ± 0.62	20 ± 1.0
	F	19.4 ±0.62	16 ± 0.75	18.2 ± 0.20	20 ± 1.4

All the Values are expressed as mean±SEM. (*n*=5)

Table 4: Effect of Glimepride + Metformin andAtovastatin + Fenofibrate on food consumption in Albino Wistar Rats.					
Time duration	Sex	Control	Control*	Test	Test*
0 Days	M	16 ± 1.58	17 ± 2.1	16 ± 1.60	17.5 ± 1.4
	F	16.2 ± 1.69	18 ± 1.71	16.5 ± 1.70	18.2 ± 1.55
7 Days	M	17 ± 2.1	18 ± 1.60	17.5 ± 1.49	18.2 ± 4.5
	F	17 ± 1.71	16.5 ± 1.70	17.8 ± 1.55	19.2 ± 2.3
14 Days	M	18 ± 2.5	19 ± 1.69	18.1 ± 2.6	19.2 ± 1.56
	F	17 ± 2.83	17.2 ± 1.70	16 ± 1.23	20 ± 1.4
21 Days	M	19 ± 4.5	20 ± 2.5	16 ± 1.8	20 ± 2.75
	F	18 ± 2.5	16 ± 2.2	17 ± 2.5	21 ± 2.3
28 Days	M	20 ± 3.6	19 ± 4.5	19 ± 4.5	21 ± 8.95
	F	19 ± 3.5	17 ± 4.7	16 ± 3.75	22 ± 0.5
35 Days	M	16 ±2.4	20.2 ± 4.3	17 ±2.4	22 ± 6.5
	F	18 ±3.2	18 ± 2.7	16 ±3.4	23 ± 1.75
42 Days	M	17 ±4.2	21 ± 2.5	18 ±5.4	23±7.5
	F	16 ±2.6	19 ± 5.5	17 ± 2.4	23 ± 2.75

All the Values are expressed as mean±SEM. (*n*=5)

| Table 5: Effect of Glimepride + Metformin and Atovastatin + Fenofibrate on heamoglobin level in Albino Wistar Rats.					
Time Duration	Sex	Control	Control*	Test	Test*
0 Days	M	13.32±0.14	13.58± 0.15	13.76±0.13	13.92 ±0.11
	F	12.46±0.14	12.58±0.15	12.46±0.21	12.76±0.15
7 Days	M	13.20±0.13	13.62±0.17	13.52±0.17	14.30±0.20
	F	12.80±0.12	12.70±0.12	12.52±0.18	13.20±0.15
14 Days	M	13.02±0.23	13.40±0.17	13.61±0.22	13.90±0.16
	F	12.50±0.18	12.60±0.15	12.27±0.09	12.90±0.21
21 Days	M	13.30±0.23	13.20±0.16	13.90±0.11	14.30±0.13
	F	12.6 ± 0.13	12.60±0.19	12.80 ±0.13	13.20±0.11
28 Days	M	13.70±0.12	13.80±0.12	13.60±0.15	13.67±0.19
	F	12.30±0.15	12.80±0.13	12.50±0.14	12.93±0.18

All the Values are expressed as mean±SEM. (*n*=5)
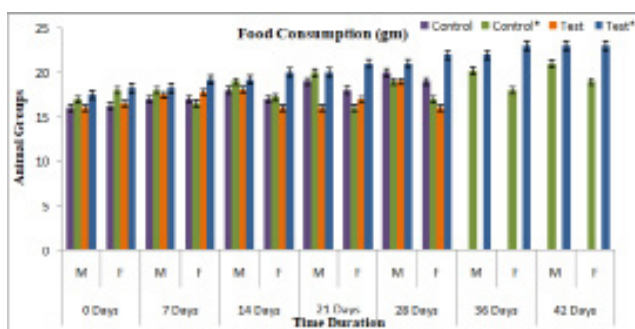
Figure 3: Animals mean food consumption during dosing, Number of animals per group=5. All the Values are expressed as mean±SEM (*n*=5).

imental animals showed some change. At the beginning of the experiment the observed body weight, for control was 168.8 ± 1.16, but at the end of 42 days, increase in body weight was observed. Similarly, water consumption (Table 3 Figure 2) and food consumption (Table 4, Figure 3) was found to be increased very less after 35 days. Consequently, Hematological parameters were also observed with no marked increase in the hemoglobin level (Table 5, Figure 4) during the activity. A slight increase in neutrophils level was observed (Table 6, Figure 5), Changes in the platelet level (Table 7, Figure 6) at the end of the activity was also not much signifi-
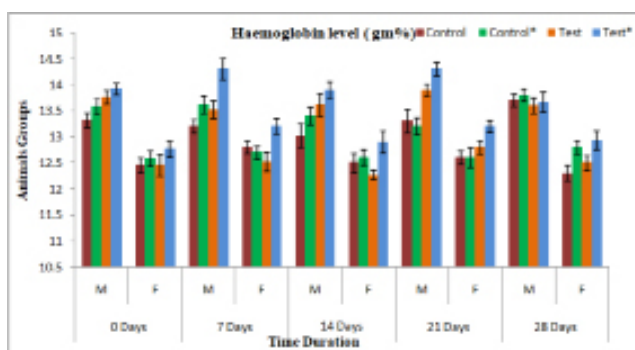
Figure 4: Animals mean Haemoglobin level during dosing, number of animals per group=5. All the Values are expressed as mean±SEM (*n*=5).
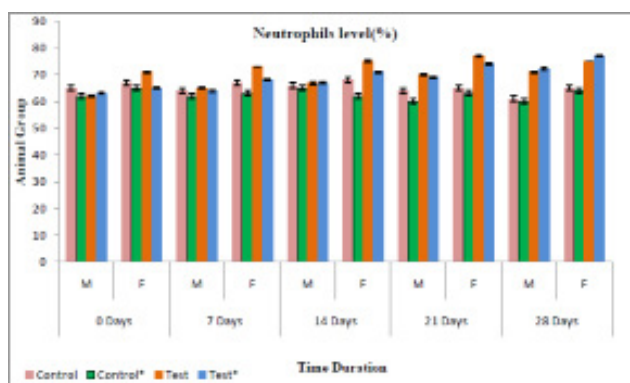

Figure 5: Animals mean neutrophils level during dosing, Number of animals per group=5. All the Values are expressed as mean±SEM (*n*=5).

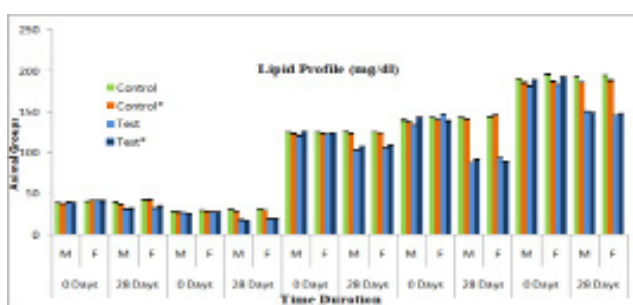| Table 6: Effect of Glimepride + Metformin and Atovastatin + Fenofibrate on nutrophils levelin Albino Wistar Rats.					
Time Duration	Sex	Control	Control*	Test	Test*
0 Days	M	65 ±0.411	62 ±0.412	62 ± 0.313	63 ± 0.412
	F	67 ±0.314	65 ±0.513	71 ± 0.314	65 ± 0.310
7 Days	M	64 ± 0.412	62 ± 0.515	65 ± 0.211	64 ± 0.511
	F	67 ± 0.514	63 ± 0.514	73 ± 0.112	68 ± 0.410
14 Days	M	66 ± 0.311	65 ± 0.312	67 ± 0.513	67 ± 0.317
	F	68 ± 0.412	62 ± 0.410	75 ± 0.513	71 ± 0.409
21 Days	M	64 ± 0.418	60 ± 0.513	70 ±0.412	69 ± 0.412
	F	65 ± 0.313	63 ± 0.415	77 ± 0.315	74 ± 0.317
28 Days	M	61 ± 0.413	60 ± 0.518	71 ± 0.312	72 ± 0.514
	F	65 ± 0.517	64 ± 0.313	75 ± 0.016	77 ± 0.212

All the Values are expressed as mean±SEM. (*n*=5)

Table 7: Effect of Glimepride + Metformin and Atovastatin + Fenofibrate on Platelet count level in Albino Wistar Rats.					
Time Duration	Sex	Control	Control*	Test	Test*
0 Days	M	3.75 ± 0.014	3.70 ±0.008	3.75 ± 0.005	3.60 ±0.003
	F	3.80 ± 0.006	3.90 ± 0.005	3.90 ± 0.016	3.80 ±0.006
7 Days	M	3.79 ± 0.015	3.75 ± 0.004	3.85 ± 0.004	3.85 ±0.004
	F	3.85 ± 0.006	3.80 ±0.006	4.20 ± 0.003	4.10 ±0.016
14 Days	M	3.80 ± 0.017	3.60 ± 0.007	4.10 ± 0.004	4.15 ±0.005
	F	3.80 ± 0.006	3.90 ± 0.006	4.30 ± 0.025	4.30 ±0.006
21 Days	M	3.65 ± 0.040	3.50 ± 0.014	4.25 ± 0.004	4.25 ± 0.004
	F	3.70 ±0.006	3.70 ± 0.005	4.45 ± 0.005	4.45 ±0.005
28 Days	M	3.90 ± 0.004	3.70 ± 0.004	4.30 ± 0.009	4.30 ±0.005
	F	3.50 ± 0.005	3.80 ± 0.012	4.50 ± 0.006	4.50 ±0.006

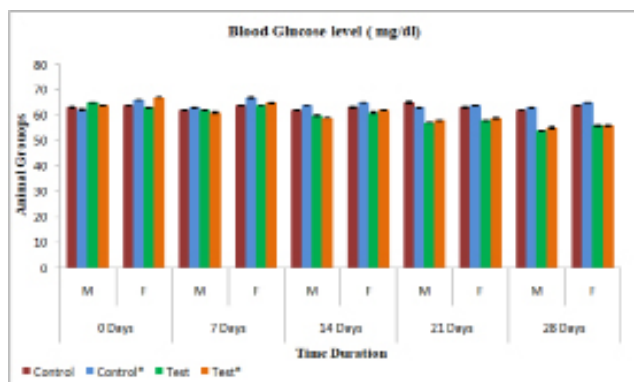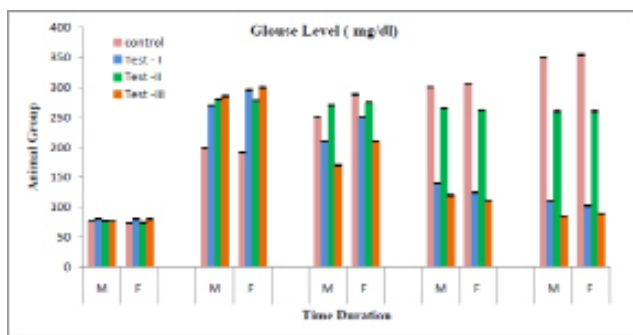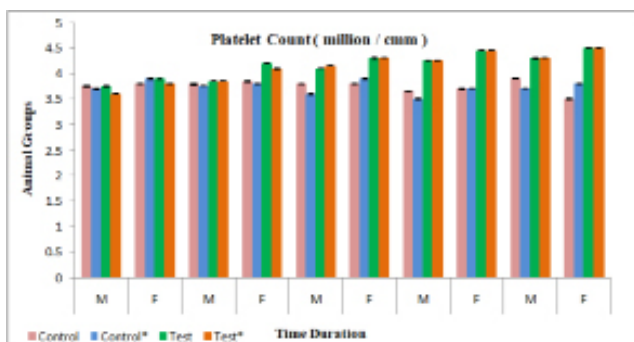All the Values are expressed as mean±SEM. (*n*=5)

Figure 6: Animals mean platelets level during dosing, Number of animals per group=5. All the Values are expressed as mean±SEM (*n*=5).

Figure 8: Animals mean glucose level during dosing, Number of animals per group=5

All the Values are expressed as mean±SEM (*n*=5).

Figure 7: Animals mean glucose level during dosing, number of animals per group=5. All the Values are expressed as mean±SEM (*n*=5).

Figure 9: Animals Mean lipid profile during dosing, Number of animals per group=5. All the Values are expressed as mean±SEM (*n*=5).

Table 8: Effect of Glimepride + Metformin and Atovastatin + Fenofibrate on blood glucose level in Albino Wistar Rats.					
Time Duration	Sex	Control	Control*	Test	Test *
0 Day	M	76±0.054	81± 0.23	77± 0.67	76±0.12
	F	73± 0.23	80 ± 0.56	74± 0.34	80 ± 0.34
24 Hr	M	198 ± 0.45	270± 0.12	280±0.23	285± 0.234
	F	191 ± 0.67	295± 0.34	278± 0.34	300± 0.56
7th Day	M	250± 0.23	210 ± 0.198	270± 0.987	170± 0.78
	F	288 ± 0.11	250± 0.14	275 ± 0.34	210 ± 0.12
21 Day	M	300 ± 0.234	140± 0.13	265 ± 0.56	120 ± 0.34
	F	305 ± 0.123	124 ± 0.167	262± 0.23	112 ± 0.124
28 Day	M	350± 0.87	110 ± 0.34	260 ± 0.45	85 ± 0.16
	F	355 ± 0.178	102 ± 0.234	260 ± 0.23	90 ± 0.012

All the Values are expressed as mean±SEM. (*n*=5)

Table 9: Effect of Glimepride + Metformin and Atovastatin + Fenofibrateon Lipid profile level in Albino Wistar Rats.

Parameter	Time Duration	Sex	Control	Control*	Test	Test*
HDL	0 Days	M	38±0.25	37.2±0.27	39.5±0.33	38.2±0.34
		F	40.2±0.34	41.3±0.31	41.3±0.2	40.6±0.32
	28 Days	M	39.2±0.23	36.4±0.27	30.7±0.33	31.6±0.34
		F	42.1±0.34	42.4±0.31	32.3±0.2	34.3±0.32
VLDL	0 Days	M	27.82±0.23	26.35±0.27	26±0.33	25±0.34
		F	28.5±0.34	27.5±0.31	26.5±0.2	27±0.32
	28 Days	M	30±0.28	28±0.27	17.48±0.33	17±0.34
		F	31.25±0.34	29.2±0.31	18.35±0.2	18.25±0.32
LDL	0 Days	M	124.18±0.27	122.35±0.27	120.35±0.33	125.2±0.34
		F	124.5±0.34	122.36±0.3	122.05±0.2	123.5±0.36
	28 Days	M	125.3±0.23	122.7±0.27	102.45±0.33	106.5±0.34
		F	124.45±0.34	123.8±0.31	104.9±0.2	109.1±0.2
S-TG	0 Days	M	139.1±0.26	136.7±0.28	133.5±0.33	142.3±0.34
		F	142.3±0.36	139.5±0.35	146.4±0.2	138.4±0.34
	28 Days	M	142.5±0.23	140.5±0.27	87.4±0.33	91.2±0.34
		F	143.4±0.34	145.5±0.31	93.4±0.2	88.5±0.34
S-CHOL	0 Days	M	190±0.23	185.4±0.27	180.7±0.33	188.4±0.34
		F	195.2±0.34	187.2±0.33	182.25±0.2	192±0.32
	28 Days	M	192±0.23	186±0.27	150±0.33	148.5±0.34
		F	194±0.34	188±0.3	145±0.2	147.5±0.32

All the Values are expressed as mean±SEM. (*n*=5).

Table 10: Effect of Glimepride + Metformin and Atovastatin + Fenofibrate on lymphocyte level in Albino Wistar Rats.

| Time Duration	Sex	Control	Control*	Test	Test*
0 Days	M	25±0.311	24±0.332	25±0.313	26±0.532
	F	26±0.314	27±0.452	27±0.314	28±0.367
7 Days	M	26±0.422	24±0.515	22±0.3167	24±0.522
	F	26±0.512	25±0.534	25±0.112	25±0.418
14 Days	M	27±0.331	26±0.312	20±0.513	21±0.317
	F	28±0.412	27±0.41	24±0.553	24±0.439
21 Days	M	25±0.418	26±0.513	19±0.412	19±0.412
	F	27±0.363	26±0.425	23±0.315	22±0.317
28 Days	M	26±0.413	25±0.518	17±0.312	19±0.534
	F	26±0.513	28±0.313	20±0.016	21±0.442
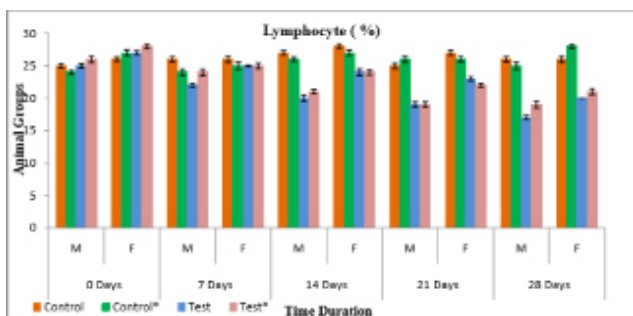
Figure 10: Animals Lymphocyte % during dosing, Number of animals per group=5. All the Values are expressed as mean±SEM (*n*=5).
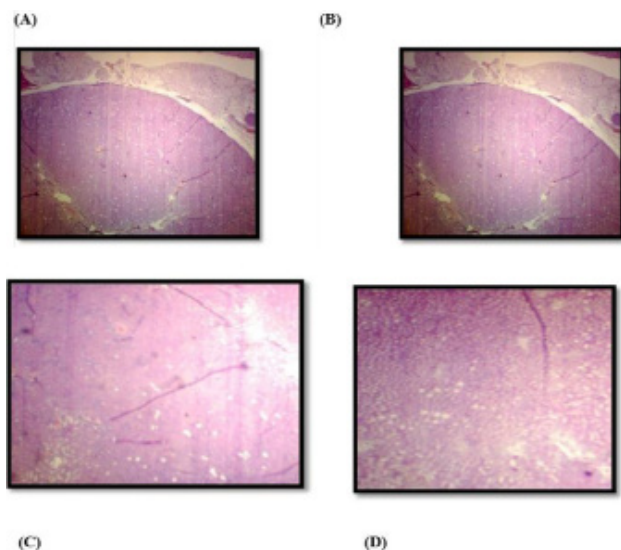

Figure 11: Histopathological observation of kidney tissue in rats (magnification 100x).
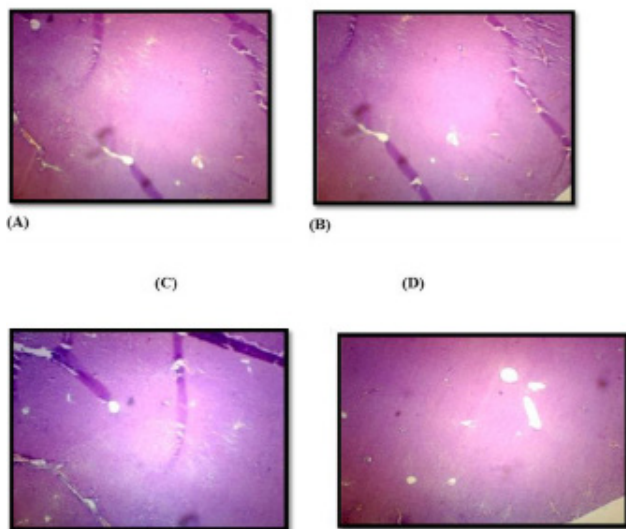

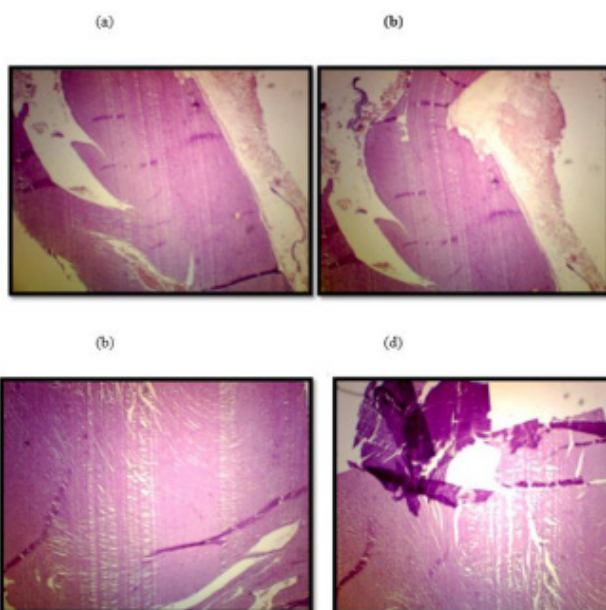Figure 12: Histopathological observation of liver tissue in rats (magnification 100x).

Figure 13: Histopathological observation of heart tissue in rats (magnification 100x).

Note: In the Figure (A) Histopathology of section of control group (B) Histopathology of section of control° group (C) Histopathology of section of Test group (D) Histopathology of section of Test° group

cant. The result of most important parameter, blood glucose level (Table 8, Figure 7,8) showed a significant decrease. In lipid profile (Table 9, Figure 9), HDL level, VLDL level, LDL level, S-TG and S-Cholesterol level were decreased in a very significant manner. A slight decrease in lymphocyte level (Table 10, Figure 10) was observed i.e. showed not much significant increase.

Histopathological observation of kidney liver and heart tissues (Figures 11-13) suggests that the combination of these Antidiabetic and hypolipidemic drugs is safe in all aspects for the diabetic patients.

ACKNOWLEDGEMENT

CONFLICT OF INTEREST

The authors declare no conflict of interest

Ethical permission for pre-clinical study

The protocol used in the study was permitted by Institutional animal ethics committee (IAEC) approved by CPCSEA New Delhi, Columbia Institute of Pharmacy, Raipur (C.G.) approval No is CIP/IAEC/2017/085 and Regd.No.1321/PO/ ReBi/S/10/CPCSEA.

ABBREVIATIONS

IAEC: Institutional Animal Ethicalcommittee; **CIP:** Columbia Institute of Pharmacy; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **STZ:** Streptozotocin; **GOD:** Glucose oxidase; **POD:** Glucose peroxidase; **SD:** Standard deviation.

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PICTORIAL ABSTRACT
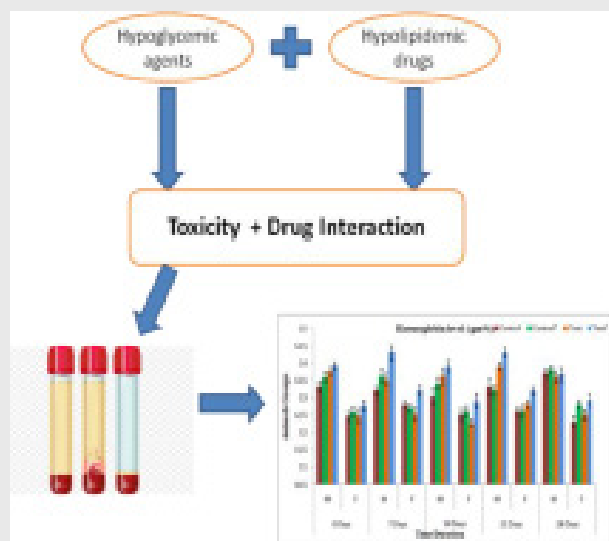
SUMMARY

On the basis of the above study we found that treatment of diabetic patients with hypoglycemic agents (Glimepride, Metformin) with hypolipidemic drugs (Atovastatin + Fenofibrate) in combination has no significant drug-drug interaction. But the blood glucose level, other pathological condition and other drug therapy must be taken in to consideration before prescribing the therapy. Physians now a dose do not take consideration of drug- drug interaction before prescribing the medications. This paper therefore may be a vital tool for them before prescribing Antihyperlepidemic drugs with anti-diabetic drugs.

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