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Synergistic Effects of Resveratrol and Naringin in Ameliorating Diabetic Nephropathy: Targeting Hyperglycemia, Dyslipidemia, Oxidative Stress, and Inflammation in wistar rats

Prashant V Tapadiya[1*], Kuldeep S Patel[2]

[1]Research Scholar, Department of Pharmacology, Sunrise University, Ramgarh, Dist. Alwar, Rajasthan, India.

[2]Professor, Department of Pharmacology, Sunrise University, Ramgarh, Dist. Alwar, Rajasthan, India.

Address for Correspondence:

Prashant V.Tapadiya,
Research Scholar,
Department of pharmacology,
Sunrise University, Alwar, Rajasthan.
Email:prash4u1135@gmail.com

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ABSTRACT

Diabetic nephropathy (DN) is a serious complication of diabetes mellitus characterized by renal dysfunction and structural abnormalities. This study induced diabetes in rats using streptozotocin (STZ) and explored the therapeutic effects of resveratrol and naringin, natural compounds known for their antioxidant and anti-inflammatory properties. The combination treatment of resveratrol and naringin significantly lowered serum glucose levels compared to diabetic controls. Resveratrol demonstrated renal protective effects by reducing inflammation and oxidative stress, while naringin enhanced insulin sensitivity and shielded beta cells from oxidative damage. Resveratrol and naringin also mitigated dyslipidemia, a common issue in diabetic nephropathy, by adjusting lipid metabolism markers. Markers of renal function, including serum creatinine, albumin, total protein, and blood urea nitrogen (BUN), were examined to assess treatment effectiveness. Resveratrol decreased urinary total protein levels, alleviated albuminuria, and enhanced renal function markers. Naringin contributed protective effects through antioxidant mechanisms and modulation of renal injury biomarkers. Both compounds exhibited potent antioxidant activities by increasing glutathione (GSH) levels and decreasing lipid peroxidation. They additionally suppressed inflammatory cytokines such as TNF-α and IL-6, thereby reducing inflammation and preserving renal function. In conclusion, the combined therapy of resveratrol and naringin synergistically improved diabetic nephropathy by targeting multiple pathways involved in hyperglycemia, dyslipidemia, oxidative stress, and inflammation. These findings highlight the therapeutic potential of resveratrol and naringin in managing diabetic complications, emphasizing their comprehensive approach to preserving renal function.

Keywords: diabetic nephropathy, resveratrol, naringin, oxidative stress, inflammation, renal function, etc.

INTRODUCTION

The prevalence of diabetes continues to grow worldwide, posing a significant public health challenge. In 2003, an estimated 194 million people aged 20 to 79 had diabetes, and this number is projected to rise to 333 million by 2025 (Dinneen et al., 2007). Notably, while North America and Europe currently house the bulk of the world's diabetic population, it is anticipated that by 2025, South East Asia will have more diabetics than any other region. Over the last three decades, the global diabetes prevalence has surged dramatically. In 2021, approximately 537 million adults were affected, with projections indicating an escalation to 643 million by 2030 and a staggering 783 million by 2045 [1].

Managing diabetes and its complications remains a significant challenge. Monotherapy with oral hypoglycemic agents is often insufficient to manage diabetic complications, as glycemic control alone does not provide adequate protection against the diverse mechanisms involved [2,3]. Consequently, combination therapy is being investigated as a means of successfully managing diabetes, with several combinations currently available on the market, such as pioglitazone plus metformin, rosiglitazone plus metformin, and rosiglitazone plus Glibenclamide. These combinations primarily aim to achieve better control of hyperglycemia. However, it is necessary to develop pharmaceuticals that can significantly improve outcomes by targeting different mechanisms of action [4,5].

Resveratrol (RSV), is a naturally occurring polyphenolic compound found in various foods and beverages, including red wine. Due to its potential therapeutic benefits in diabetic heart failure and kidney protection, RSV has garnered increased interest in diabetic nephropathy (DN)-related research. Studies have shown that RSV can reduce oxidative stress in rats with type 2 diabetes by increasing superoxide dismutase activity [6]. RSV's properties include antioxidative, anti-inflammatory, cardioprotective, neuroprotective, antihypertensive, and blood glucose-lowering effects [7].

Naringin, known for its antioxidant properties, serves as a protective agent against nephrotoxicity and renal injury by scavenging free radicals and suppressing pro-inflammatory cytokines. Naringin significantly hinders the proliferation of high glucose-induced rat mesangial cells by downregulating the pyrin domain-containing-3 (NLRP3) inflammasome, which is associated with inflammatory mediators like IL-1β and IL-18 [8]. Additionally, naringin has been shown to mitigate renal damage induced by streptozotocin in DN rats by suppressing the expression of NADPH oxidase 4 (NOX4) [9].

Despite the promising individual effects of resveratrol and naringin, their combination has not yet been explored in the context of diabetes treatment. Therefore, this study aims to evaluate the effect of co-administration of resveratrol with naringin on the development and progression of diabetic nephropathy in streptozocin-induced diabetic rats. This research could potentially lead to a novel combination therapy for managing diabetes and its complications.

MATERIAL AND METHOD

Experimental animals

A total of 36 albino rats of the Wistar strain, weighing between 200-250g, were used in the study. These rats were procured from Lacsmi Breeders, Pune, Maharashtra, India. Approval for the experimental protocols was obtained from the Institutional Animal Ethics Committee of SCITESLA Lab, Bombay (IAEC registration no.1785/PO/Re/S/11/CPCSEA). The rats were housed under standard laboratory conditions with a 12-hour light/dark cycle and were provided with standard pellet diet (Nutrivet Life Sciences, Pune, India) and tap water ad libitum for 45 days.

Induction of diabetes

Diabetes was induced in the rats using a single intraperitoneal injection of streptozotocin (STZ) at a dose of `45mg/kg body weight, freshly prepared in citrate buffer (pH 4.5). After 72 hours, diabetes was confirmed by measuring fasting blood glucose levels. Rats with blood glucose levels greater than 250 mg/dL were considered diabetic and included in the study.

Experimental design

The rats were assigned to six groups, each consisting of six rats, and treated from day 1 to day 45. All treatments were administered orally using drugs dissolved in 1% Na CMC. NC: Non-diabetic control rats receiving 1% Na CMC, DC: Diabetic control rats receiving 1% Na CMC, MET: Diabetic rats receiving Metformin (250 mg/kg), NAR: Diabetic rats receiving Naringin (50 mg/kg), RES: Diabetic rats receiving Resveratrol (5 mg/kg), RN: Diabetic rats receiving a combination of Naringin (50 mg/kg) and Resveratrol (5 mg/kg).

Biochemical analysis

At the end of the treatment period, the rats were fasted overnight and then anesthetized. Blood samples were collected via retro-orbital puncture for biochemical analysis. Serum was separated by centrifugation and used for the determination of various biochemical parameters, including fasting blood glucose, serum creatinine, and blood urea nitrogen (BUN) etc.

Estimation of antioxidants and cytokines from kidney homogenate

The kidneys were excised and homogenized in phosphate buffer (pH 7.4). The homogenate was centrifuged at 10,000 g for 15 minutes at 4°C to obtain the supernatant, which was used for further analysis. The GSH levels were estimated using the method described by Moron et al. [8]. LPO levels were determined by measuring the formation of thiobarbituric acid reactive substances (TBARS) according to the method described by Slater and Sawyer. The supernatant was also used for the estimation of cytokines IL-1β, IIL-6, and Tumor Necrosis Factor-α TNF-α. These cytokines were measured using commercially available ELISA kits as per the manufacturer's protocol.

Statistical analysis

Data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using One way ANOVA followed by Bonferroni’s test for multiple comparisons.

RESULTS

Effect of the combination of naringin and resveratrol on blood glucose and lipid profile

The combination therapy of Naringin and Resveratrol significantly improved blood glucose levels in diabetic rats. Compared to the diabetic control group, as well as individual treatment groups the combination treatment resulted in a marked reduction in blood glucose levels, demonstrating a synergistic hypoglycemic effect. Additionally, the lipid profile of the rats treated with the combination of Naringin and Resveratrol showed substantial improvement. There was a significant decrease in total cholesterol, triglycerides, and low-density lipoprotein (LDL) levels, along with an increase in high-density lipoprotein (HDL) levels. These changes indicate that the combination therapy not only aids in blood glucose regulation but also exerts a positive influence on lipid metabolism, thereby potentially reducing the risk of cardiovascular complications associated with diabetes (Table No: 1).

Table No: 1 Effect of Naringin and reservetrol alone and in combination on serum glucose and lipid profilein STZ induced diabetes in rats.

Groups	Serum glucose	Serum Triglyceride	Serum total cholesterol	Serum HDL-cholesterol	Serum LDL-cholesterol
NC	112.4 ± 3.32	81.12± 2.32	152.3 ± 3.35	63.99 ± 2.18	58.47 ± 6.90
DC	384.1 ± 5.61$^{###}$	162.3 ± 3.43$^{###}$	236.1 ± 3.12$^{###}$	42.71 ± 2.24$^{###}$	99.45 ± 5.17$^{###}$
MET	144.2 ± 4.57***	98.22± 4.13***	165.3 ± 2.25***	59.24 ± 1.42***	65.11 ± 3.22***
NR	152.4 ± 4.57***	96.13± 2.19***	173.12 ± 5.22***	57.78 ± 1.23***	72.32 ± 2.21***
RES	135.5 ± 3.21***	90.10± 2.14***	163.1 ± 5.22***	58.02 ± 1.51***	69.35 ± 5.33***
RN	114.2 ± 3.42^{***,aaa,} ^{bbb}	82.34± 3.23$^{***,aa,\ bbb}$	151.2 ± 4.11***$^{,aaa,\ bbb}$	62.73 ± 2.19$^{***,a,\ bb}$	59.44 ± 2.57^{***,aaa,bbb}

Na CMC- Sodium Carboxyl Methyl Cellulose, NC- Normal control, DC-Diabetic Control, MET- Metformin, NAR - Naringin, RES – Resveratrol, RN -. Resveratrol and Naringin
Results are presented as means ± SD (n=6). One way ANOVA followed by Bonferroni's test for multiple comparison:$^{###}$p<0.001when compared to normal control (NC); ***p<0.001 when compared to diabetic control (DC); ^{aaa}p<0.001 when compared to NR; ^{bbb}p<0.001 when compared to RES group.

Table No: 2 Effect of Naringin and reservetrol alone and in combination on serum albumin, creatinine, and total protein and BUN levels in STZ induced diabetes in rats.

Group	Albumin (mg/dl)	BUN (mg/dl)	Total Protein (mg/dl)	Serum Creatinine (mg/dl)
NC	5.85± 1.77	34.91 ± 3.25	8.79 ± 1.16	0.59 ± 0.04
DC	2.97 ± 0.78$^{###}$	94.42 ± 4.24$^{###}$	3.84 ± 0.97$^{###}$	1.95 ± 0.02$^{###}$
MET	5.67± 0.64***	45.76 ± 4.55***	6.47 ± 0.44***	0.93 ± 0.01***

NR	5.78± 0.23***	44.12 ± 5.23***	6.12 ± 0.40***	0.98 ± 0.03***
RES	4.41± 0.35***	36.87 ± 5.52***	6.77 ± 0.40***	0.87 ± 0.03**
RN	5.34 ± 0.43$^{***,a, b}$	31.35 ± 4.09$^{***, aaa, bbb}$	7.79 ± 0.89$^{***, a, b}$	0.77 ± 0.03$^{***, aaa, bbb}$

Na CMC- Sodium Carboxyl Methyl Cellulose, NC- Normal control, DC-Diabetic Control, MET- Metformin, NAR - Naringin, RES – Resveratrol, RN -. Resveratrol and Naringin. Results are presented as means ± SD (n=6). One way ANOVA followed by Bonferroni's test for multiple comparison: $^{###}p<0.001$when compared to normal control (NC); $^{***}p<0.001$ when compared to diabetic control (DC); $^{aaa}p<0.001$ when compared to NR; $^{bbb}p<0.001$ when compared to RES group.

Naringin and Resveratrol, whether administered individually or in combination, significantly restored serum levels of total protein, creatinine, albumin, and blood urea nitrogen compared to the diabetic control group. The combination of Naringin and Resveratrol resulted in even greater restoration of these levels compared to the groups treated with each compound alone(Table No: 2).

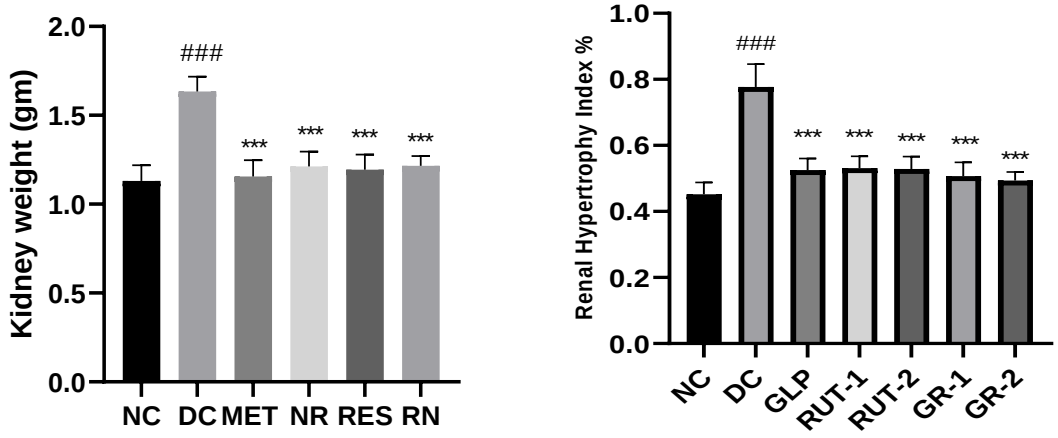
Effect of the Combination of Naringin and Resveratrol on body weight and renal hypertrophy

Diabetic rats exhibited a significant reduction in body weight and an increase in renal hypertrophy, characterized by an increase in kidney size and weight, compared to the non-diabetic control group over the 45-day period.

Treatment with Naringin (Group IV), Resveratrol (Group V), and their combination (Group VI) mitigated the weight loss observed in diabetic rats. Notably, the combination therapy (Group VI) resulted in the most pronounced improvement, with treated rats showing significant weight gain compared to the diabetic control group as well as individual treated groups. This suggests a synergistic effect of Naringin and Resveratrol in preserving body weight in diabetic rats.

Similarly, all treatment groups (Groups III to VI) showed a significant reduction in renal hypertrophy compared to the diabetic control group (Group II). Among these, the combination of Naringin and Resveratrol (Group VI) was the most effective in reducing kidney weight and size, as compared to individual treated groups indicating a potential protective effect against diabetes-induced renal hypertrophy(Figure No: 1).

Figure No: 1 Effect of the Combination of Naringin and Resveratrol on body weight and renal hypertrophy

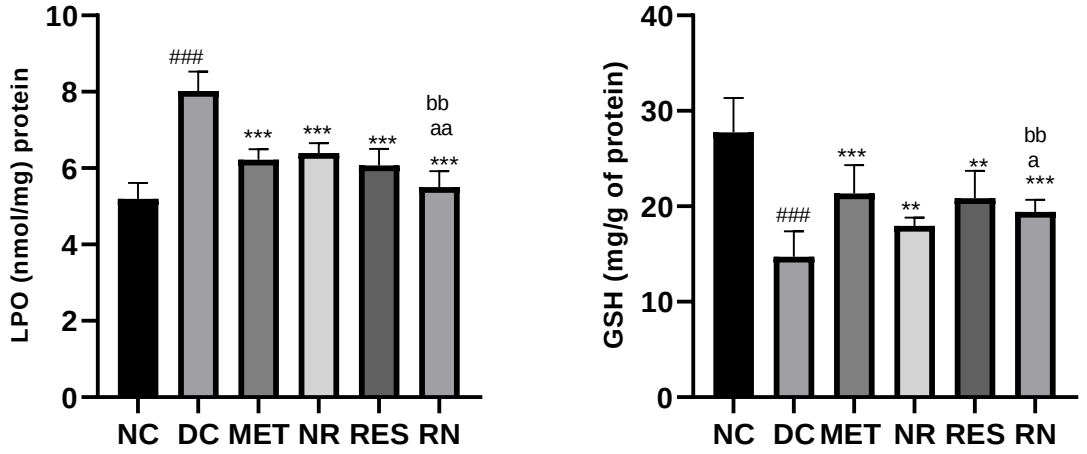


Na CMC- Sodium Carboxyl Methyl Cellulose, NC- Normal control, DC-Diabetic Control, MET- Metformin, NAR - Naringin, RES – Resveratrol, RN -. Resveratrol and Naringin. Results are presented as means ± SD (n=6). One way ANOVA followed by Bonferroni's test for multiple comparison: $^{###}p<0.001$when compared to normal control (NC); $^{***}p<0.001$ when compared to diabetic control (DC); $^{aaa}p<0.001$ when compared to NR; $^{bbb}p<0.001$ when compared to RES group.

Effect of co-administration of Naringin and reservetrol on GSH and LPO levels.

Naringin and Resveratrol, when administered individually or in combination, significantly increased GSH levels and decreased LPO levels in kidney homogenates compared to the diabetic control group. The combination of Naringin and Resveratrol resulted in even greater increases in GSH levels and reductions in LPO levels compared to the groups treated with each compound alone (Figure No: 2).

Figure No: 2 Effect of co-administration of Naringin and reservetrol on GSH and LPO levels.



Na CMC- Sodium Carboxyl Methyl Cellulose, NC- Normal control, DC-Diabetic Control, MET- Metformin, NAR - Naringin, RES – Resveratrol, RN -. Resveratrol and Naringin.

Results are presented as means ± SD (n=6). One way ANOVA followed by Bonferroni's's test for multiple comparison: $^{###}p<0.001$when compared to normal control (NC); $^{***}p<0.001$ when compared to diabetic control (DC); $^{aaa}p<0.001$ when compared to NR; $^{bbb}p<0.001$ when compared to RES group.

Table No: 3 Effect of Naringin and reservetrol alone and in combination on cytokines levels in STZ induced diabetes in rats.

Group	IL-6 level (pg/mL)	IL-1β level (pg/mL)	TNF-α level (pg/mL)
NC	57.48 ± 6.36	65.12 ± 6.67	244.7 ± 11.21
DC	134.6 ± 10.43$^{###}$	132.6 ± 7.32$^{###}$	404.5 ± 11.13$^{###}$
MET	102.34 ± 5.57***	103.56 ± 9.13***	312.7 ± 12.76***
NR	99.23 ± 7.33***	108.43 ± 10.29***	309.4 ± 11.23***
RES	91.35 ± 10.17***	97.12 ± 6.81***	313.4 ± 9.35***
RN	79.73 ± 4.08***, aa, bbb	89.43 ± 6.45***, a, bb	290.6 ± 11.43***, a, bbb

Na CMC- Sodium Carboxyl Methyl Cellulose, NC- Normal control, DC-Diabetic Control, MET- Metformin, NAR - Naringin, RES – Resveratrol, RN -. Resveratrol and Naringin. Results are presented as means ± SD (n=6). One way ANOVA followed by Bonferroni's test for multiple comparison: $^{###}p<0.001$when compared to normal control (NC); $^{***}p<0.001$ when compared to diabetic control (DC); $^{aaa}p<0.001$ when compared to NR; $^{bbb}p<0.001$ when compared to RES group.

Both Naringin and Resveratrol, when administered individually or in combination, significantly decreased pro-inflammatory cytokine levels compared to the diabetic control group. The combination of Naringin and Resveratrol resulted in an even greater reduction in levels compared to the groups treated with each compound alone (Table No: 3).

DISCUSSION

Diabetes was induced in rats using streptozotocin (STZ), which selectively targets pancreatic beta cells due to its structural similarity to glucose. STZ enters beta cells via GLUT2 transporters and induces DNA alkylation, leading to oxidative stress, beta cell apoptosis, and ultimately, hyperglycemia [11].

The combination therapy of resveratrol and naringin significantly reduced serum glucose levels compared to diabetic controls. Resveratrol improves renal function by reducing inflammation and oxidative stress [12], while naringin enhances insulin sensitivity and protects beta cells from oxidative stress [13, 14].

Diabetic rats showed elevated levels of total cholesterol, triglycerides, and LDL, with decreased HDL levels. Resveratrol and naringin treatments effectively modulated these lipid markers by reducing synthesis and enhancing metabolism, thereby mitigating renal complications associated with dyslipidemia [8,15].

The study assessed markers such as serum creatinine, albumin, total protein, and blood urea nitrogen (BUN) to evaluate renal function. Resveratrol decreased total protein levels in urine, mitigated albuminuria, and improved renal function markers by reducing oxidative stress and inflammation [16,17]. Naringin's effects on renal function were attributed to its antioxidant properties and modulation of renal injury biomarkers [18].

Both resveratrol and naringin exhibited potent antioxidant activities by increasing glutathione (GSH) levels and reducing lipid peroxidation [19]. They also inhibited inflammatory cytokines such as TNF-α and IL-6, thereby attenuating inflammation and preserving renal function in diabetic nephropathy [20].

Resveratrol activates pathways like SIRT1/AMPK and Nrf2, crucial for antioxidant defense and cellular metabolism regulation [21, 22]. Naringin modulates NF-κB and MAPK pathways to reduce inflammation and oxidative stress, contributing to its protective effects on kidney function [23, 24].

CONCLUSION

The combination therapy of resveratrol and naringin demonstrates synergistic effects in ameliorating diabetic nephropathy by targeting multiple pathways involved in hyperglycemia, dyslipidemia, oxidative stress, and inflammation. These findings suggest their potential as therapeutic agents for managing diabetic complications, emphasizing their holistic approach in preserving renal function.

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