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Research Article
Fenofibrate Potentiates the Antihyperglycemic, Antidyslipidemic and Hepatoprotective Activity of Pioglitazone on Alloxan-Induced Diabetic Rats

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Abstract

Background and Objectives: The present study was designed to investigate the hypoglycemic, hypolipidemic and hepatoprotective activity of the fixed dose combination of pioglitazone and fenofibrate. **Methodology:** For the study purpose, pioglitazone at a dose of 15 mg/70 kg b.wt. and fenofibrate at a dose of 72.5 mg/70 kg b.wt., were administered on alloxan (120 mg kg^{-1} b.wt.) induced diabetic rats. Both the drugs (pioglitazone and fenofibrate), singly and in combination, separately were tested *in vivo* for 14 days to determine blood glucose level, lipid profile and hepatoprotective activity using Long-Evans male rats as test animals. In addition, to investigate any possible side effects of the combined therapy, the survival rate and the weight of different groups of rats were also measured. **Results:** The study showed that in alloxan induced diabetic rats, combination therapy significantly decreased the blood glucose level from 16.00±0.01 to 7.85±0.03 mmol L^{-1} 2 h later of last dose administration in comparison to the diabetic control group, after daily treatment for 2 weeks. In case of dyslipidemic effect, combination therapy reduced total cholesterol level by 31%, triglyceride level by 46% and LDL-cholesterol level by 37% significantly and increased HDL-cholesterol level by 77% in comparison with their respective diabetic control groups. It was also observed that combination therapy decreased alanine transaminase (ALT) level by 53% and aspartate transaminase (AST) level by 40% in comparison to diabetic control group effectively. These changes were significantly better than those of pioglitazone and fenofibrate monotherapy. After 2 weeks of treatment, it was observed that combined drug-treated rats were healthy and gained weight (112.5±0.04 g) in parallel to the diabetic groups (110.5±0.02 g). No rats were died after combined treatment while, the survival rates were 80, 80 and 60% for pioglitazone, fenofibrate and diabetic groups (alloxan induced), respectively. **Conclusion:** This study suggest that the combination of pioglitazone and fenofibrate might be efficacious in patients with diabetic dyslipidemia and might provide better hepatoprotection in these patients but brief clinical trial is necessary before using the combined drug in practice.

Key words: Alloxan, combination therapy, fenofibrate, hepatoprotection, pioglitazone

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Now a days, diabetes has become an alarming to the public health globally and day by day its prevalence is getting severe. Recent statistics showed that total 4% of the world population is affected by diabetes and this matter is very alarming, because this percentage will rise to 5.4% in 2025. By 2030, this disease may become the 7th leading cause of death[1]. Diabetes is a chronic disease that is responsible for long-term tissue damage and complications such as liver-kidney dysfunctions, often associated with serious diseases like organ damage[2,3]. Diabetes mellitus is associated with a marked increase in the risk of Coronary Heart Disease (CHD) or stroke (by a factor of two to three compared with non-diabetic patients) and cardiovascular disease (CVD), which account for the majority of deaths among patients with diabetes[4,5].

Treatment with combination therapy has an effect on reviving ß-cells and restoring the fluctuation in glucose level and cholesterol biosynthetic pathway. At present, various types of drugs such as biguanides, thiozolidinediones and sulfonylureas are used to treat diabetes. But to control diabetes alone with CVD and other complications, monotherapy of these drugs are not enough[6,7]. As a result, combination therapy has become very popular for controlling glucose level[8] and inhibiting cholesterol level[5]. Treatment with combination therapy also protects β-cells, controls glucose level and other related parameters. The current study is aimed at providing strong view on experimental studies carried out on the most effective and commonly used hypoglycemic and lipid-lowering drugs alone and in combination. There are no reports of combination of pioglitazone and fenofibrate. In this study, the combined effects of pioglitazone and fenofibrate has been investigated for the first time. It is also investigated whether, lipid lowering agents (fenofibrate) potentiate the antihyperglycemic, antidyslipidemic and hepatoprotective effect of antidiabetic drug (pioglitazone) or not.

MATERIALS AND METHODS

Raw materials collection: The antidiabetic drug (Pioglitazone) and lipid lowering drug (fenofibrate) were collected from Beximco Pharmaceuticals Limited, Tongi, Gazipur, Bangladesh.

Selection and grouping of animal: Long-Evans male rats weighing about 100-120 g, age two months were purchased from animal's house of Jahangirnagar University, Bangladesh. Prior to commencement of the experiments, all the rats were acclimatized to the new environmental condition for a period of one week. Animals received human care according to the criteria outlined in the 'Guide for the Care and Use of Laboratory Animals', 8th edition, prepared by the National Academy of Sciences and published by the National Institute of Health (US). Ethical clearance was obtained from the institutional ethical committee of Southeast University, Bangladesh. During the experimental period, the rats were kept in a well-ventilated animal house at room temperature of 25°C and were supplied with standard pellets and fresh drinking water. All the rats were kept in cages and maintained with natural 12 h light and dark cycle. Long-Evans rats were randomly assigned into five groups; each group consisting of 5 rats for the respective two weeks treatment protocols, namely for determination of blood glucose, lipid profile and liver function test studies.

Group 1: Normal control group
Group 2: Diabetic control group (untreated group)
Group 3: Diabetic group (treating with pioglitazone)
Group 4: Diabetic group (treating with fenofibrate)
Group 5: Diabetic group (treating with combination of pioglitazone and fenofibrate)

Drugs and chemicals: The active drugs (Pioglitazone and fenofibrate) were a generous gift from Beximco Pharmaceuticals Limited, Tongi, Gazipur, Bangladesh. Alloxan was purchased from Loba Chemie, Bombay, India. Total Cholesterol (TC), triglyceride (TG), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL) kits were purchased from Human, Germany. The SGPT (ALT) and SGOT (AST) kits were purchased from Linear Chemicals, Spain.

Experimental induction of diabetes: Animals were allowed to fast for 12 h were rendered diabetic by injection of freshly prepared solution of alloxan (120 mg kg^{-1} b.wt.) in distilled water intraperitoneally. The alloxan treated animals were allowed and drink 10% glucose solution overnight to overcome drug-induced hypoglycemia. After 24 h, blood glucose content was measured by using Clever Check glucose test meter (Bioland, Germany) from the blood samples, collected from the tail vein of the rats. Animals were selected for the study, when the condition of diabetes was established with blood glucose levels above 11.1 mmol L^{-1}.

Preparation of dosage of active drugs

Fenofibrate: Fenofibrate was in off white powder form and freely soluble in dimethyl sulfoxide (DMSO). The dosage was

prepared in solution form using dimethyl sulfoxide (DMSO) in such a concentration that each 0.1 mL of solution contained fenofibrate according to the dose of 72.5 mg/70 kg b.wt., since fenofibrate is effective in such dose in human.

Pioglitazone: Pioglitazone was in white powder form and freely soluble in dimethyl sulfoxide (DMSO). The dosage was prepared in solution form using dimethyl sulfoxide (DMSO) in such a concentration that each 0.1 mL of solution contained pioglitazone according to the dose of 15 mg/70 kg b.wt., since pioglitazone is effective in such dose in humans.

Combination (pioglitazone and fenofibrate): The dosage was prepared in solution form using dimethyl sulfoxide (DMSO) in such a concentration that each 0.1 mL of solution contained fenofibrate and pioglitazone according to the dose of 72.5 and 15 mg/70 kg b.wt., respectively since fenofibrate and pioglitazone are effective in such dose in human.

Treatment: The animals were divided into five groups. Each group comprised five rats. The treatment of animals began on the 3rd day after alloxan injection and this was considered as 1st day of treatment. Blood sample was collected from rats to get the serum. After completing the two weeks treatment, the animals were fasted for at least 16 h and sacrificed. The rats were anesthetized with phenobarbital sodium. Blood samples were collected in centrifuge tubes without anticoagulants and allowed to clot. The clotted blood was then centrifuged at 4000 rpm for 30 min. Serum was separated and then quickly stored at refrigerator for biochemical analyses.

Two weeks dose treatment of pioglitazone, fenofibrate and combination: Pioglitazone, fenofibrate and combination of drugs were injected intraperitoneally daily for two weeks in alloxan-induced diabetic rats. After 2 weeks treatment, blood glucose was determined 2 h after last dose using glucometer. In addition, serum lipid profiles were assessed after 2 weeks in the pioglitazone, fenofibrate, normal and combination drug-treated diabetic rats. All assays were carried out using diagnostic kits.

Determination of biochemical parameters: Serum glucose was determined by the glucose oxidase method using Clever Check glucose test meter (Bioland, Germany). Serum High Density Lipoprotein Cholesterol (HDLC) was estimated by the UV spectrophotometric method, using HDL cholesterol liquicolor test kit. Serum Low Density Lipoprotein Cholesterol (LDLC) was estimated by UV spectrophotometric method, using cholesterol LDL reagent precipitate test kit. Serum Total Cholesterol (TC) and triglycerides (TG) were estimated by UV spectrophotometric method, using cholesterol liquicolor and triglycerides liquicolor test kits. The liver enzyme parameters (AST, ALT) were determined using fully automated clinical chemistry analyzer (Hitachi 912, Boehringer Mannheim, Germany).

Statistical analysis: The results are expressed as Mean±SEM using Graph Pad Prism (version 4.0) computer program (Graph pad Software San Diego, CA, USA). One-way analysis of variance (ANOVA) was used and *post-hoc* test or students paired or unpaired t-test was followed by Dunnett's test. The statistical method applied in each analysis was described in each figure. Results were considered to be significant when p-values were less than 0.05 ($p<0.05$).

RESULTS

Effect of pioglitazone, fenofibrate and combination on blood glucose level: After 2 weeks treatment, blood glucose of all the rats of five groups was measured and found out that in pioglitazone group, glucose level (8.15±0.015 mmol L^{-1}) was less than the fenofibrate group (9.1±0.025 mmol L^{-1}) but in combination group this glucose level (7.85±0.03 mmol L^{-1}) was even lower than the pioglitazone group rats, compared to untreated diabetic group rats (glucose level 16±0.01 mmol L^{-1}) (Fig. 1).

Effects of pioglitazone and fenofibrate and their combination therapy on lipid profile: In our study, it is observed that the triglyceride level, LDL-cholesterol level and

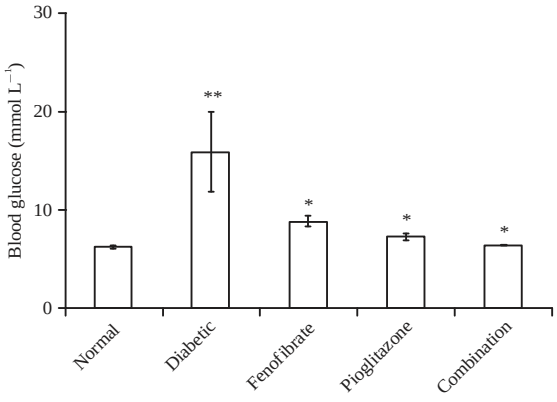

Fig. 1: Effects of pioglitazone, fenofibrate and combination of pioglitazone and fenofibrate for two weeks on blood glucose level in alloxan-induced diabetic rats. The values are expressed as Mean±SEM, n = 5 in each group, **p<0.05 compared with normal control group, *p<0.05 compared with diabetic control group

total cholesterol level were reduced and HDL-cholesterol level was increased in alloxan induced diabetic rats in comparison with their respective normal rats after two weeks treatment (Fig. 2a-d).

From our experiment, it is clear that there was no significant improvement in serum TC, TG, LDL-cholesterol and HDL-cholesterol levels by the treatment with pioglitazone and fenofibrate alone in comparison with single drug therapy. But the combination therapies (pioglitazone and fenofibrate) showed significant reduction in serum Total Cholesterol (TC) level by 31%, Triglyceride level (TG) level by 46%, LDL-cholesterol level by 37% and significant increment in HDL-cholesterol level by 77% compared to the diabetic control group after two weeks treatment protocols.

Hepatoprotective effect of drugs and combination therapy: In our study, it was observed that there were significant increments in alanine transaminase (ALT) level by 61% and aspartate aminotransferase (AST) level by 78% level in diabetic control group compared to the normal control group (Fig. 3). It was also observed that the combination therapy of pioglitazone and fenofibrate significantly reduced ALT level by 53% and AST level by 40% rather than the single therapy of pioglitazone and fenofibrate after two weeks treatment (Fig. 3).

Survival rate of diabetic treated rats: Figure 4 graphically represented the survival rate of normal, diabetic and diabetic treated rat groups. After two weeks treatment, it was found

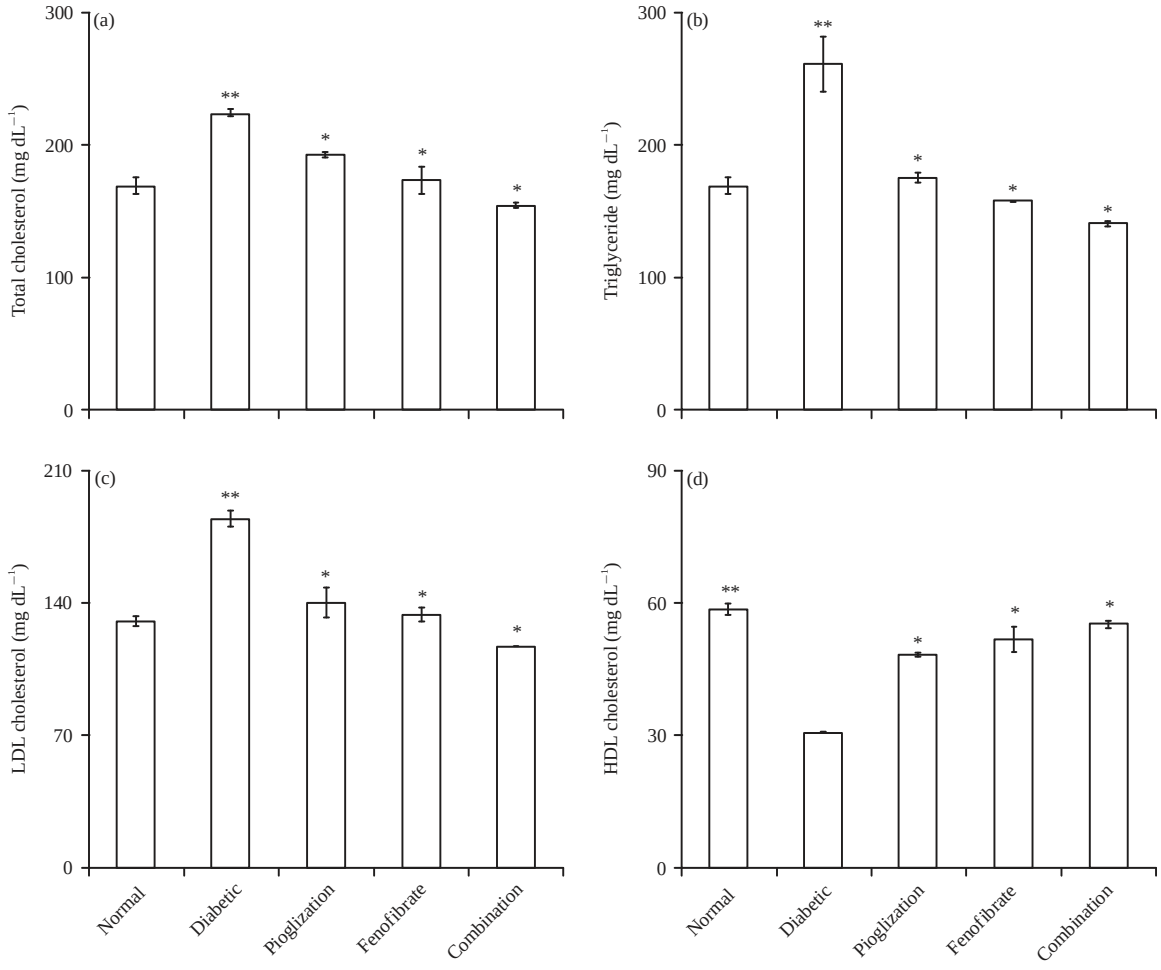

Fig. 2(a-d): Effects of pioglitazone, fenofibrate and combination for two weeks on TC, TG, LDL and HDLC levels, respectively on alloxan induced diabetic rats. Changes in (a) TC level, (b) TG level, (c) LDLC level and (d) HDLC level. All values were presented as Mean±SEM, n = 5 in each group, **p<0.05 compared with normal control group, *p<0.05 compared with diabetic control group

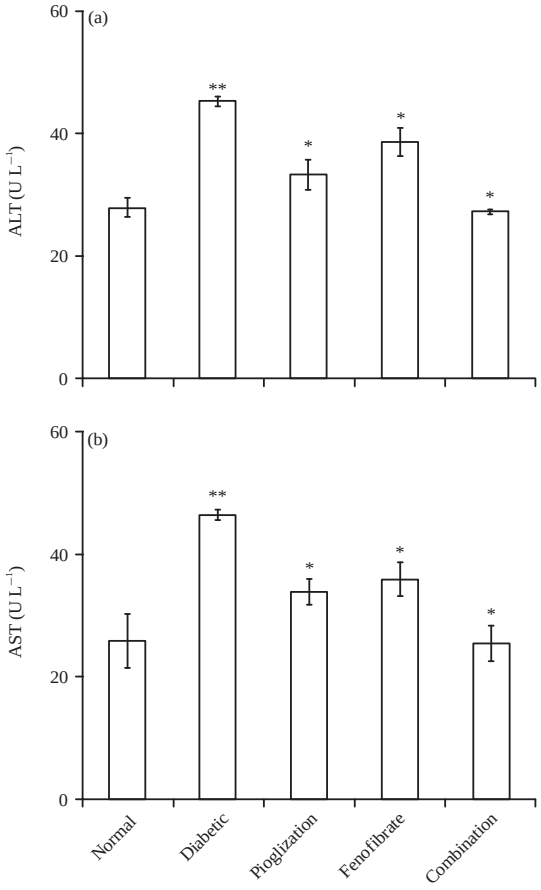

Fig. 3(a-b): Effects of pioglitazone, fenofibrate and combination for two weeks on ALT and AST level, respectively in diabetic rats. All values were presented as Mean±SEM, n = 5 in each group, **p<0.05 compared with normal control group, *p<0.05 compared with diabetic control group

that combination therapy is much more effective and having full percentage (survival rate 100%) of survival rate rather than other groups of pioglitazone (survival rate 80%) and fenofibrate (survival rate 80%) compared to diabetic group (survival rate 60%).

Comparison of weight of different groups and justification among them: Figure 5 graphically represented the weight of diabetic treated rat groups. After two weeks treatment it is found that in combination treating group, rats are healthy and gained weight (average 112.5 g) compared to the pioglitazone (average 111.5 g), fenofibrate (average 111 g) and diabetic groups (average 110 g) which indicate that the combination therapy is effective on rats health.

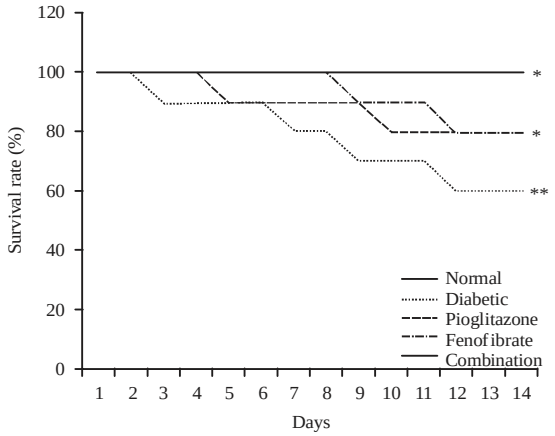

Fig. 4: Effects of pioglitazone, fenofibrate and combination for two weeks on the survival rate with the monotherapy of fenofibrate and pioglitazone on diabetic rats. All values were presented as Mean±SEM, n = 5 in each group, **p<0.05 compared with normal control group, *p<0.05 compared with diabetic control group

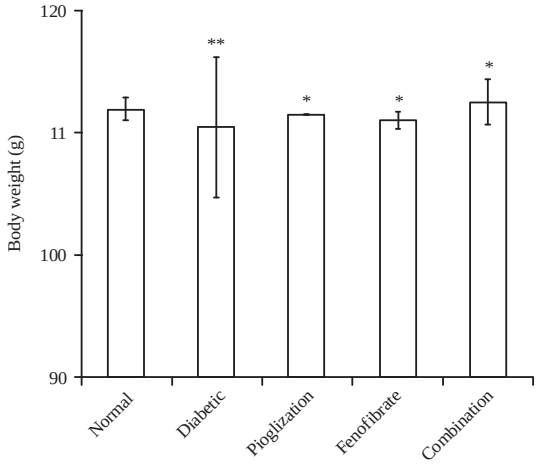

Fig. 5: Effects of pioglitazone, fenofibrate and combination for two weeks on body weight in diabetic rats. All values were presented as Mean±SEM, n = 5 in each group, **p<0.05 compared with normal control group, *p<0.05 compared with diabetic control group

DISCUSSION

Uncontrolled glucose level or hyperglycemia can cause severe damage to our body organs like heart, kidney, eyes even brain but this risk level can be controlled and minimized if diabetes can be effectively managed[9]. Diabetes,

hyperlipidemia, CVD and even kidney disease are very common in both rich and underdeveloped countries. But simple lifestyle like healthy diet and exercise can be very efficacious in controlling diabetes and other related diseases. In many cases, it has seen that even 90% of all cases of diabetes can be prevented by changing lifestyle. Though, it may be true but it is a matter of fact that the majority of the diabetic patient fail to prevent the diabetes through only lifestyle innervations. For this reason, researchers and scientists all over the world are trying to find out new drug combination therapy to control diabetes with CVD and hepatic disease. Researchers find out that combination therapy works better than monotherapy in controlling diabetes and other related complications. Combination of pioglitazone (antidiabetic agent) and fenofibrate (lipid lowering agent) can be used in the treatment of diabetes and its related diseases[10]. In this present study, diabetes in rats was induced by injecting alloxan (120 mg kg^{-1} b.wt.). The accurate mechanism of alloxan induced diabetic is still not clear but earlier studies established that alloxan destroys islets cells by accumulation of harmful free radicals[11]. Alloxan mainly stored and concentrated in liver and islets where, it is mainly converted to dialuric acid. In aqueous solution, this acid is unsaturated and undergoes oxidation back to alloxan which is accompanied by the generation of free radicals that is harmful to islets cells[11]. Thus, alloxan destroys insulin-secreting β-cell, resulting in reduced endogenous insulin secretion. Studies showed that alone with hyperglycemia, hyperlipidemia is very common[12]. This study has evaluated the combination effect of pioglitazone and fenofibrate on alloxan-induced diabetic rats and also other important biochemical parameters such as TG, LDL-C, HDL-C, cholesterol MR, AST, ALT, etc., which caused hepatotoxicity and CVD after long term induction of diabetes.

In this study, it is find out that pioglitazone produced a significant decrease in blood glucose level in alloxan-induced diabetic rats. On the other hand, fenofibrate was not capable of producing any change to these parameters[13,14]. Interestingly, we found that combination therapy is more effective in case of lowering glucose level.

Factors that influence glucose metabolism are also responsible for lipid metabolism[15]. In diabetes mellitus, there is an increase in TG, cholesterol and glucose level[16,17]. Significant increase in TC, TG, LDL-C level and decrease in HDL-C level was observed in this experiment as compared to normal rats and diabetic rats. After two weeks treatment with fenofibrate TC, TG, LDL-C levels were decreased and HDL-C level was increased compared to the alloxan-induced diabetic rats. It is also found that pioglitazone alone was lack of significant effect on these lipid profile parameters after two weeks treatment[13,14]. But the combination therapy was more significant and provides better result than monotherapy.

It is also found that increased glucose level in blood also increased the amount of AST and ALT level in blood of diabetic rats. High level of AST and ALT cause hepatic disease[18-20]. In this study, it is observed that combination therapy reduced ALT and AST level more effectively than that of monotherapy after two weeks treatment. Thus, this study showed that increased level of AST and ALT seen in alloxan-induced diabetic rats[18,21] and monotherapy of drug[22-24] can be reduced more when we use combination therapy. But this study needs further investigation. In this study, it is also found that the body weight and mortality rate are high in combination therapy rather than monotherapy after two weeks treatment.

CONCLUSION

The present study shows that, the combination of pioglitazone and fenofibrate had a synergistic effect on glucose lowering capacity in diabetes treatment. They gave better cardiovascular benefits from reducing the lipid levels and they had low toxicity profile compared to monotherapy requiring higher doses of hypoglycemic agents. Combination therapy of pioglitazone and fenofibrate increased HDL level significantly but reduced TC, TG, LDL, ALT and AST level. It is also had found that combination therapies of pioglitazone with fenofibrate showed more significant and beneficiary results in all respects than single drug therapy of pioglitazone and fenofibrate after two weeks. A similar study in human subjects is desirable to determine if these results can be appropriately extrapolated to human diabetes. There is a need of further study to determine the mechanism of action responsible for anti-diabetic activity.

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