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Original Article

Exploring the Synergistic Effects of Telmisartan in Combination with Naringin in Alleviating Diabetic Nephropathy in Streptozotocin Induced Diabetes in Rats

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ABSTRACT

Background: A serious circumstance attributed with diabetes mellitus, Diabetic Nephropathy (DN) is indicated by hyperglycaemia-induced renal damage, inflammation, along with oxidative stress. An angiotensin II receptor blocker and a flavonoid, which have shown capability in ameliorating diabetes-induced complications are telmisartan and naringin respectively. **Objectives:** The present investigation studied the effects of the combination of Telmisartan with Naringin on DN in Streptozotocin induced diabetes in experimental animals. **Material and Methods:** Diabetes was induced in rats using streptozotocin, followed by a 28-day period to allow disease progression. Subsequently, the animals received oral treatment with telmisartan, naringin, or their combination for 45 days. Various parameters, including biochemical markers (glucose, HbA1c, CRP, renal and lipid profiles), inflammatory cytokines, and oxidative stress indicators, were evaluated, along with histopathological analysis of kidney tissue. **Results:** Disease control rats exhibited significantly elevated serum glucose, HbA1c levels, creatinine, BUN, albumin along with impaired lipid metabolism and severe oxidative stress in renal tissues. Administration of Telmisartan and Naringin individually improved these parameters, but their combination therapy demonstrated more profound effect. The combination of Telmisartan and Naringin had significant reductions in serum-glucose, HbA1c, creatinine, and BUN levels, alongside improvements in lipid profiles and restoration of renal antioxidant capacity. Furthermore, combined therapy showed enhanced anti-inflammatory effects by reducing levels of TNF-α, IL-1β, IL-6 and oxidative stress markers (LPO), while increasing antioxidant (GSH, NO). **Conclusion:** The combined administration of Telmisartan with Naringin showed protection against diabetic nephropathy through multifaceted mechanisms, including anti-inflammatory, antioxidant, and renoprotective effects. This study highlights the therapeutic potential of integrating Telmisartan and Naringin for managing diabetic nephropathy, suggesting a promising strategy for mitigating diabetes-induced renal complications.

Keywords: Diabetic Nephropathy, Streptozocin, Telmisartan, Naringin.

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INTRODUCTION

Diabetes mellitus, a chronic metabolic disorder, remains a significant global health concern, in 2021, approximately 537 million adults were affected by diabetes, with projections indicating a rise to 643 million by 2030 and an alarming 783 million by 2045, as reported by the International Diabetes Federation (IDF).[1] Among its numerous complications, Diabetic Nephropathy (DN) stands out as a major long-term consequence of sustained hyperglycemia, leading to considerable morbidity and mortality.[2]

Diabetic nephropathy is characterized by structural changes such as basement membrane thickening, mesangial expansion, extracellular matrix accumulation, glomerulosclerosis, and hypertrophy.[3] Functionally, these alterations lead to increased serum urea and creatinine levels, indicating renal impairment.[4] The progression of DN is primarily driven by elevated pro-inflammatory cytokines and infiltration of inflammatory cells into renal tissues, exacerbating kidney damage.[5]

Current treatment strategies for diabetes mellitus involve a multifaceted approach, including dietary management, physical exercise, oral antidiabetic medications, and insulin therapy.[6]

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However, modern antidiabetic drugs, such as thiazolidinediones, biguanides, sulfonylureas, and glucosidase inhibitors, are associated with adverse effects, including weight gain, edema, frequent diarrhoea, hypoglycemia, hepatotoxicity, lactic acidosis, dyslipidemia, hypertension, and hypercoagulability.[7] These limitations necessitate the search for novel therapeutic agents with alternative mechanisms of action. Research suggests that combining antioxidants with oral hypoglycemic agents may provide superior benefits compared to monotherapy in managing DN.[8]

PPARγ agonists have emerged as a promising class of drugs that selectively modulate insulin sensitivity-related gene expression.[9] Telmisartan, a partial PPARγ agonist, is favoured over full agonists such as pioglitazone and rosiglitazone due to its reduced risk of heart failure, edema, and weight gain.[10] Beyond its antihypertensive effects, telmisartan exhibits antioxidant, anti-inflammatory, and insulin-sensitizing properties through its interaction with PPARγ.[11] Additionally, telmisartan has been shown to mitigate oxidative stress induced by fatty acids and inhibit NADPH oxidase activity, particularly in pancreatic β-cells.[12]

Naringin (4′,5,7-trihydroxyflavanone-7-rhamnoglucoside), a prominent flavonoid found in various plant sources, has gained attention for its diverse bioactive properties.[13] It is known for its antioxidant, cardiovascular protective, hypolipidemic, anti-atherosclerotic, antidiabetic, neuroprotective, hepatoprotective, and anticancer properties, making it a valuable compound in therapeutic research.[14] Studies have reported that naringin's antioxidant effects protect against nephrotoxicity and renal injury by scavenging free radicals and suppressing pro-inflammatory cytokines.[15]

Despite these promising properties, the combination of naringin with telmisartan has not been extensively investigated in a preclinical setting for the treatment of DN. Therefore, the present study aims to evaluate the therapeutic impact of this combination on the onset and progression of DN in streptozotocin-induced diabetic rats. This research seeks to explore whether the combined administration of naringin and telmisartan offers superior renoprotective effects compared to individual treatments, potentially paving the way for a novel therapeutic approach in managing diabetic nephropathy.

MATERIALS AND METHODS

Chemicals

Telmisartan, naringin, streptozotocin were received from Ottochemi Chemicals Co., Mumbai. The drugs were stored at 2-4°C, kept out of direct sunlight, with all other chemicals being of analytical grade from Sigma Aldrich, India.

Experimental animals

White albino rats of either sex, of 200-250 g, were received from Lacsmi Bioform Pvt. Ltd., Pune7. The rats were kept in standard polypropylene cages under controlled conditions: temperature maintained at 22°C±2°C, humidity at 55±5%, and a 12-hr light-dark cycle.[16,17]

Development of diabetes

Diabetes was induced by streptozotocin (intra-peritoneal) of dose 55 mg/kg after being dissolved in cold citrate buffer of pH 4.5 injected to overnight fasted rats. After 72 h, rats with serum Glucose levels of 250 mg/dL or higher were categorized as diabetic and included in subsequent pharmacological assessments. The diabetic animals were then kept on a water and normal diet for 4 weeks (28 days) to allow the development of diabetic nephropathy, after which treatment was initiated for 45 days.[18]

Experimental design

Seven groups of rats were done to assess the effects of telmisartan and naringin on diabetes. Group 1 was normal control and Group 2 to 7 were diabetic. Group no 1 Normal control (NC) and Group 2 Disease Control (DC) received 1% Na CMC orally. Groups 3 and 4 (TEL-1 AND TEL-2) respectively received telmisartan at 5 mg/kg and 10 mg/kg. Group 5 (NR) received naringin at 50 mg/kg. Groups 6 and 7 received a combination groups receiving telmisartan (5 mg/kg) and naringin (50 mg/kg) and telmisartan (10 mg/kg) and naringin (50 mg/kg) respectively. All doses were given p.o for 45 days, with the aim to compare the individual and combined effects of telmisartan and naringin on diabetic rats.[19]

Physiological parameters

On day 1st and 45th of treatment, body weights of each rat from group one to group seven were noted.

Serum Parameters

On the 45th day of the study, collection of blood samples from the rats' retroorbital plexus was performed. The serum glucose, CRP, kidney function markers, lipid profile, HbA1c, ions such as Na^+ and K^+ levels were analysed using Meril Autoquant 200i diagnostics kit.

Inflammatory cytokines analysis was done via ELISA assays as per the manufacturer's instructions at Shribios innovations laboratory, Pune.[20]

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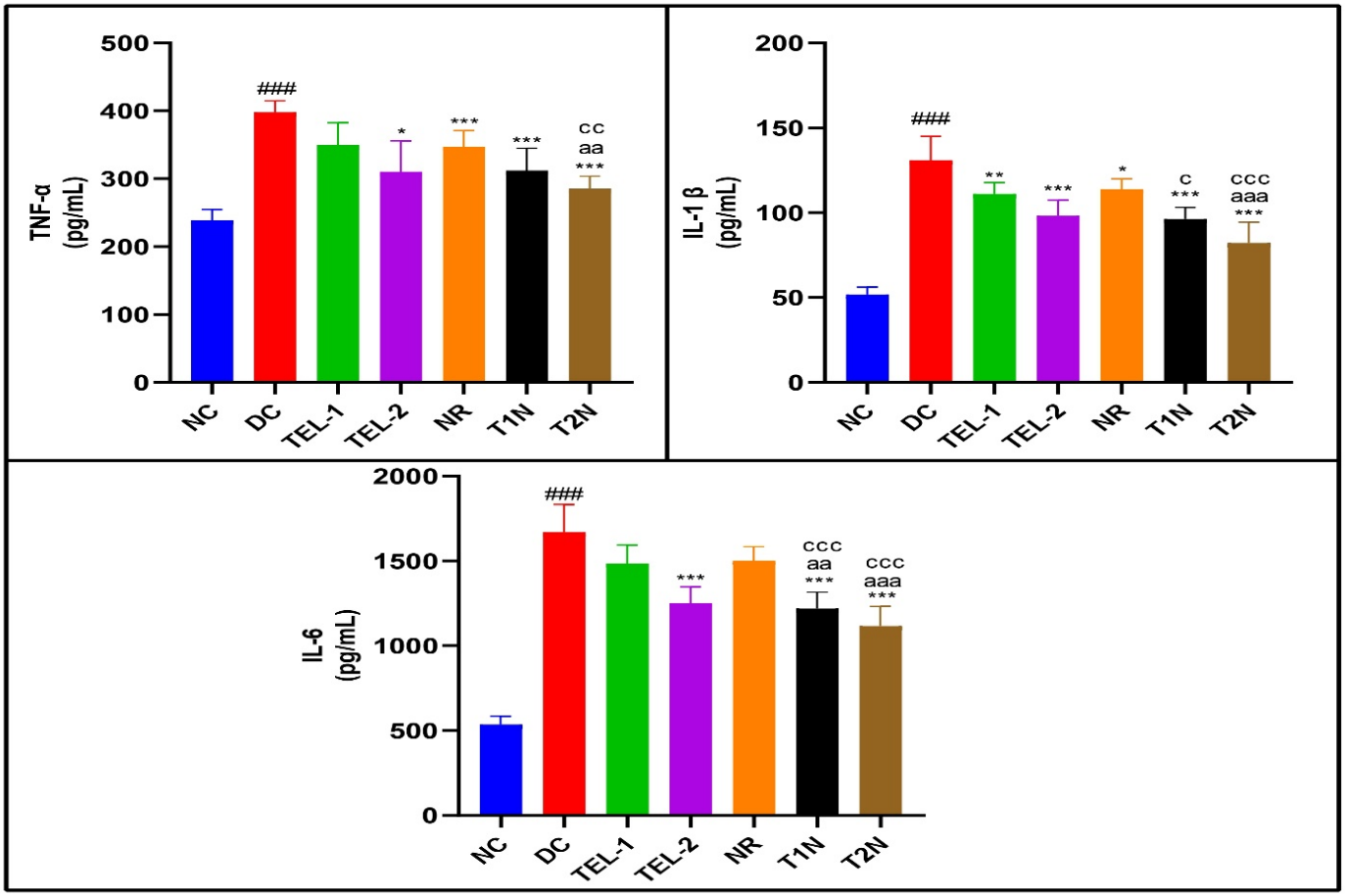


Figure 1: Result of Telmisartan and Naringin on Pro-inflammatory cytokine's in STZ induced diabetes in rats. Data are presented as means±SD (*n*=6/group). One-Way ANNOVA followed by Bonferroni test for multiple comparison. $^{###}p<0.001$when compared to normal control (NC); $^{***}p<0.001$ and $^{*}p<0.05$ when compared to disease control (DC); $^{aaa}p<0.001$ and $^{aa}p<0.01$ compared to TEL1 group; $^{ccc}p<0.001$, $^{cc}p<0.01$ and $^{c}p<0.05$ when compared to NR group.

Renal hypertrophy and histopathology

By the last day of the study, isoflurane was used to euthanize rats. Kidneys, then were isolated and weighed to calculate kidney-to-BW ratio.

In 10% neutral buffered formalin, one kidney was excised from each animal and was promptly Fixed (NBF) for histopathological examination, while the other kidney served to be reserved for the preparation of tissue homogenate for oxidative stress parameters.[18]

Antioxidant markers from Kidney homogenate

The isolated kidney was sliced into small pieces in chilled 0.25 M sucrose solution and homogenized in 10% w/v tris hydrochloride buffer (10 mM, pH 7.4) and centrifuged. Supernatant was used for analyzing oxidative stress biomarkers including Lipid Peroxidation (LPO), Glutathione (GSH), Nitric Oxide (NO) levels were assessed using established methods as described in previous publications.[21–23]

Statistical analysis

Statistical analysis included one-way ANOVA followed by the Bonferroni *post hoc* test for intergroup comparisons. Results are presented as mean±SD. A significance level of $p>0.05$ indicated no significant difference, while $p<0.05$ and $p<0.01$ indicated significant and highly significant differences, respectively.

RESULTS

Indicators of Hyperglycemia (levels of Glucose and $HbA1_c$)

Serum analysis for glucose and HbA1c levels reflects the severity of diabetes by displaying substantial differences between the disease control rats and normal rats. The current research study demonstrated that disease control rats indicate poor glycaemic control in contrast to regular control rats. However, the combination treatment of Telmisartan and Naringin resulted in the most pronounced improvement in serum glucose and HbA1c levels in relation to disease control rats (Table 1).

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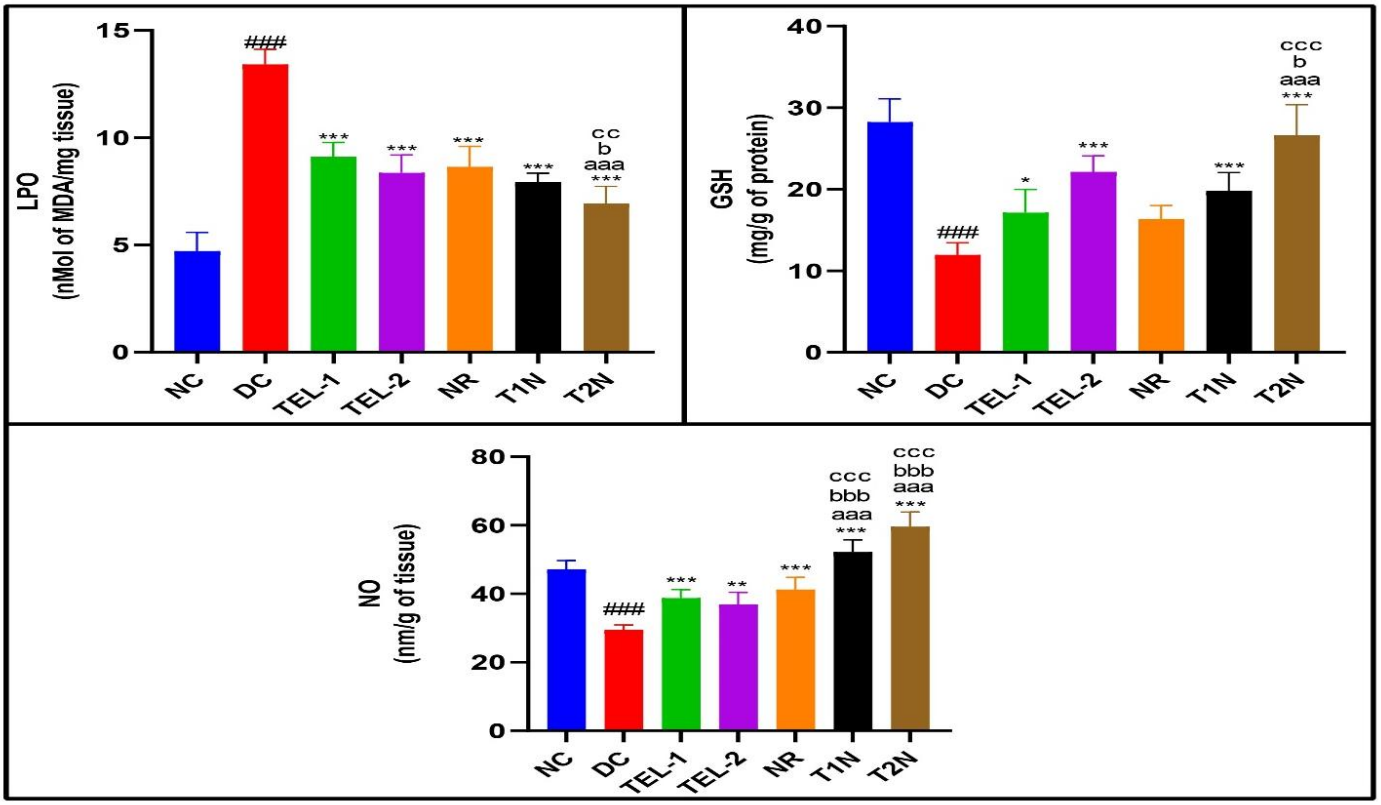


Figure 2: Result of Telmisartan and Naringin on Oxidative stress markers in STZ induced diabetes in rats. Data are presented as means±SD (*n*=6/group). One-Way ANNOVA followed by Bonferroni test for multiple comparison. $^{###}p$<0.001when compared to normal control (NC); $^{***}p$<0.001, $^{**}p$<0.01 and $^{*}p$<0.05 when compared to disease control (DC); ^{aaa}p<0.001 compared to TEL1 group; ^{bbb}p<0.001 and ^{b}p<0.05 when compared to TEL2 group; ^{ccc}p<0.001 and ^{cc}p<0.01 when compared to NR group.

Renal Function Markers (levels of Creatinine, BUN and albumin)

In disease control rats, significant alterations were seen in the concentration of creatinine, BUN and albumin, indicating impaired renal function. The administration of Telmisartan and Naringin together resulted in a marked attenuation of serum renal parameters, with significant decreases in creatinine and BUN levels, suggesting improved kidney filtration. Additionally, albumin levels were restored towards normal, indicating reduced proteinuria in the combination group.

Telmisartan and Naringin also demonstrated significant efficacy in maintaining the balance of sodium and potassium in disease control rats. Both agents individually helped regulate serum levels of these essential ions, preventing the electrolyte imbalance commonly associated with diabetic nephropathy (Table 2). Notably, the combination treatment of Telmisartan and Naringin exhibited the most pronounced effect, more effectively restoring sodium and potassium homeostasis than either agent alone. This synergistic interaction suggests an enhanced capacity of the combination therapy to stabilize ion imbalances, indicating improved kidney function.

Table 1: Effect of Telmisartan and Naringin on serum glucose and HbA1c in STZ induced diabetes in rats.

Group	Glucose (mg/dL)	HbA1c (%)
NC	105.60±6.31	5.56±0.65
DC	394.2±7.20$^{###}$	10.74±0.90$^{###}$
TEL-1	199.80±4.626***	9.25±0.93*
TEL-2	188.9±4.637***	8.747±0.69**
NR	200.4±8.18***	9.01±0.84**
T1N	114.10±5.98***, aaa, bbb, ccc	7.53±0.60***, aa, c
T2N	109.00±6.72***, aaa, bbb, ccc	6.42±0.82***, aaa, bbb, ccc

Data are presented as means±SD (*n*=6/group). One-Way ANNOVA followed by Bonferroni test for multiple comparison. $^{###}p$<0.001when compared to normal control (NC); $^{***}p$<0.001, $^{**}p$<0.01 and $^{*}p$<0.05 when compared to disease control (DC); ^{aaa}p<0.001 and ^{aa}p<0.01 compared to TEL1 group; ^{bbb} p<0.001 when compared to TEL2 group; ^{ccc}p<0.001 and ^{c}p<0.05 when compared to NR group.

Indicators of Inflammations (levels of CRP, TNF-α, IL-1β and Il-6)

In disease control rats, elevated levels of pro-inflammatory cytokines and CRP confirmed the inflammation associated with diabetic nephropathy. Both Telmisartan and Naringin effectively attenuated these inflammatory markers compared to normal

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Table 2: Effect of Telmisartan and Naringin on Renal function markers in STZ induced diabetes in rats.

Group	Albumin (mg/dL)	Creatinine (mg/dL)	BUN (mg/dL)
NC	4.89±0.65	0.59±0.05	24.41±7.90
DC	1.963±0.68$^{###}$	1.818±0.07$^{###}$	90. 74±9.05$^{###}$
TEL-1	3.52±0.46**	1.19±0.04***	44.47±3.77***
TEL-2	3.963±0.74***	1.142±0.07***	41.42±5.28***
NR	3.803±0.47***	1.207±0.08***	45.88±4.86***
T1N	4.23±0.54***	0.99±0.04$^{***, aa, bb, ccc}$	36.49±6.60***
T2N	4.51±0.80***	0.80±0.09$^{***, aaa, bbb, ccc}$	32.26±4.13$^{***, a, cc}$

Data are presented as means±SD (*n*=6/group). One-Way ANNOVA followed by Bonferroni test for multiple comparison. $^{###}p$<0.001when compared to normal control (NC); $^{***}p$<0.001 and $^{**}p$<0.01 when compared to disease control (DC); ^{aaa}p<0.001, ^{aa}p<0.01 and ^{a}p<0.05 compared to TEL1 group; ^{bbb}p<0.001 and ^{bb}p<0.01 when compared to TEL2 group; ^{ccc}p<0.001 and ^{cc}p<0.01 when compared to NR group.

Table 3: Outcome of Telmisartan and Naringin on lipid profile in STZ induced diabetes in rats.

Group	Cholesterol mg/dL	HDL-c (mg/dL)	LDL-c (mg/dL)	Triglyceride (mg/dL)
NC	69.79±7.45	33.47±2.31	69.33±4.748	79.02±7.57
DC	124.40±4.80$^{###}$	23.19±1.78$^{###}$	225.8±6.281$^{###}$	191.1±8.33$^{###}$
TEL-1	114.50±6.56	27.14±1.49**	107.2±3.68***	123.40±5.67***
TEL-2	112.00±4.55*	28.87±1.69***	105.1±5.727***	115.5±8.22***
NR	115.90±5.78	30.59±1.59***	113±4.302***	120.1±7.68***
T1N	93.13±7.28$^{***, aaa, bbb, ccc}$	31.13±1.47$^{***, aa}$	88.41±6.116$^{***, aaa, bbb, ccc}$	96.06±7.30$^{***, aaa, b, ccc}$
T2N	89.33±6.10$^{***, aaa, bbb, ccc}$	32.55±2.44$^{***, aaa, bb}$	81.94±5.054$^{***, aaa, bbb, ccc}$	93.46±8.80$^{***, aaa, bb, ccc}$

Data are presented as means±SD (*n*=6/group). One-Way ANNOVA followed by Bonferroni test for multiple comparison. $^{###}p$<0.001when compared to Normal Control (NC); $^{***}p$<0.001, $^{**}p$<0.01 and $^{*}p$<0.05when compared to disease control (DC); ^{aaa}p<0.001 and ^{aa}p<0.01 compared to TEL1 group; ^{bbb}p<0.001, ^{bb}p<0.01 and ^{b}p<0.05 when compared to TEL2 group; ^{ccc}p<0.001 when compared to NR group.

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control rats. When used together, Telmisartan and Naringin reduced inflammatory markers more significantly than either treatment alone or the disease control group (Figure 1).

Serum Lipid Levels (levels of Total Cholesterol, LDL, HDL and triglyceride)

The analysis of lipid profile markers showed a notable rise in total cholesterol, LDL and TG, alongside HDL level were reduced in disease-treated rats in comparison to normal control rats, indicating impaired lipid metabolism. The combination treatment groups significantly normalized LDL, HDL, total cholesterol, and TG levels in relation to disease control rats (Table 3).

Oxidative Stress Indicators (Levels of LPO, NO, GSH)

Disease control rats demonstrated a considerable rise in lipid peroxidation levels alongside a marked decrease in glutathione and nitric oxide levels, indicating severe oxidative stress in renal tissues. Treatment with Telmisartan (both low and high doses) and Naringin resulted in a notable reduction in LPO levels and rise in GSH and NO levels in renal tissues of diabetic rats. The combined therapy of telmisartan with naringenin exhibited even more profound reductions in LPO and greater elevations in GSH and NO levels, suggesting a synergistic potential in mitigating oxidative stress in renal tissues (Figure 2).

Renal hypertrophy and Body weight

The disease control group displayed marked elevations in renal weight and renal hypertrophy index relative to the normal control group, signifying the onset of diabetes-induced renal hypertrophy. Administration of Telmisartan and Naringin resulted in significant reductions in renal weight and hypertrophy index compared to the DC group, underscoring their potential to attenuate diabetic renal hypertrophy. The combination treatment rats produced even more substantial decreases in these parameters than monotherapy.

The study also evaluated the impact of different treatments on diabetes-induced weight loss. The diabetic control group experienced significant weight reduction, emphasizing severe diabetes. While Telmisartan and Naringin individually improved weight loss, they did not fully restore initial weight. However, the combination of Telmisartan with a high dose of Naringin showed enhanced efficacy, demonstrating the most pronounced improvement in weight loss, surpassing individual treatments.

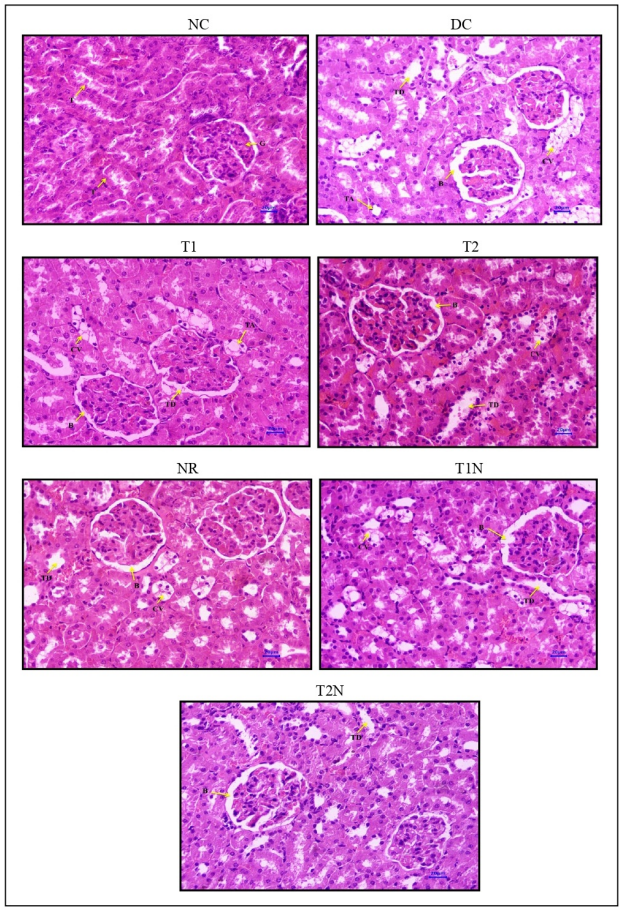


Figure 3: Histopathology. NC- Normal control; DC- Disease control; TEL-1-Telmisartan 5mg/kg; TEL-2-Telmisartan 10mg/kg; NR-Naringin 50mg\kg; T1N-Telmisartan+Naringin 5 mg/kg+50 mg/kg; T2N-Telmisartan+ Naringin 10 mg/kg+50 mg/kg.

These findings suggest that combined treatments, of telmisartan with naringenin may offer an effective strategy for managing diabetes-induced weight loss.

Histopathological analysis

Analysing kidney tissues under a microscope didn't show any lesions of pathological importance. Rats in the other groups, however, showed a variety of pathological alterations in their renal tissues, such as cytoplasmic vesiculation, tubular dilatation, tubular atrophy, and dilatation of Bowman's gap. The disease control group, in particular, exhibited significant nephropathic lesions. Treatment groups showed a reduction in these lesions, with less severity and distribution with respect to the disease control group. Among the treated groups, the higher dose combination (T2N) demonstrated the greatest efficacy, showing minimal nephropathic lesions (Figure 3).

DISCUSSION

In present investigation, diabetes was induced by single intraperitoneal dose of Streptozotocin (STZ) in wistar rats. STZ, a glucose analog, is absorbed by pancreatic beta cells via GLUT2 and decomposes into methyl diazonium ion, inducing oxidative stress and apoptosis.[24] This results in reduced insulin secretion, beta-cell death and chronic hyperglycemia, closely resembling diabetes mellitus, making STZ a common agent for experimental diabetes induction.[25]

HbA1c levels in the diabetic control group were elevated, reflecting persistent hyperglycemia and inadequate glycemic control hallmarks of diabetes.[26] Elevated HbA1c is also a key marker linked with the progression of diabetic complications.

PPARγ is a key regulatory protein in lipogenesis that enhances adipocyte differentiation, enhances sensitivity of insulin, and lowers blood glucose levels.[27] Telmisartan's glucose-lowering effect can be attributed to its partial agonism of PPARγ and its capacity to suppress Reactive Oxygen Species (ROS).[11] Naringin has been shown to increase the expression of PPARγ, which may contribute to its potential to reduce hyperglycemia and restore HbA1c levels in combination treated rats.[28] Naringin exhibited antihyperglycemic effects by regulating major enzymes involved in carbohydrate metabolism, enhancing insulin sensitivity, and promoting beta-cell activity.[29]

In diabetic control rats, high levels of triglycerides, total cholesterol and Low-Density Lipoprotein (LDL), coupled with decreased High-Density Lipoprotein (HDL), were observed.[30] These lipid abnormalities are significant contributors to the development and progression of Diabetic Nephropathy (DN). Telmisartan's triggering of PPAR-γ partially improved lipid metabolism, [11] while naringin targeted inflammatory markers, such as Tumor Necrosis Factor-Alpha (TNF-α) and Nuclear Factor-kappa B (NF-κB), both of which regulate lipid metabolism.[31]

A assessment of renal function was conducted by measuring serum creatinine level, an indicator of Glomerular Filtration Rate (GFR),[32] and albumin, a reliable marker for Diabetic Nephropathy (DN).[33] Blood Urea Nitrogen (BUN) levels were also monitored, as BUN is a byproduct of protein metabolism, primarily excreted by the kidneys. Abnormal levels of albumin, creatinine and BUN indicates development of diabetic nephropathy. The combined administration of telmisartan and naringin demonstrated a protective effect on kidney function, as evidenced by improved restoration in creatinine, albumin, and BUN levels in rats. Telmisartan provides Reno protective effect by ameliorating kidney hypertrophy and glomerular damage, as evidenced by decreased urinary albumin excretion and improved creatinine clearance.[34] Naringin might have inhibited the ERK1/2 and JNK MAPK signaling pathways, which are associated in renal fibrosis. This action reduces the protein expression of fibronectin and intercellular adhesion molecules, further protecting renal function.[35]

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Chronic inflammation, mediated by these cytokines, plays a crucial role in the development of Diabetic Kidney Disease (DKD). The study evaluated inflammatory markers, including C-Reactive Protein (CRP), TNF-α, interleukin-1 beta (IL-1β), and interleukin-6 (IL-6). Telmisartan and naringin together suppressed pro-inflammatory cytokine production by targeting NF-κB and MAPK pathways, thereby reducing renal inflammation and protecting against progressive kidney damage.[36,37]

Oxidative stress, a major contributor to diabetic complications, including diabetic nephropathy. Glutathione (GSH), a critical non-enzymatic antioxidant, It's vital for sustaining the cellular redox equilibrium and neutralizing reactive oxygen species.[38] Both telmisartan and naringin demonstrated the ability to restore GSH levels, thereby reducing oxidative stress and preventing further damage. Telmisartan inhibited NADPH oxidase 4 (NOX4) and regulated mitochondrial oxidative phosphorylation, leading to improved mitochondrial function.[39] Meanwhile, naringin upregulated PPARα and AMPK,[40] further contributing to oxidative stress reduction. Additionally, naringin may have activated HO-1 and Nrf2 pathways,[41] reducing Lipid Peroxidation (LPO) levels, while also improving endothelial function and lowering oxidative stress by downregulating NADPH oxidase and LOX-1.[42] Collectively, these mechanisms may be accountable for restoring lipid peroxidation in diabetic rats.

The critical role of potassium and sodium ions in managing renal diseases has been highlighted in various studies. Imbalances in these electrolytes are closely linked to the development of kidney damage and complications in conditions such as diabetic nephropathy. Telmisartan and naringin helped maintain electrolyte balance by reducing oxidative stress and by inflammation of renal tissues (Figure 4).[43,44]

Overall, combined administration of telmisartan and naringin not only ameliorated hyperglycemia but also provided multifaceted protection against diabetic nephropathy, particularly through their anti-inflammatory, antioxidant, and renoprotective mechanisms. This research suggests that the integration of telmisartan and naringin might be a promising therapeutic approach for the management of diabetic nephropathy.

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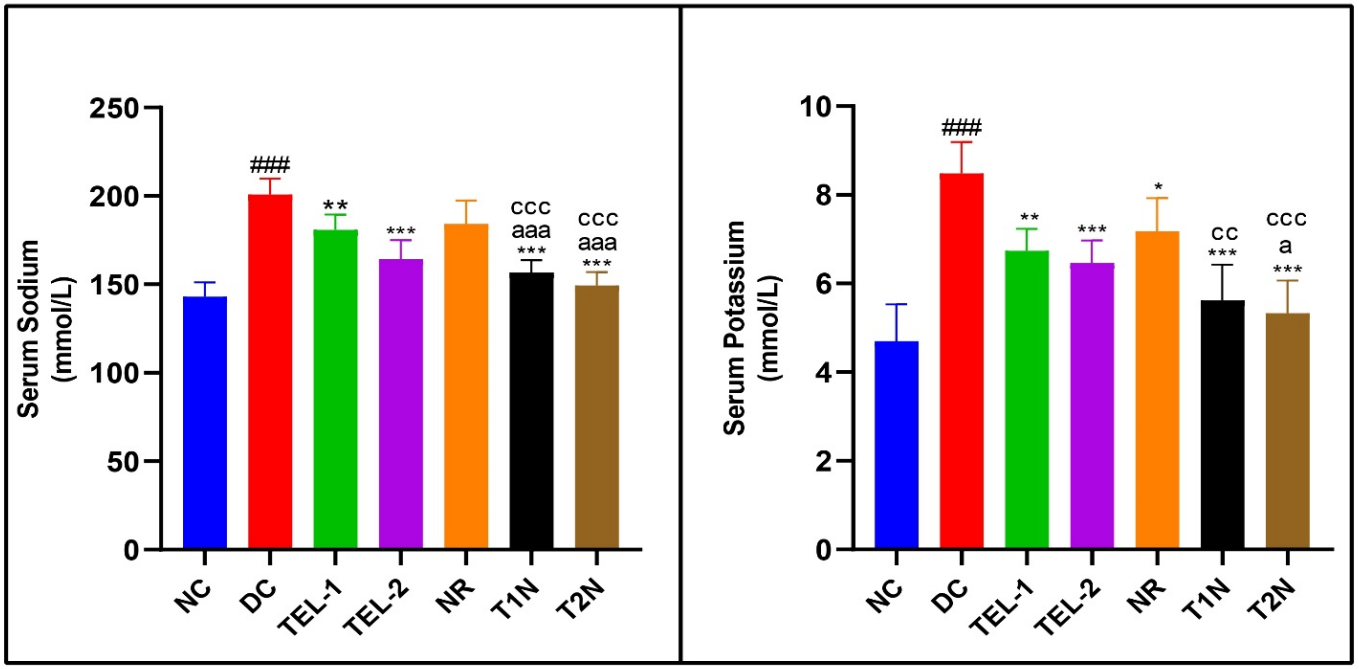


Figure 4: Outcome of Telmisartan and Naringin on Serum Ion level in STZ induced diabetes in rats. Data are presented as means±SD (*n*=6/group). One-Way ANNOVA followed by Bonferroni test for multiple comparison. $^{###}p<0.001$when compared to normal control (NC); $^{***}p<0.001$ and $^{**}p<0.01$ when compared to disease control (DC); $^{aaa}p<0.001$ and $^{a}p<0.05$ compared to TEL1 group; $^{ccc}p<0.001$ and $^{cc}p<0.01$ when compared to NR group.

CONCLUSION

Present study highlights the potential of Telmisartan and Naringin combination therapy in mitigating diabetic complications, particularly nephropathy, in STZ-induced diabetic rats. The combination demonstrated superior glycaemic control, improved renal function, and reduced inflammation and oxidative stress. Histopathological analysis further confirmed reduced nephropathic lesions, especially at higher doses. In the treatment of diabetic nephropathy, this combination therapy could offer a promising strategy for managing it. However, further clinical studies are essential to evaluate its safety, efficacy, of combination in humans for treatment of diabetic nephropathy.

ACKNOWLEDGMENT

Nil.

ABBREVIATIONS

AMPK: AMP-Activated Protein Kinase; **BUN:** Blood Urea Nitrogen; **BW:** Body Weight; **CRP:** C - reactive protein; **DN:** Diabetic Nephropathy; **DKD:** Diabetic Kidney Disease; **ERK1/2:** Extracellular Signal-Regulated Kinase ½; **GFR:** Glomerular Filtration Rate; **GSH:** Glutathione; **HbA1c:** Haemoglobin A1c; **HDL:** High-Density Lipoprotein; **HO-1:** Heme Oxygenase-1; **IL-1β:** Interleukin-1 Beta; **IL-6**: Interleukin-6; **JNK:** c-Jun N-terminal kinase; **K⁺:** Potassium; **LDL:** Low-Density Lipoprotein; **LOX-1:** Lectin-like Oxidized Low-Density Lipoprotein Receptor 1; **LPO:** Lipid Peroxidation; **MAPK:** Mitogen-Activated Protein Kinase; **Na⁺:** Sodium; **Na CMC**: Sodium Carboxymethyl Cellulose; **NADPH:** Nicotinamide Adenine Dinucleotide Phosphate; **NOX4:** NADPH Oxidase 4; **NBF:** Neutral Buffered Formalin; **NF-κB:** Nuclear Factor Kappa B; **NO:** Nitric Oxide; **Nrf2:** Nuclear Factor Erythroid 2–Related Factor 2; **PPARα:** Peroxisome Proliferator-Activated Receptor Alpha; **PPARγ:** Peroxisome Proliferator-Activated Receptor Gamma; **ROS:** Reactive Oxygen Species; **SD:** Standard Deviation; **STZ:** Streptozotocin; **TG:** Triglycerides; **TNF-α:** Tumor Necrosis Factor Alpha.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

The present research work is not financially supported by any funding agency.

ETHICAL APPROVAL

All animal handlings and experiments were approved by the Institutional Animal Ethical Committee (IAEC) of KBHSS Trust's Institute of Pharmacy, Malegaon, Nashik, During IAEC meeting held on 09/11/2023 with approval no. KBH/IAEC/2023/12-03

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SUMMARY

An angiotensin II receptor blocker with partial PPAR-gamma agonist properties, telmisartan and naringin, a flavonoid known for its antioxidant effects, have demonstrated potential in mitigating diabetes-related complications. This study was directed to evaluate the combined effects of Telmisartan and Naringin on various parameters like hyperglycemia, inflammation, and ROS, focusing on their impact on kidney function, lipid metabolism, and renal health using a Streptozocin (STZ)-induced diabetic model in Wistar rat. The combined therapy produced significantly better outcomes than either treatment alone, notably improving glycemic control, renal function, and markers of inflammation and oxidative stress. Furthermore, histopathological findings indicated a marked reduction in the severity and extent of nephropathic lesions, particularly at higher doses of the combination treatment. The above findings indicate the potential of Telmisartan and Naringin as a synergistic therapeutic approach for addressing diabetes complications, though further studies are needed to confirm their effectuality and clinical applications.

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