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Effect of Co-Administration of Telmisartan with a Luteolin in Dexamethasone Induced Insulin Resistance in Mice

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ABSTRACT: Current investigation was planned to evaluate co-administering low and high doses of telmisartan with luteolin in mice with insulin resistance caused by dexamethasone. The grouping of mice into eight different groups was done randomly (n=6): DC, NC, TEL-I, TEL-II, LUT, PIO, TL-I, and TL-II. From 1st day to 22nd day, all groups of mice were injected dexamethasone with at a dosage of 1 mg per kg per day and their respective drugs from day 8 to day 22, except NC group. Glucose as well as triglyceride levels were assessed on 1st, 7th and 22nd days. Mice were euthanized and their livers separated to determine content of antioxidant enzymes and glycogen, while hemidiaphragm was isolated for estimation of glucose uptake. Combination groups TL-I and TL-II showed a prominent increase in utilization of glucose uptake and % change in body weight when compared to DC, TEL-I, TEL-II, and LUT groups. TL-II group demonstrated a remarkable reduction in levels of glucose as well as triglycerides when matched to DC, TEL-I, TEL-II, and LUT groups. Furthermore, TL-I and TL-II showed a remarkable rise in liver antioxidants as well as glycogen content with LPO concentration was reduced significantly in correlation to DC, LUT, TEL-I, and TEL-II groups. From present investigation, concludes that combination of telmisartan with luteolin exhibited synergistic effects in normalizing all estimated parameters compared to individual treated groups in experimental animals with dexamethasone-induced insulin resistance.

Keywords: Telmisartan, Dexamethasone, Insulin resistance, Type 2 diabetes, Luteolin.

INTRODUCTION

The International Diabetes Federation predicts that the number of people between the ages of 20 and 79 who have diabetes mellitus will reach 537 million in the year of 2021. It is projected that the figure will rise to 643 million in 2030 and to 783 million in 2045 based on current estimates (Ogurtsova *et al.,* 2022). Type 2 diabetes mellitus makes up the majority of diabetes cases, accounting for 90% to 95% of them, while type 1 diabetes mellitus is responsible for only 1% to 3% of cases. NIIDM as well as IDDM, complex genetic disorders, as opposed to the rare monogenic forms of diabetes (Tuomilehto *et al.,* 2001; Ingale *et al.,* 2023). Diabetes mellitus, especially type 2, is widely acknowledged as a major public health concern that has a significant impact on both human well-being and healthcare costs (Federation, 2019, Chaturved *et al.,* 2023).

The present management of diabetes mellitus is accompanied by significant challenges, including polypharmacy, the struggle to achieve glycemic goals, adherence of patient, and clinical lethargy. Despite the availability of numerous anti-diabetic medications, achieving proper control of hyperglycemia in diabetic patients often proves to be challenging (Ayza *et al.,* 2020). Intensive control of glycemia in T2DM typically needs combining oral hypoglycemic agents as well as insulin, results in weight gain. Additionally, the risk of cerebral haemorrhages, psychological disorders, loos of memory, high blood pressure, and kidney disease increases with increased hypoglycemia (Opie, 2014).

The currently available drugs for T2DM have various adverse effects, such as GI adverse effects and lactic acidosis with metformin, weight gain and hypoglycemia with sulfonylureas, and fluid retention and weight gain with thiazolidinediones (Shurrab and Arafa, 2020; Alam *et al.,* 2018; Bonora, 2007). Therefore, it is important to discover a more effective and safer alternative agent for the treatment of T2DM (Chakraborti, 2010).

PPARγ partial agonists, precisely alter expression of the genes needed just for sensitivity to insulin avoiding ones that cause edema and weight gain. Unlike full PPARγ agonists, partial agonists avoids heart failure and edema, body weight gain. Thus, partial PPARγ agonists like telmisartan are preferred over full agonist drugs like

pioglitazone and rosiglitazone (Chang *et al.*, 2008; Agrawal *et al.*, 2012).

Luteolin has been shown to have potent antioxidant activity and can remove reactive oxygen species ROS as well as free radicals both can lead to oxidative harm to β cells islets of langerhans which contribute to the development of diabetes. Luteolin can also inhibit the enzymes involved in ROS production, further reducing oxidative stress and protecting against diabetes-related complications. Additionally, luteolin has been found to have anti-inflammatory properties, which may also contribute to its protective effects against diabetes (Chen *et al.*, 2023). Luteolin has been shown to have antioxidant properties, which may help protect the pancreas and promote insulin secretion. Luteolin is also believed to increase sensitivity to insulin by influencing the function of Akt2, a kinase that regulates signaling of insulin. The function of Akt2 involves facilitating translocation of GLUT4 transporters to plasma membrane of cells, which enables the cells to take up glucose. By enhancing Akt2 activity, luteolin may help improve glucose uptake and utilization, leading to improved glycemic control (Babu *et al.*, 2013). The current experiment was planned to find out conclusion of co-administration of partial PPARγ agonists-Telmisartan with antioxidant-Luteolin in dexamethasone induced Type 2 diabetes in mice.

MATERIAL AND METHODS

Drugs and chemicals. Pioglitazone as well as telmisartan, as since samples were sent to us by Cipla Pharmaceutical Company, Ascend Laboratories, Mumbai, and Maharashtra, India respectively. Luteolin were procured from Sigma Aldrich, USA.

Experimental animals. Swiss albino mice weighing between 20-30g and of both sexes were obtained from LACSMI, Biopharms PVT. LTD., Pune.

A research design was given approval by Institutional Animal Ethics Committee of Institute of Pharmacy College run by KBHSS trusts in Malegaon city (Reg. No. IAEC 1566/PO/Re/S/11/CPCSEA), and all procedures performed in the experiment followed the recommendations of CPCSEA.

Experimental protocol. Animals were fasted overnight were randomly separated into 8 groups (each group consisting of 6 animals) in the following manner (Ghaisas *et al.*, 2011)

Group I (NC): Animals were given 1% CMC orally at the dose of 1 ml per kg per day from 1st day to 22nd day i.e. last day of study.

Group II (DC): Animals were given intramuscularly dexamethasone at the dose of 1 mg per kg per day starting from 1st day till 22nd day of study.

Group III (PIO): Animals were given intramuscularly dexamethasone at the dose of 1 mg per kg per day starting from 1st day till 22nd day of study and also pioglitazone orally at the dose of 2 mg per kg per day starting from 8th day till 22nd day of study.

Group IV (TEL-I): Animals were given intramuscularly dexamethasone at the dose of 1 mg per kg per day starting from 1st day till 22nd day of study and also telmisartan orally at the dose of 5 mg per kg per day starting from 8th day till 22nd day of study.

Group V (TEL-II): Animals were given intramuscularly dexamethasone at the dose of 1 mg per kg per day starting from 1st day till 22nd day of study and also telmisartan orally at the dose of 10 mg per kg per day starting from 8th day till 22nd day of study.

Group VI (LUT): Animals were given intramuscularly dexamethasone at the dose of 1 mg per kg per day starting from 1st day till 22nd day of study and also luteolin orally at the dose of 10 mg per kg per day starting from 8th day till 22nd day of study.

Group VII (TL I): Animals were given intramuscularly dexamethasone at the dose of 1 mg per kg per day starting from 1st day till 22nd day of study and also telmisartan orally at the dose of 5 mg per kg per day plus luteolin orally at the dose of 10 mg per kg per day starting from 8th day till 22nd day of study.

Group VIII (TL II): Animals were given intramuscularly dexamethasone at the dose of 1 mg per kg per day starting from 1st day till 22nd day of study and also telmisartan orally at the dose of 10 mg per kg per day plus luteolin orally at the dose of 10 mg per kg per day starting from 8th day till 22nd day of study.

Parameters from blood. On the first and twenty-second days, blood samples were taken from the retro-orbital plexus employing thin glass capillary tubes after the mice received a brief ether anesthesia. Epindorff tubes were used to collect the blood, which was then centrifuged to obtain serum. The levels of serum glucose (measured by the GOD/POD method) and triglycerides (measured by the GPO/POD method) were estimated using Meril biochemistry diagnostic kits.

Morphological Parameter. On days 1 and 22 of the experiment, each mice weights were noted.

Hepatic antioxidant enzymes assay. At the last day after biochemical estimation, the mice were euthanized by using urethane at lethal dose. The livers of were excised as well as weighed, then keep under liquid nitrogen-frozen state. 10% homogenate of tissue was created with a phosphate buffer at 0°C (pH 7.4). Using a high-speed centrifuge, homogenate was spun around at 7000 rpm for twenty minutes. The collected supernatant was then utilised to calculate biochemical parameters.

Lipid peroxidation in the hepatocytes. Malondialdehyde (MDA) concentration was measured using a method established by Okhawa in 1979 by measuring the concentration of thiobarbituric acid reactive substance (TBARS). MDA levels were measured using 1, 1, 3, 3-tetraethoxypropane, and were represented as g/mg of protein. The resulting homogenate was combined with 600 millilitres of 1% orthophosphoric acid (pH 3.5) plus one hundred

millilitres of 0.6% thiobarbituric acid in 100 l. After being heated for 60 minutes at 95 °C, the resulting solution was allowed to cool on a bath of ice. Following cooling down the solution was agitated with 1.0 ml of distilled water and 1.0 ml of n-butanol. The resultant mixture was subsequently spun for twenty minutes at a speed of 5000 rpm (Ohkawa *et al.*, 1979).

Catalase in the hepatocytes. The procedure outlined by Aebi in 1974 was used to estimate the activity of the endogenous antioxidant catalase. Catalase levels were quantified and reported as micrograms per milligram of protein. To elaborate, 50 µl of tissue supernatant was mixed with a mixture containing one ml of 50 mM phosphate buffer having pH 7 and 0.1 ml of 30 mM hydrogen peroxide was prepared. The reduction in absorbance at 240 nm was then determined at 30-second intervals up to 260 seconds using a UV spectrophotometer (Aebi, 1974).

Reduced glutathione (GSH) in hepatocytes. To determine liver GSH, the Maron et al. in 1979 method was applied. Using readily accessible standards GSH, a standard curve was created, then the amount measured was expressed as g/mg of protein for wet tissue. To further explain, 100 l of homogenized tissue and 100 l of 10% trichloroacetic acid were combined and vortexed. A reaction solution made up of 3.0 ml of 0.3 M phosphate buffer (pH 8.4) and 0.5 ml of DTNB was added to the solution after it had been spun at 5000 rpm for a period of ten minutes. After ten minutes, with the help of UV spectrophotometer sample absorbance measured at wavelength of 412 nm (Moron *et al.*, 1979).

Superoxide dismutase in hepatocytes. The method created by Mishra and Fridovich in 1978 was employed for assessing SOD activity. A mixture of one hundred millilitres of 500 mM Na2CO3, 100 l of 1 mM/l EDTA, 100 l of 240 M/l NBT, 640 l of purified water, 10 l of 0.3% Triton x 100, and 25 l of 10 mM Hydroxylamine has been added to 25 l of tissue effluent. At a maximum of three minutes, kinetic values at 560 nm were obtained at every one minute. Enzyme concentrations were given as g/mg protein (Misra and Fridovich 1972).

Glycogen content in hepatocytes. Liver quantification utilizing a method described by Suzuki et al. in 2002. 0.5 g of tissue was cooked for five minutes in 0.5 ml of 30% KOH (m/v) to determine the amount of glycogen present. Using 1.2 ml of ethyl alcohol and 0.06 ml of saturated Na_2SO_4, glycogen was subsequently accumulated, then the resulting solution was then removed by spinning in Epindorff tubes at 1900 rpm for twenty minutes at a time. 0.3 cc of 1.2 mol/l HCl had been added to every pellet before samples were heated up for two hours. Following cooling down a drop of the phenol red indicator was put in and 0.5 mol/l of NaOH was subsequently added to accomplish neutralization. A glucose oxidase kit and the GOD/POD technique were used for estimating the amount of glucose in the solution (Ghaisas *et al.*, 2011).

Glucose uptake in isolated Mice hemidiaphragm. On the last day of experiments after biochemical estimation the mice were used to obtain diaphragms, which were carefully removed to prevent any damage and then split into 2 parts. After being cleaned with tyrode solution (0 ^{0}C), the hemi diaphragms without glucose to prevent clots in the blood from forming, and then placed in graduated test tubes with two ml solution of tyrode and 2000 mg/dl glucose. They were then incubated for half an hour at 37^o C in an atmosphere 140 rotations every minute of shaking to determine uptake of glucose in mice hemi-diaphragm (Ghaisas *et al.*, 2011).

Statistical analysis. The statistical evaluation, was done by using one-way analysis of variance (ANOVA) was used with post hoc Bonferroni's multiple comparison for hemodynamic variables. Results were examined for every variable utilizing one-way ANOVA and Dunnett's post hoc test with Graph Pad, Prism software, and version 8.2, USA.

RESULT

Effect on serum glucose level. DC Group exhibited raised in level of glucose in serum which was found to be significant ($p<0.001$) day 7th onwards when compared with NC group respectively. TEL- I, TEL- II and LUT Groups revealed decrease, in serum glucose level significantly ($p<0.05$), ($p<0.001$), ($p<0.001$) at 22nd day as related to DC respectively. Combination treated groups TL-I and TL-II Groups exhibited reduction in serum glucose level significantly ($p<0.001$) at 22nd day when compared with DC group.

Table 1: Effect of combination of telmisartan with luteolin on serum glucose level in dexamethasone-induced insulin resistance in mice.

Group	Serum glucose (mg/dl) on		
	Day 1	Day7	Day 22
NC	61.89 ± 0.82	61.25 ± 0.87	59.42 ± 1.57
DC	60.52 ± 0.59	82.44 ± 1.41$^{\#\#}$	80.52 ± 1.05$^{\#\#\#}$
PIO	61.88 ± 1.01	81.15 ± 1.03	61.27 ± 1.01***
TEL- I	58.25 ± 1.51	80.51 ± 1.21	78.02 ± 2.25*
TEL- II	59.98 ± 0.75	78.78 ± 0.96	76.54 ± 1.10***
LUT	59.22 ± 0.87	81.25 ± 0.98	77.68 ± 0.87**
TL- I	60.87± 0.96	82.15 ± 0.89	75.82 ± 0.96$^{***, a}$
TL- II	61.78± 0.88	80.78 ± 0.69	68.57 ± 1.78^{***,aaa,bbb,ccc}

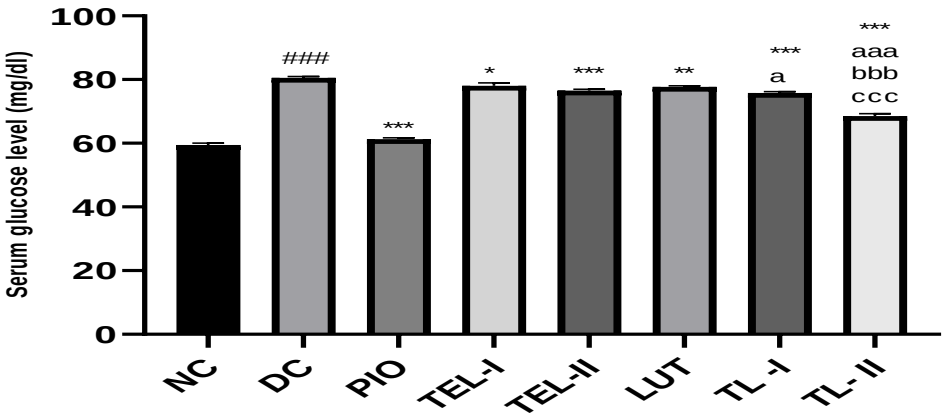

Fig. 1. Effect of combination of telmisartan with a luteolin on serum glucose level in dexamethasone treated mice.

TL-I Group revealed decrease, in serum glucose level significantly ($p<0.05$), at 22nd day when compared TEL-I. TL- II Group revealed decrease, in serum glucose level significantly ($p<0.001$), at 22nd day when compared to LUT, TEL- I and TEL- II groups (Table 1 and Fig. 1).

Effect on serum triglyceride level. DC Group exhibited raised in level of glucose in serum which was found to be significant ($p<0.001$) day 7th onwards when compared with NC. TEL- I, TEL-II and LUT Groups revealed decrease, in serum triglyceride level significantly ($p<0.01$), ($p<0.001$), ($p<0.05$) on day 22 as matched with DC. TL- I and TL-II Groups showed reduction in serum level of triglyceride significantly ($p<0.001$) on day 22 as matched with DC. TL- I Group revealed decrease, in serum triglyceride level significantly ($p<0.001$) on day 22 as matched with LUT, TEL- I (telmisartan - 5mg/kg) groups. TL- II Group revealed decrease, in serum triglyceride level significantly ($p<0.001$) on day 22 as matched with LUT, TEL- I as well as TEL- II groups (Table 2 and Fig. 2).

Table 2: Effect of combination of telmisartan with luteolin on serum triglyceride level in dexamethasone-induced insulin resistance in mice.

Group	Serum triglyceride (mg/dl) on		
	Day- 1	Day- 07	Day- 22
NC	89.42 ± 2.60	90.42 ± 2.09	84.55 ± 2.43
DC	88.81 ± 3.31	141.11 ± 2.25$^{###}$	147.79 ± 2.80$^{###}$
PIO	86.18 ± 2.83	139.68 ± 2.29	95.25 ± 2.35***
TEL- I	91.45 ± 2.72	141.31 ± 1.54	142.01 ± 2.51**
TEL- II	82.45 ± 2.47	136.51 ± 2.37	132.00 ± 2.48***
LUT	80.98 ± 2.01	136.66 ± 3.02	143.71 ± 2.70*
TL- I	89.25 ± 2.89	139.32 ± 1.47	128.59 ± 2.22^{***,aaa,ccc}
TL- II	87.58 ± 2.78	128.14 ± 2.57	101.70 ± 1.53^{***,aaa,bbb,ccc}

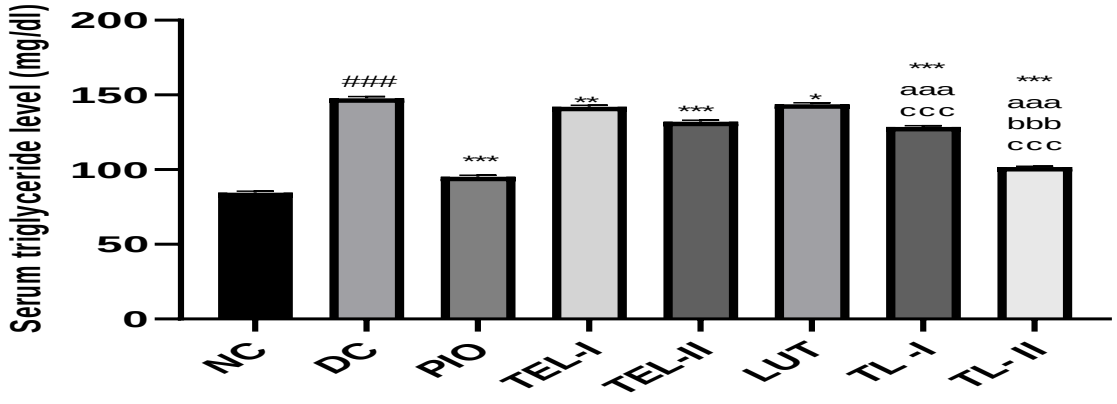

Fig. 2. Effect of combination of telmisartan with a luteolin on serum triglyceride level in dexamethasone treated mice.

Glucose uptake in isolated hemidiaphragm. DC Group exhibited reduction in non-insulin as well as insulin assisted uptake of glucose significantly ($p<0.001$) as correlated NC group. TEL- I, TEL- II and LUT Groups exhibited raise which was noteworthy ($p<0.05$), ($p<0.01$), ($p<0.05$) in non-insulin and insulin assisted uptake of glucose when compared with DC respectively. Combination treated both groups TL- I and TL- II significant increase ($p<0.001$) in non-insulin as well as insulin assisted glucose uptake when compared with DC, TEL- I, TEL- II and LUT Groups (Table 3, Fig. 3 and Fig. 4).

Table 3: Effect of combination of telmisartan with luteolin on non-insulin assisted and insulin assisted glucose uptake using isolated hemidiaphragm of mice.

Non-insulin dependent glucose uptake		Insulin assisted dependent glucose uptake	
Groups	**mg /g /30 min**	**Groups**	**mg /g /30 min**
NC	10.58 ± 0.37	NC	17.56 ± 0.17
DC	4.34 ± 0.26$^{###}$	DC	8.59 ± 0.21$^{###}$
PIO	8.43 ± 0.17***	PIO	12.13 ± 0.12***
TEL- I	4.81 ± 0.33*	TEL- I	8.97 ± 0.28*
TEL- II	4.96 ± 0.34**	TEL- II	9.11 ± 0.36**
LUT	4.87 ±0.23*	LUT	8.99 ± 0.22*
TL- I	08.98±0.37$^{***, aaa,bbb,ccc}$	TL- I	11.73 ± 0.18$^{***, aaa,bbb,ccc}$
TL- II	10.28±0.25$^{***, aaa,bbb,ccc}$	TL- II	13.80 ± 0.24 $^{***, aaa,bbb,ccc}$

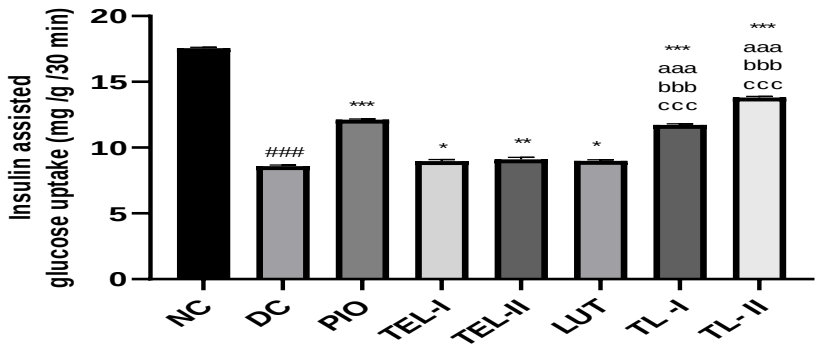

Fig. 3. Effect of combination of telmisartan with luteolin on insulin assisted glucose uptake using isolated hemidiaphragm in mice of dexamethasone-induced insulin resistance in mice.

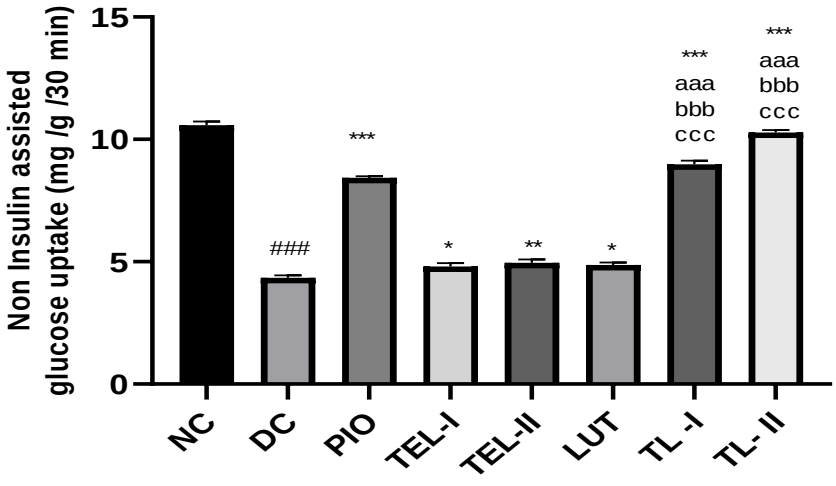

Fig. 4. Effect of combination of telmisartan with luteolin on non-insulin assisted glucose uptake using isolated hemidiaphragm in mice of dexamethasone-induced insulin resistance in mice.

Effect on percentage change in body weight. DC Group exhibited reduction in the % change in body weight significantly ($p<0.001$) as related to NC group. TEL- I, TEL- II and LUT Groups exhibited increase ($p<0.01$), ($p<0.001$), ($p<0.05$) in % change in body weight significantly on day 22 when compared DC. Combination treated TL- I and TL-II groups exhibited rise in % change in body weight on day 22 significantly ($p<0.001$) as compared with DC, TEL-I, TEL-II and LUT groups (Table 4 and Fig. 5).

Table 4. Effect of combination of telmisartan with luteolin on % change in body weight in dexamethasone-induced insulin resistance in mice.

Group	Change in Body weight (%)
NC	+1.25 ± 0.12
DC	-2.14 ± 0.05$^{###}$
PIO	+1.22 ± 0.05***
TEL- I	-1.97 ± 0.08**
TEL- II	-1.69 ± 0.09***
LUT	-1.99 ± 0.06*
TL- I	+0.87 ± 0.07$^{***, aaa,bbb,ccc}$
TL- II	+1.12 ± 0.10$^{***, aaa,bbb,ccc}$

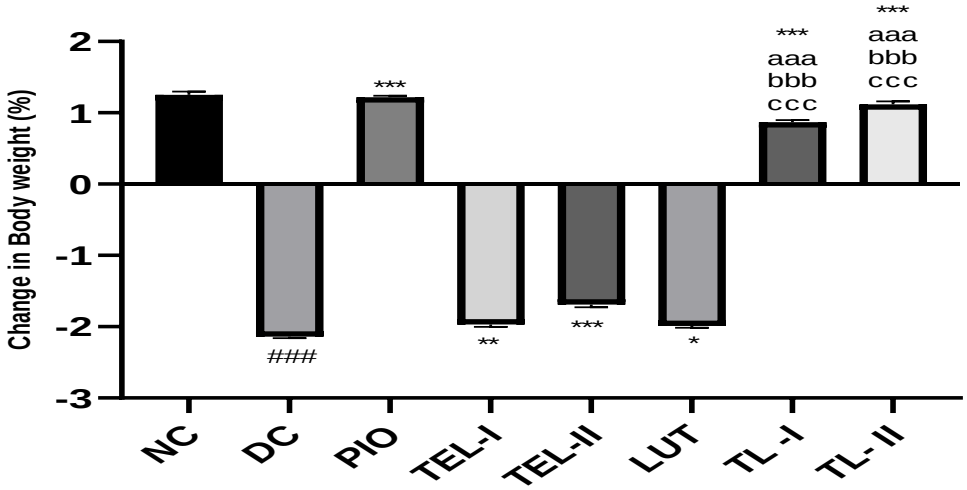

Fig. 5. Effect of combination of telmisartan with a luteolin on % change in body weight in dexamethasone treated mice.

Effect on liver antioxidant levels. DC Group showed noteworthy reduction ($p<0.001$) in the levels of Catalase, Superoxide dismutase, glutathione whereas significant rise ($p<0.001$) in lipid peroxide level of liver in relation with NC group. TEL- I Group showed significant increased levels of glutathione ($p<0.05$), SOD ($p<0.05$) and catalase ($p<0.01$) while showed noteworthy reduction ($p<0.05$) in the level LPO when compared with DC group. TEL- II Group treated with dexamethasone plus telmisartan (10mg/kg) exhibited increase in hepatic levels of GSH significantly ($p<0.05$) in relation with DC. TEL- II Group treated with dexamethasone plus telmisartan (10mg/kg) exhibited rise in hepatic levels of Catalase significantly ($p<0.001$) in relation with DC. TEL- II Group exhibited noteworthy elevated ($p<0.01$) in Superoxide dismutase level however exhibited decreased in LPO level significant ($p<0.01$) in relation with DC. LUT, TL-I and TL-II Group showed noteworthy elevated ($p<0.001$) in hepatic levels of Superoxide dismutase, glutathione, Catalase whereas reduction in LPO level ($p<0.001$) in correlation with DC group. Combination groups TL- I and TL- II exhibited raised levels of Superoxide dismutase, glutathione, Catalase significantly ($p<0.001$) whereas showed marked reduction($p<0.001$) in LPO level in relation with DC, LUT, TEL- I and TEL- II groups (Table 5 and Fig. 6, 7, 8 and 9).

Table 5: Effect of combination of telmisartan with luteolin on hepatic levels of GSH, SOD, Catalase, and LPO in dexamethasone-induced insulin resistance in mice.

Groups	GSH (µg of GSH/g of tissue)	SOD (units/ mg of tissue)	Catalase (µM of H_2O_2/g of tissue/min)	LPO (nM of MDA/ g of tissue)
NC	25.22 ± 0.45	70.51 ± 0.62	8.55 ± 0.25	12.57 ± 0.27
DC	13.82 ± 0.36$^{###}$	25.64 ± 0.62$^{###}$	3.36 ± 0.20$^{###}$	32.14 ± 0.31$^{###}$
PIO	15.51 ±0.49***	51.63 ± 0.57***	4.82 ± 0.35***	29.13 ± 0.25***
TEL- I	13.02 ±0.52*	26.60 ± 0.31*	4.02 ± 0.28**	31.70 ± 0.34*
TEL- II	12.95 ± 0.44*	26.76 ± 0.23**	4.99 ± 0.36***	31.56 ± 0.29**
LUT	15.56 ± 0.50***	45.45 ± 0.58***	6.01 ± 0.37***	21.14 ± 0.13***
TL- I	17.24 ± 0.26***, aaa,bbb,ccc	49.75± 0.61***, aaa,bbb,ccc	6.98 ± 0.12***, aaa,bbb,ccc	19.96 ± 0.21***, aaa,bbb,ccc
TL- II	20.07 ± 0.58***, aaa,bbb,ccc	52.52 ± 0.44***, aaa,bbb,ccc	7.19 ± 0.19***, aaa,bbb,ccc	15.54 ± 0.15***, aaa,bbb,ccc

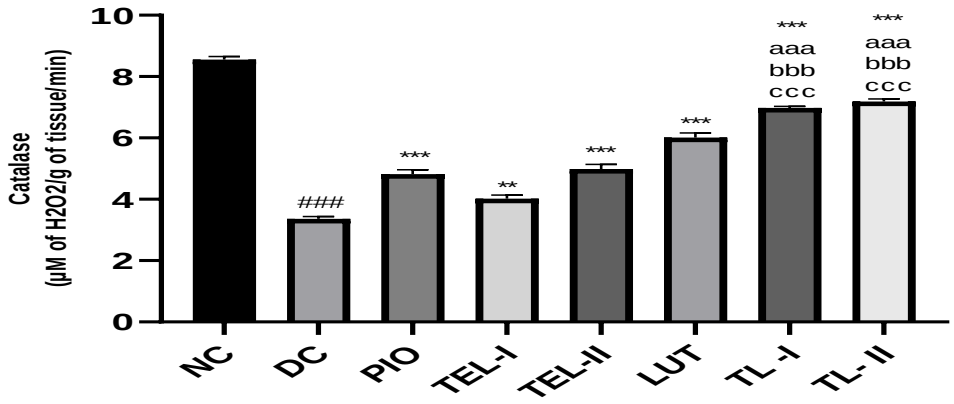

Fig. 6. Effect of combination of telmisartan with luteolin on hepatic catalase level in dexamethasone-induced insulin resistance in mice.

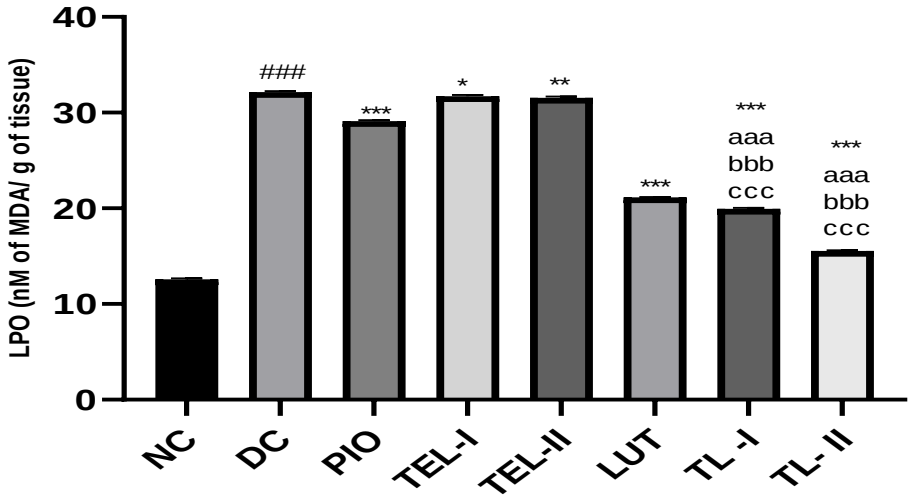

Fig. 7. Effect of combination of telmisartan with luteolin on hepatic LPO level in dexamethasone-induced insulin resistance in mice.

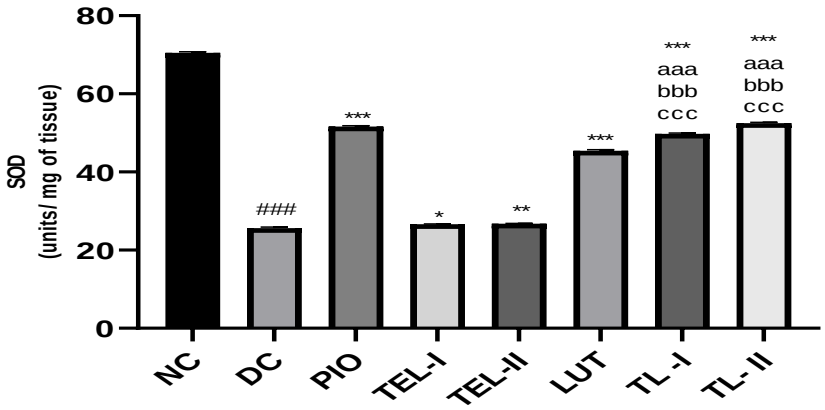

Fig. 8. Effect of combination of telmisartan with luteolin on hepatic SOD level in dexamethasone-induced insulin resistance in mice.

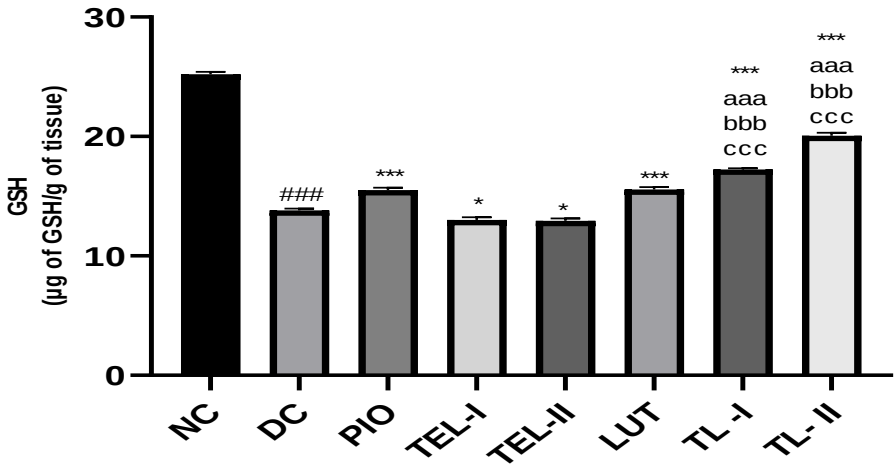

Fig. 9. Effect of combination of telmisartan with luteolin on hepatic GSH level in dexamethasone-induced insulin resistance in mice.

Effect on liver glycogen content. DC Group exhibited noteworthy reduction ($p<0.001$) in liver glycogen content in relation to NC group. TEL- I, TEL- II and LUT Group exhibited raised in liver glycogen content significantly ($p<0.01$), ($p<0.001$), ($p<0.01$) as related to DC group respectively. Combination treated both groups TEL- I and TEL-II showed raised in liver glycogen content significantly ($p<0.001$) when compared to DC, LUT, TEL-I and TEL-II groups (Table 6 and Fig. 10).

Table 6. Effect of combination of telmisartan with luteolin liver glycogen content in dexamethasone-induced insulin resistance in mice.

Group	Glucose equivalent to glycogen (mg/g)
NC	2.13 ± 0.05
DC	0.67 ± 0.03$^{###}$
PIO	1.46 ± 0.05***
TEL- I	0.76 ± 0.04**
TEL- II	0.79 ± 0.03***
LUT	0.78 ± 0.03**
TL- I	1.11 ± 0.07***, ^{aaa,bbb,ccc}
TL- II	1.46 ± 0.05^{***,aaa,bbb,ccc}

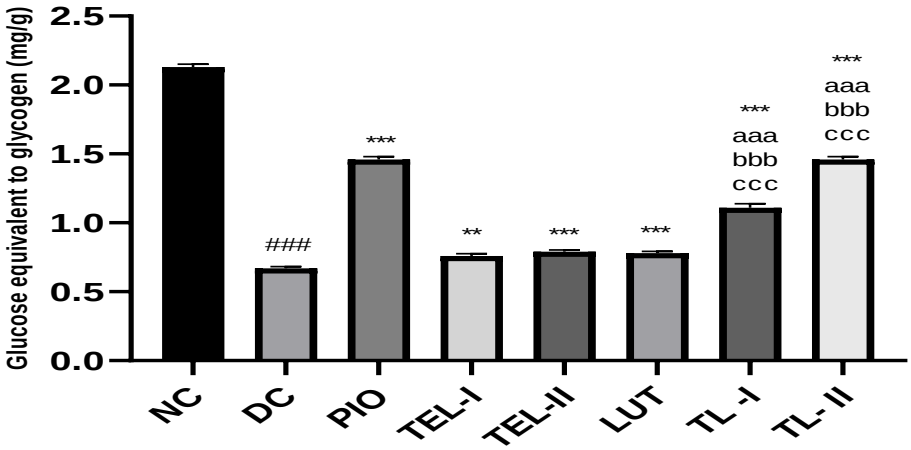

Fig. 10. Effect of combination of telmisartan with luteolin liver glycogen content in dexamethasone-induced insulin resistance in mice.

DISCUSSION

Dexamethasone has a dual effect on various cellular processes, either promoting or inhibiting them, depending on their involvement in anabolic or catabolic activities. For example, it induces the production of enzymes such as tyrosine aminotransferase that participate in transmination, while simultaneously inhibiting theactivity of phosphofructokinase, leading to decreased glucose metabolism. Additionally, dexamethasone blocks the conversion of pyruvate to acetyl-CoA, thereby redirecting pyruvate towards gluconeogenesis. These inhibitory effects are likely the result of gene repression. Moreover, dexamethasone enhances lipid metabolism, possibly through the stimulation of cAMP formation (Fullerton, 1977).

In comparison to cortisol, the synthetically produced glucocorticoid dexamethasone has a fifty times higher affinity for the glucocorticoid receptor. Dexamethasone has unfavorable consequences such muscular catabolism, hyperphagia, increased obesity, and enhanced resistanceto insulin when given in excessive (Prelovsek *et al.*, 2006). Dexamethasone can trigger peripheral resistance to insulin by a numerous different ways, like GLUT4 translocation stoppage (Dimitriadis *et al.*, 1997), a rise in lipoprotein lipase activity in adipose tissue (Ong et al., 1992), a decrease in phosphatidylinositol-3 kinase (PI-3K) activity that reduces signaling pathway of insulin and results in resistance to it. Tissues like muscular shows higher levels of triglyceride as result of increased free fatty acid competition with pyruvate for mitochondrial oxidative metabolism (Ong *et al.*, 1992). In current investigation, dexamethasone administration caused remarkable raised triglyceride as well as glucose levels as compared with vehicle treated group i.e. normal control. In the combination treated group, higher doses of telmisartan with luteolin significantly reduced blood glucose and triglyceride levels which were elevated.

As telmisartan has been shown to enhance insulin sensitivity, induce the transport of GLUT4 from cytoplasm towards membrane of cell, and stimulate uptake of the glucose in peripheral tissues such as adipose tissue, likely through the activation of PPAR-gamma which could be reason for maintaining blood glucose level (Fang *et al.*, 2018; Fujimoto *et al*., 2004; Furukawa *et al*., 2011).

Luteolin exertsits effects on adipose tissue, resulting in a decrease in glucose levels by reducing lipid peroxidation, boosting glucose absorption and sensitivity to insulin, lowering adipocyte hypertrophy, which restricting mast cell infiltration into adipose tissue, decreasing inflammatory inside fat tissue, and increasing the production of antioxidant enzymes are all ways to do this (Wang *et al.*, 2021). Both telmisartan and luteolin activate the PPAR-gamma receptor, thereby increasing insulin sensitivity through the Akt2 kinase pathway (Ding *et al.*, 2010). This kinase activation serves two purposes: firstly, it promotes glucose uptake by facilitating the translocation of GLUT4 to the cell membrane; secondly, it prevents the dephosphorylation of the insulin receptor, thereby avoiding the attenuation of the insulin-signaling process. Consequently, it can be concluded that both drugs work synergistically to reduce glucose levels by enhancing insulin sensitivity and facilitating GLUT4 translocation (Xu *et al.*, 2014).

Telmisartan and luteolin combination group may have contributed to a reduction in levels of triglycerides (Kwon *et al.*, 2015).

This effect may be attributed to the action of telmisartan on hepatic cells, targeting PPARα gene expression, which aids in reducing triglyceride levels by increasing the induction of lipoprotein lipase expression (Yin). In combination with telmisartan, luteolin inhibits pancreatic lipase and reduces the expression of genes associated with fat production in liver cells (Habtemariam, 2013; Monika and Geetha, 2015) contributing to a decrease in triglyceride levels in the

treated groups.

In current investigation, Dexamethasone-treated mice showed an apparent drop in the uptake of glucose in their isolated hemidiaphragm in comparison to a normal control group of mice. Combination groups, telmisartan plus luteolin exhibited rise uptake of the glucose in mice isolated hemidiaphragm significantly when compared with dexamethasone control as well as individual groups of telmisartan as well as luteolin treated groups. The mechanisms behind increasing glucose uptake in isolated hemidiaphragm may be due to action of telmisartan may increase the mRNA levels of PPARγ target genes, including aP2 and adiponectin, in an amount that depends on dosage. Additionally, telmisartan increased the GLUT4 protein expression in skeletal muscles via PPAR- δ activation (Li *et al.*, 2013) and the uptake of 2-deoxy glucose in both basal and insulin-stimulated states (Fujimoto *et al.*, 2004). Luteolin as well as telmisartan both has the potential to activate AKT, insulin receptor substrate 1, AS160 and PI3K signal pathways as well as AMPK in myocytes which is self-governing that are resistant to insulin. This activation by both luteolin as well as by telmisartan leads to the movement of GLUT4 to membrane of cell, resulting in a significant increase in glucose uptake as compared to individually treated groups (Kukhtar *et al.*, 2017).

The administration of dexamethasone leads to an increase in *ob* gene expression, which induces a range of metabolic changes including hyperleptinaemia. These changes can cause a reduction in food consumption and weight loss (Yoon *et al.*, 2018; Kim *et al.*, 2002).

In the present investigation, when compared to a normal control, dexamethasone treatment resulted in a considerable drop in body weight. Weight loss has been reported as a consequence of hyperglycemia-induced structural protein atrophy and muscle wasting.

As comparison to the dexamethasone control group as well as TEL-I, TEL-II and LUT groups, telmisartan plus luteolin combination treatment groups demonstrated an enormous increase in weight gain. The mechanism underlying weight gain in the TL-I and TL-II could be due to that luteolin had a significant impact in mitigating weight loss in rats with diabetes, effectively bringing their weight back to near-normal levels. This result implies that by controlling blood sugar levels, luteolin can enhance protein synthesis and improve the overall qualityof life for individuals with diabetes (Shalam *et al.*, 2006).

According to a recent study by Baydas et al., hyperglycemia has been shown to lower innate antioxidant levels despite raising the production of free radicals. This oxidative stress can impair insulin signaling, as highlighted by Hoyer and Lannert (1999). Insulin resistance, on the other hand, releases cytokines such TNF-alpha as well as IL- 8, that decrease the amount of Cu/Zn SOD and glutathione in the mitochondria and produce H_2O_2 free radicals, causing oxidative damage in the hepatocytes, according to the findings (Marfella *et al*., 2001).

In the present investigation, individual treated groups of telmisartan, luteolin showed significant raised in the levels of Superoxide dismutase, glutathione as well as catalase and significant reduction in LPO levels in homogenate of liver cells in relation with DC group. Increase in antioxidant levels was more significant in the combination treated groups telmisartan with luteolin at higher doses as compared with individually treated groups. The presence of potential for antioxidants activity by both telmisartan plus luteolin possibly as a result of luteolin's powerful antioxidant abilities, that remove a number of oxygen and nitrogen species that are reactive as well as its capacity to inhibit the oxidation of lipids (Marfella *et al*., 2001). The oxidative stress reducing effect of telmisartan has been found to activate the expression of PPAR- γ, resulting in anti-oxidative effect which may be through the reduction of protein expressions of NADPH oxidase sub-units, leading to a decrease in oxidative stress (Yoo *et al.*, 2015). The combination of telmisartan and luteolin demonstrated the ability to scavenge free radicals by inhibiting NF-κB-mediated inflammation by both synergistically. As well as activation the Nrf2 pathway by luteolin alone. As a result, it effectively combats oxidative stress and suppresses the majority of proinflammatory responses (Morsy *et al.*, 2022; Li *et al.*, 2019).

Luo and Toyama studies have shown that luteolin and telmisartan activate the eNOS pathway and enhance SOD activity. NOS and SOD interaction is crucial, as NOS down-regulation can result in free radical-induced injury (Luo *et al.*, 2017; Toyama *et al.*, 2011). Overall, the combination of telmisartan and luteolin enhanced antioxidant properties each other which works synergistically by inhibition nuclear factor-κB, activating eNOS which results in a greater reduction in oxidative stress.

Dexamethasone treatment can lead to a decrease in insulin-stimulated glucose uptake and muscle glycogen synthesis, accompanied by reduced phosphorylation of PKB and GSK-3. Insulin is a key controller of synthesis of glycogen in both cells of muscle as well as hepatocytes, and diabetic rats, there is a notable decrease in hepatic glycogen content (Toyama *et al.*, 2011).

While glucocorticoids have been shown to decrease degree of glucose absorption at baseline and insulin-stimulated levels, they also result in decreased glycogen accumulation. The insulin resistance that occurs with glucocorticoid treatment is largely due to deterioration in action of insulin at post-receptor site, although it cannot lead to a decrease in isoform of an insulin-sensitive transporter of glucose GLUT4 or GLUT4 mRNA (Kreutner and Goldberg, 1967).

In the present investigation, the glycogen content in hepatocytes in DC group was decreased in relation to normal control. Glycogen content was raised in the TL-I and TL-II significantly as in relation to DC group as well as TEL-I, TEL-II and LUT groups. Probable mechanism behind increased glycogen content in liver in the combination treated groups, may be due to the ability of telmisartan to trigger PPARγ, a transcription factor that regulates metabolism of fat and carbohydrates like glucose. Also it hasbeen reported that telmisartan decrease glycogenolysis, which is the breakdown of glycogen to glucose, in the liver of diabetic mice (Thomas et al., 1998; Lu *et al.,* 2015). Recently it has been discovered that luteolin increases the sensitivity of insulin and absorbs glucose via altering the function of AKT2 kinase. This may be accomplished by activating AMP-activated protein kinase (AMPK), which in turn promotes AKT2 and promotes absorption of glucose (Lu *et al*., 2015). Combination therapies using luteolin enhance glycolysis and glycogenesis while suppressing gluconeogenesis and glycogenolysis (Sugimoto *et al.,* 2006; Eid *et al.,* 2015).

CONCLUSION

From current investigation, we determined, combination of telmisartan with luteolin demonstrated significant as well as ensuring results in dexamethasone-induced diabetes of type 2 treatment, compared to individual treatment groups. Both telmisartan and luteolin exhibited antidiabetic, antihyperlipidemic, and antioxidant potential, and their combination exhibited a synergistic effect in relation to various biochemical, morphological parameters. Further research is needed to evaluate the potential of the combination of telmisartan with luteolin on the long-term complications of type 2 diabetes preclinically.

FUTURE SCOPE

To carry out preliminary studies on its pharmacokinetics and pharmacodynamics. It's also crucial to evaluate this study combination against currently available, commercially available dosages. This further investigation is required to establish that the medication is appropriate for use in human beings.

Abbreviations. Na CMC- Sodium Carboxy methyl cellulose, NC- Normal control, DC- Dexamethasone control, PIO- Pioglitazone, TEL- Telmisartan, LUT- Luteolin, TL - Telmisartan plus Luteolin.

Results are presented as mean ± SEM, (n=6). ANOVA followed by Dunnett test.

$^{###}p$ <0.001 when compared with NC. $^{***}p<0.001$, $^{**}p<0.01$, $^{*}p<0.05$ when compared with DC. $^{aaa}p<0.001$, $^{aa}p<0.01$, $^{a}p<0.05$ when compared with TEL- I. $^{bbb}p<0.001$, $^{bb}p<0.01$, $^{b}p<0.05$ when compared with TEL-II, $^{ccc}p<0.001$, $^{cc}p<0.01$, $^{c}p<0.05$ when compared with LUT.

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