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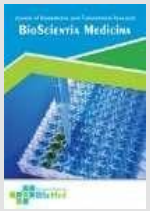

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Adjuvant Resveratrol Reduces Albuminuria and Serum Transforming Growth Factor-β Without Improving Glomerular Filtration Rate in Diabetic Kidney Disease: A 12-Week Randomized Controlled Trial

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A B S T R A C T

Background: Diabetic kidney disease (DKD) progresses through inflammation and fibrosis, with transforming growth factor-β (TGF-β) as the principal profibrotic mediator and albuminuria as a clinical surrogate of glomerular injury. **Methods:** We conducted a 12-week, double-blind, placebo-controlled randomized trial at Dr. Mohammad Hoesin General Hospital, Palembang, between October 2025 and January 2026 to evaluate adjuvant resveratrol on serum TGF-β, urinary albumin-to-creatinine ratio (UACR), and estimated glomerular filtration rate (eGFR). **Results:** Of 61 randomized adults with DKD on standard care, 54 were analyzed (resveratrol n=27 received 25 mg twice daily, derived from Polygonum cuspidatum in 95% lecithin; placebo n=27). Within the resveratrol group, serum TGF-β fell from 123.7 to 77.1 pg/mL (p=0.008) and UACR from 94.1 to 89.8 mg/g (p=0.017); within placebo, UACR rose from 81.9 to 112 mg/g (p=0.029) while TGF-β change was non-significant (p=0.428). Between-group ΔUACR was significant (p<0.001), whereas ΔTGF-β (p=0.303) and ΔeGFR (p=0.567) were not. Multivariable linear regression identified resveratrol as an independent predictor of UACR reduction (B=−394.12 mg/g; 95% CI −659.53 to −128.71; p=0.004; adjusted R^2=0.129). Baseline TGF-β was the dominant predictor of ΔTGF-β (B=−0.81; p<0.001; adjusted R^2=0.701), and baseline LFG stage predicted ΔeGFR (B=−4.76; p=0.021). Mild bloating was reported in 14.8% of resveratrol versus 11.1% of placebo recipients; no serious adverse events occurred. **Conclusion:** Adjuvant low-dose resveratrol reduces albuminuria and serum TGF-β over 12 weeks in DKD without short-term improvement in eGFR, supporting an antifibrotic biomarker signal that warrants longer trials.

1. Introduction

Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD) and kidney failure worldwide and a major contributor to cardiovascular morbidity and excess mortality among people with diabetes.[1,2] Global Burden of Disease analyses confirm that DKD-attributable disability-adjusted life-years have risen substantially over the past decade, with the steepest increases in middle-income regions where the prevalence of type 2 diabetes is expanding.[3] In China,

contemporary cohorts attribute a substantial share of premature death in middle-aged and older adults with diabetes to coexistent CKD,[4] underscoring the urgency of strategies that slow nephropathy progression in everyday practice.

Pathophysiologically, persistent hyperglycemia, advanced glycation end-products, mitochondrial reactive oxygen species, and dysregulated renin–angiotensin–aldosterone signaling converge on the transforming growth factor-β (TGF-β)/Smad axis. This axis drives mesangial expansion, podocyte loss, and tubulointerstitial fibrosis—the histological substrate of glomerulosclerosis and progressive renal-function decline.[5,6] Although TGF-β is generated locally, the activated profibrotic milieu is partially reflected in the systemic circulation, where serum TGF-β1 has been shown to discriminate DKD severity, correlate with cystatin C, and precede measurable albuminuria.[7,8] Albuminuria itself, expressed as the urinary albumin-to-creatinine ratio (UACR), remains the most clinically actionable surrogate of glomerular injury and an independent predictor of kidney-failure progression and cardiovascular events.[9,10] The KDIGO 2024 framework operationalizes the joint use of UACR and estimated glomerular filtration rate (eGFR) categories for risk stratification, and the 2026 Standards of Care in Diabetes endorse this approach for routine surveillance in patients with diabetes.[11,12]

Despite progress with renin–angiotensin system blockers, sodium-glucose cotransporter-2 (SGLT2) inhibitors, non-steroidal mineralocorticoid receptor antagonists, and glucagon-like peptide-1 receptor agonists, residual fibrogenic risk persists in DKD; many patients continue to lose nephrons even on optimized standard care.[1,2,13] This therapeutic gap has revived interest in adjuvant anti-fibrotic strategies that target the TGF-β axis, oxidative stress, and inflammation simultaneously.[5,14] Trials of direct anti-TGF-β biologics in DKD have been disappointing—LY2382770 produced no benefit on serum creatinine over 12 months and was halted prematurely—suggesting that selectively neutralizing TGF-β may interfere with its homeostatic roles, while more upstream, multi-target modulation of the oxidative–inflammatory–profibrotic network may be a more tractable strategy.[5,14] Polyphenol activators of SIRT1/AMPK fit this multi-target framework and have a long history of safety in human exposure through dietary intake.

Resveratrol (3,5,4′-trihydroxystilbene), a naturally occurring polyphenolic stilbene, activates SIRT1 and AMP-activated protein kinase (AMPK), restores autophagy, and downregulates the NF-κB/TGF-β/Smad pathway in pre-clinical models of nephropathy.[14-16] Animal dose–response meta-analyses confirm reductions in serum creatinine, urea, and proteinuria across diverse DKD models, with the most consistent effects achieved at low oral doses,[17] and in vivo work shows protection of podocytes through restored autophagy via SIRT1/SphK1 signaling.[18,19] In human studies, however, the evidence remains heterogeneous. The single previously published placebo-controlled randomized trial in patients with diabetes and albuminuria reported a clinically meaningful reduction in UACR with adjunct resveratrol 500 mg/day for 90 days, without measurable eGFR change over the trial window.[20] Smaller trials in non-dialysis CKD and on peritoneal dialysis have yielded mixed signals on inflammatory and angiogenic markers,[21-23] and the most current systematic review and dose–response meta-analysis concluded that improvements in renal-function indices are most evident in non-diabetic subgroups and at intervention durations exceeding eight weeks.[24,25] Critically, serum TGF-β has been measured in only a small minority of resveratrol clinical trials, despite its mechanistic centrality to fibrogenesis on which the molecule is hypothesized to act.[5,7,8]

To address this evidence gap, we designed a 12-week, double-blind, placebo-controlled randomized trial in adults with DKD to evaluate the effect of adjuvant low-dose resveratrol (25 mg twice daily, derived from Polygonum cuspidatum in 95% lecithin) on three pre-specified outcomes: serum TGF-β as a profibrotic biomarker, UACR as a clinical surrogate of

glomerular injury, and eGFR as the gold-standard measure of renal function. We hypothesized that the intervention would reduce serum TGF-β and UACR and slow eGFR decline relative to placebo while remaining well tolerated on top of contemporary standard therapy.

2. Methods

Study design and setting

This was a single-centre, double-blind, placebo-controlled randomized clinical trial conducted at the outpatient Department of Internal Medicine, Dr. Mohammad Hoesin General Hospital (RSMH), Palembang, Indonesia, from October 2025 through January 2026. The study followed the CONSORT 2010 reporting guidance,[26] and the protocol adhered to the principles of the Declaration of Helsinki.

Ethics

The study was approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya/Dr. Mohammad Hoesin General Hospital, Palembang. All participants provided written informed consent prior to enrolment.

Participants

Eligible participants were adults (≥18 years) with established type 2 diabetes mellitus and DKD, defined according to KDIGO criteria as persistent UACR ≥30 mg/g and/or eGFR <60 mL/min/1.73 m² for ≥3 months attributable to diabetes, or supportive evidence such as diabetic retinopathy on funduscopy.[11] Patients with CKD stages G1–G4 not yet on dialysis were considered. Exclusion criteria were systemic anti-inflammatory drug use within the preceding 10 days, pregnancy or lactation, and any history of malignancy. Participants who discontinued because of intolerable adverse events, were lost to follow-up, withdrew consent, or died were classified as drop-outs and were not analyzed for outcomes after the time of withdrawal.

Randomization, blinding, and allocation concealment

Block-permuted randomization with concealed allocation was used to assign participants 1:1 to resveratrol or placebo. Randomization codes were generated by an independent third party and held by the hospital pharmacy; sealed opaque envelopes were used to maintain concealment. Investigators, outcome assessors, and participants were all blinded to treatment assignment until database lock.

Intervention

Participants in the active arm received resveratrol 25 mg per capsule (derived from Polygonum cuspidatum, formulated with 95% lecithin to enhance bioavailability), administered orally twice daily after meals for 12 weeks. The placebo arm received identical-appearing capsules containing microcrystalline cellulose with the same dosing schedule and duration. Resveratrol and placebo were supplied by the manufacturer in matched blister packs registered with the Indonesian Food and Drug Authority (BPOM SI 174308051). All participants continued their usual standard care including renin–angiotensin system blockade (ACE inhibitor or ARB), statins, anti-hypertensive agents, and glucose-lowering therapy as clinically indicated. Adherence was monitored by family-supervised dosing logs and pill-count returns at each follow-up visit.

Outcomes

Pre-specified outcomes were measured at baseline and at week 12. The primary outcomes were the within- and between-group changes in (i) serum TGF-β1 concentration, (ii) UACR, and (iii) eGFR. Serum TGF-β1 was quantified by quantitative sandwich enzyme-linked immunosorbent assay (R&D Systems) following the manufacturer's acid-activation protocol. Briefly, 40 µL of serum was activated with 10 µL of 1 N HCl for 10 minutes at room temperature and neutralised with 10 µL of 1.2 N NaOH/0.5 M HEPES; samples were then diluted up to 40-fold in calibrator diluent, loaded into wells pre-coated with monoclonal

anti-TGF-β1, incubated for two hours, washed four times, and developed with substrate solution before reading at 450 nm with a 540/570 nm correction. Standard curves were constructed across 31.3–2000 pg/mL and concentrations of test samples were interpolated. UACR was determined on a midstream urine specimen collected per standard protocol with care to avoid contamination, with categories assigned as KDIGO A1 (<30 mg/g), A2 (30–299 mg/g), and A3 (≥300 mg/g).11 eGFR was estimated using the 2021 CKD-EPI equation and categorized as G1 (≥90), G2 (60–89), G3 (30–59), G4 (15–29), and G5 (<15) mL/min/1.73 m^2.[11] Secondary measurements included HbA1c, fasting plasma glucose, lipid profile, serum albumin, urea, and adverse event ascertainment at each scheduled visit. Adverse events were elicited at each follow-up visit using open and structured questioning, and graded by clinical severity; events leading to a change in treatment were recorded in the case report form.

Sample size

Sample size was calculated for the between-group comparison of mean change in UACR using α=0.05 (one-sided Z=1.64) and power 90% (β=0.10, Z=1.28), assuming a between-group mean difference of 28.3 with pooled SD 46.4 from previous trial data, yielding a minimum of 23 participants per arm. To accommodate up to 10% drop-out, recruitment was set at 25 participants per arm.

Statistical analysis

Analyses were performed using SPSS 26.0 (IBM Corp.). Distribution of continuous variables was assessed by the Shapiro–Wilk test; homogeneity of variance by the Levene test. Normally distributed variables are expressed as mean ± standard deviation and non-normal variables as median (range). Categorical variables are reported as frequency and percentage. Within-group changes were compared using a paired t-test or a Wilcoxon signed-rank test as appropriate; between-group comparisons of change scores used an independent t-test or the Mann–Whitney U test. Categorical comparisons used the chi-square or Fisher's exact test. Multivariable linear regression was used to identify independent predictors of change in each outcome, with candidate covariates pre-selected from bivariate analyses at $p<0.25$ (Spearman or Mann–Whitney U). Two-sided p-values <0.05 were considered statistically significant. Analyses followed the intention-to-treat principle for participants with complete baseline and end-of-study measurements.

3. Results

Participant flow and baseline characteristics

Of 72 individuals screened for eligibility, 11 were excluded (10 due to recent systemic anti-inflammatory use; 1 due to a history of malignancy). Sixty-one participants underwent randomization (resveratrol n=29; placebo n=32). During follow-up, two participants in the resveratrol arm were lost (relocation), and five in the placebo arm did not complete the trial (two withdrew consent; three were lost to follow-up). Fifty-four participants—27 in each arm—were analyzed for the pre-specified outcomes (Figure 1, CONSORT flow described narratively).

Baseline demographic, clinical, and laboratory characteristics were comparable between arms (Table 1). The cohort comprised 28 men (51.9%) and 26 women (48.1%) with a mean age of 54.46 ± 8.61 years and mean body mass index of 27.26 ± 4.40 kg/m^2. The median duration of diabetes was 6.5 years (range 0.5–25 years). A majority (80.8%) used insulin and 72.2% used an ARB; 77.8% used a statin. Albuminuria categorisation showed 41 participants (75.9%) in A2 and 13 (24.1%) in A3 at baseline, with eGFR distribution G1 35.2%, G2 31.5%, G3 25.9%, and G4 7.4%. No baseline characteristic differed significantly between arms (all $p>0.05$).

Table 1. Baseline demographic, clinical, and laboratory characteristics of study participants (n=54).

Variable	Total (n=54)	Resveratrol (n=27)	Placebo (n=27)	p-value
Gender, n (%)				0.586
Male	28 (51.9)	15 (55.6)	13 (48.1)	
Female	26 (48.1)	12 (44.4)	14 (51.9)	
Age, years (mean ± SD)	54.46 ± 8.61	53.33 ± 9.08	55.59 ± 8.12	0.340
Body mass index, kg/m² (median, range)	27.26 ± 4.40	26.8 (19.5–37.6)	25.59 (20.8–38.3)	0.604
Diabetes duration, years (median, range)	6.5 (0.5–25)	6 (2–20)	10 (0.5–25)	0.621
Smoking history, n (%)	21 (38.9)	8 (29.6)	13 (48.1)	0.163
Family history of diabetes, n (%)	42 (77.8)	20 (74.1)	22 (81.5)	0.372
— Therapy, n (%) —				
Insulin	42 (80.8)	21 (80.8)	21 (80.8)	1.000
Biguanide (metformin)	10 (18.5)	7 (25.9)	3 (11.1)	0.161
Sulphonylurea	6 (11.1)	3 (11.1)	3 (11.1)	1.000
DPP-4 inhibitor	8 (14.8)	4 (14.8)	4 (14.8)	1.000
α-glucosidase inhibitor	2 (3.7)	1 (3.7)	1 (3.7)	1.000
Statin	42 (77.8)	22 (81.5)	20 (74.1)	0.513
ARB	39 (72.2)	20 (74.1)	19 (70.4)	0.761
ACE inhibitor	15 (27.8)	7 (25.9)	8 (29.6)	0.761
Calcium-channel blocker	24 (44.4)	15 (55.6)	9 (33.3)	0.100
Mineralocorticoid antagonist	9 (16.7)	5 (18.5)	4 (14.8)	0.715
Antiplatelet	19 (35.2)	12 (44.4)	7 (25.9)	0.154
— Comorbidities, n (%) —				
Chronic coronary syndrome	5 (9.3)	2 (7.4)	3 (11.1)	0.500
Diabetic retinopathy	4 (7.4)	3 (11.1)	1 (3.7)	0.305
Stroke	13 (24.1)	8 (29.6)	5 (18.5)	0.340
— Albuminuria category, n (%) —				0.340
A2 (30–299 mg/g)	41 (75.9)	19 (70.4)	22 (81.5)	
A3 (≥300 mg/g)	13 (24.1)	8 (29.6)	5 (18.5)	
— eGFR stage, n (%) —				0.887
G1 (≥90)	19 (35.2)	9 (33.3)	10 (37.0)	
G2 (60–89)	17 (31.5)	9 (33.3)	8 (29.6)	
G3 (30–59)	14 (25.9)	8 (29.6)	6 (22.2)	
G4 (15–29)	4 (7.4)	1 (3.7)	3 (11.1)	
— Laboratory —				
HbA1c, %	8.17 ± 1.93	7.1 (5.1–12.5)	8.2 (5.0–12.3)	0.736
Albumin, g/dL	4.4 (2.8–5.4)	4.4 (3.2–4.9)	4.4 (2.8–5.4)	0.972
Urea, mg/dL	28.5 (10–112)	28 (10–67)	32 (10–112)	0.883
Fasting glucose, mg/dL	156.96 ± 59.06	131 (86–262)	158 (74–329)	0.478
LDL-C, mg/dL	128.07 ± 46.81	132.44 ± 35.02	123.70 ± 56.57	0.478
HDL-C, mg/dL	48.5 (32–98)	47 (32–65)	51 (33–98)	0.085
Triglycerides, mg/dL	199.41 (77–601)	191 (81–601)	156 (77–489)	0.622
Total cholesterol, mg/dL	201 (132–377)	201 (132–308)	201 (136–377)	0.972

Values are mean ± SD, median (range), or n (%). p-values from Chi-square, Fisher's exact, independent t-test, or Mann–Whitney U as appropriate. ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate (CKD-EPI 2021); HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

Table 2. Within- and between-group changes in serum TGF-β, urinary albumin-to-creatinine ratio, and estimated glomerular filtration rate from baseline to week 12.

Outcome/Time-point	Resveratrol (n=27)	Placebo (n=27)	Within p (R)	Within p (P)	Between-group Δ p	Effect size
Serum TGF-β (pg/mL)						
Baseline	123.7 (3.8–706)	172 (3.2–762)	—	—	—	—
Week 12	77.1 (1.5–273.7)	105.8 (1–741.1)	—	—	—	—
Within-group p (Wilcoxon)	0.008**	0.428	—	—	—	—
Δ (median, range)	−64.4 (−627.7 to 145)	+0.3 (−687 to 222.9)	—	—	0.303	—
UACR (mg/g)						
Baseline	94.1 (30.3–7617)	81.9 (30.9–4234)	—	—	—	—
Week 12	89.8 (5.6–4971)	112 (10–4909)	—	—	—	—
Within-group p (Wilcoxon)	0.017*	0.029*	—	—	—	—
Δ (median, range)	−28.78 (−2646.29 to 340.25)	+8.30 (−25.3 to 1265.53)	—	—	**<0.001*** **	—
eGFR (mL/min/1.73 m²)						
Baseline	83 (33–114)	85 (19–118)	—	—	—	—
Week 12	71 (26–120)	68 (18–117)	—	—	—	—
Within-group p (Wilcoxon)	0.232	0.058	—	—	—	—
Δ (median, range)	−1 (−27 to 15)	−2 (−61 to 24)	—	—	0.567	—

*p<0.05, **p<0.01, ***p<0.001. Within-group comparisons by the Wilcoxon signed-rank test; between-group comparisons of change scores by the Mann–Whitney U test.

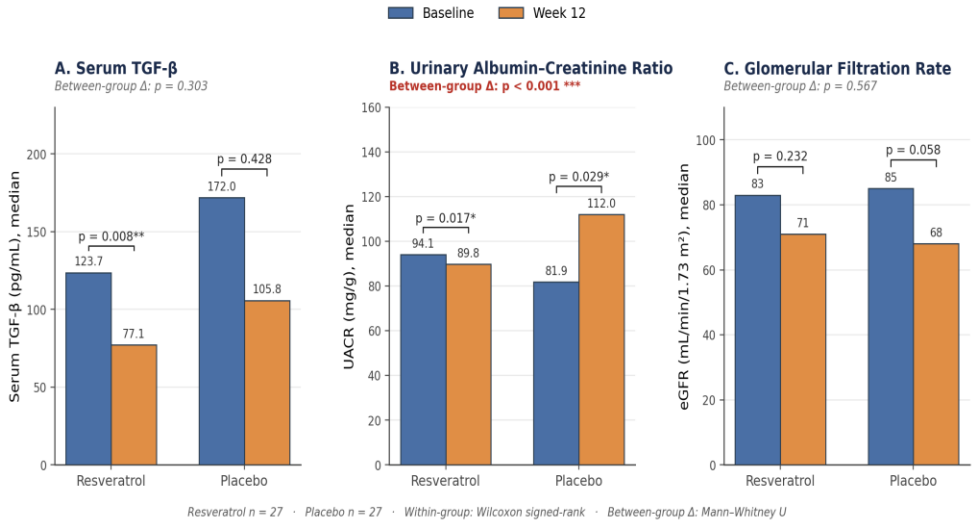

Figure 1. Pre- and post-treatment values for serum TGF-β (panel A), urinary albumin-to-creatinine ratio (panel B), and estimated glomerular filtration rate (panel C) in the resveratrol and placebo arms (n=27 per arm). Bars represent median values; significance brackets show within-group Wilcoxon p-values, with the between-group comparison of change reported below the panel.

In the resveratrol arm, median serum TGF-β decreased from 123.7 (range 3.8–706) to 77.1 (1.5–273.7) pg/mL (Wilcoxon p=0.008), and median UACR decreased from 94.1 (30.3–7617) to 89.8 (5.6–4971) mg/g (p=0.017). Median eGFR decreased numerically from 83 to 71 mL/min/1.73 m² (p=0.232). In the placebo arm, median serum TGF-β changed from 172 (3.2–762) to 105.8 (1–741.1) pg/mL (p=0.428); median UACR rose significantly from 81.9 (30.9–4234) to 112 (10–4909) mg/g (p=0.029); and median eGFR moved from 85 to 68 mL/min/1.73 m² (p=0.058). These directional patterns are summarized in Table 2 and visualized in Figure 1.

Stage distribution of glomerular filtration rate

Stage transitions over 12 weeks differed qualitatively between arms. In the resveratrol arm, 22 of 27 participants (81.5%) maintained the same eGFR stage, four (14.8%) improved by one stage, and one (3.7%) deteriorated. In the placebo arm, 14 (51.9%) remained stable, eight (29.6%) improved, and five (18.5%) deteriorated; the overall distribution did not differ statistically between arms (Fisher's exact p=0.234).

Between-group differences in change

The between-group difference in change in UACR was the most robust finding. Median ΔUACR was −28.78 mg/g (range −2646.29 to 340.25) in the resveratrol arm and +8.30 mg/g (range −25.30 to 1265.53) in the placebo arm (Mann–Whitney p<0.001). The between-group difference in ΔTGF-β was not significant (median −64.4 vs +0.3 pg/mL; p=0.303), nor was the between-group difference in ΔeGFR (median −1 vs −2 mL/min/1.73 m²; p=0.567). These results are detailed in Table 2 and depicted graphically in Figure 1B.

Multivariable analyses

Bivariate screening (Spearman for continuous variables; Mann–Whitney for categorical variables) identified candidate covariates at p<0.25 for each of the three outcomes. In the multivariable linear regression model for ΔUACR, only treatment assignment retained significance: assignment to resveratrol independently predicted a greater reduction in UACR (B = −394.12 mg/g; 95% CI −659.53 to −128.71; standardized coefficient −0.382; p=0.004), with adjusted R^2=0.129 (Table 3). For ΔeGFR, baseline eGFR stage was an independent predictor (B = −4.76 mL/min/1.73 m² per stage increment; 95% CI −8.78 to −0.74; p=0.021), while diabetes duration showed a borderline negative association (B = −0.534 per year; p=0.053); the model's adjusted R^2 was 0.089. For ΔTGF-β, baseline serum TGF-β was the dominant predictor (B = −0.81; 95% CI −0.95 to −0.66; p<0.001), with model adjusted R^2 = 0.701 (Table 3). The independent predictors are summarized graphically in Figure 2, and the relationship between baseline TGF-β and ΔTGF-β is shown in Figure 3.

Safety

No serious adverse events were attributed to either study treatment. Mild bloating was reported by 4 of 27 (14.8%) participants in the resveratrol arm and 3 of 27 (11.1%) in the placebo arm; symptoms were transient and did not require treatment discontinuation. No participants required hospitalisation for an event judged related to the intervention.

4. Discussion

In this 12-week, double-blind, placebo-controlled randomized trial of adults with diabetic kidney disease on contemporary standard care, adjuvant low-dose resveratrol (25 mg twice daily) reduced two clinically meaningful biomarkers—serum TGF-β and urinary albumin-to-creatinine ratio—within the active arm and produced a robust between-group difference in change in UACR. Glomerular filtration rate did not change significantly during the trial in either arm. Multivariable analysis confirmed that assignment to resveratrol independently predicted a reduction in UACR after adjustment for candidate covariates, while baseline serum TGF-β explained the majority of variance in ΔTGF-β.

Table 3. Multivariable linear regression — independent predictors of change in primary outcomes.

Predictor	B	95% CI	Std. β	p-value
Outcome: ΔUACR (mg/g) — adjusted R^2 = 0.129				
Constant	177.61	−10.07 to 365.29	—	0.063
Resveratrol (vs placebo)	−394.12	−659.53 to −128.71	−0.382	**0.004****
Outcome: ΔeGFR (mL/min/1.73 m²) — adjusted R^2 = 0.089				
Constant	−9.39	−18.70 to −0.08	—	**0.048***
Diabetes duration (per year)	−0.534	−1.12 to 0.05	—	0.053
Baseline eGFR stage (ordinal G1–G4)	−4.76	−8.78 to −0.74	—	**0.021***
Outcome: ΔTGF-β (pg/mL) — adjusted R^2 = 0.701				
Constant	94.06	40.37 to 147.75	—	0.307
Baseline serum TGF-β (per pg/mL)	−0.81	−0.95 to −0.66	—	**<0.001*****

Candidate covariates were screened bivariately (Spearman or Mann–Whitney U) at p<0.25; those retained in the final model are shown. *p<0.05, **p<0.01, ***p<0.001. CI, confidence interval; Std. β, standardized regression coefficient.

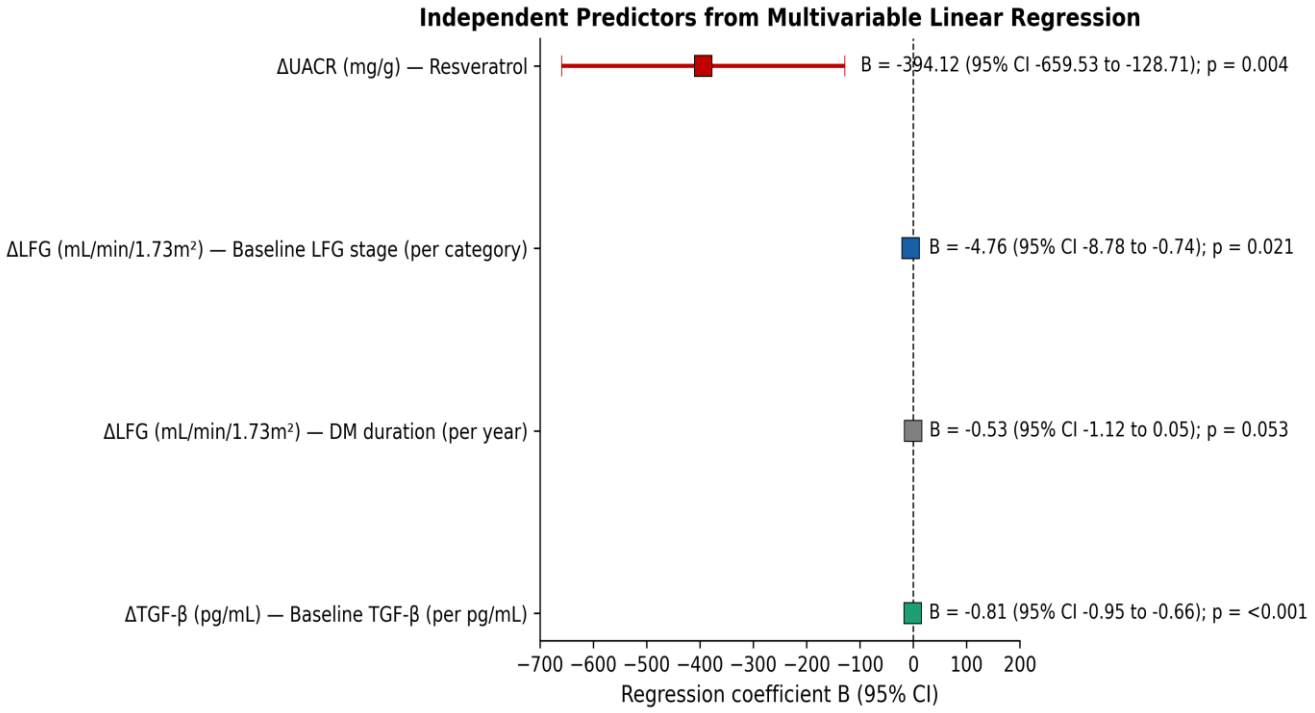

Figure 2. Forest plot of independent predictors from multivariable linear regression. Points represent regression coefficients (B) with 95% confidence intervals from separate models for ΔUACR (red), ΔeGFR (blue and grey), and ΔTGF-β (green).

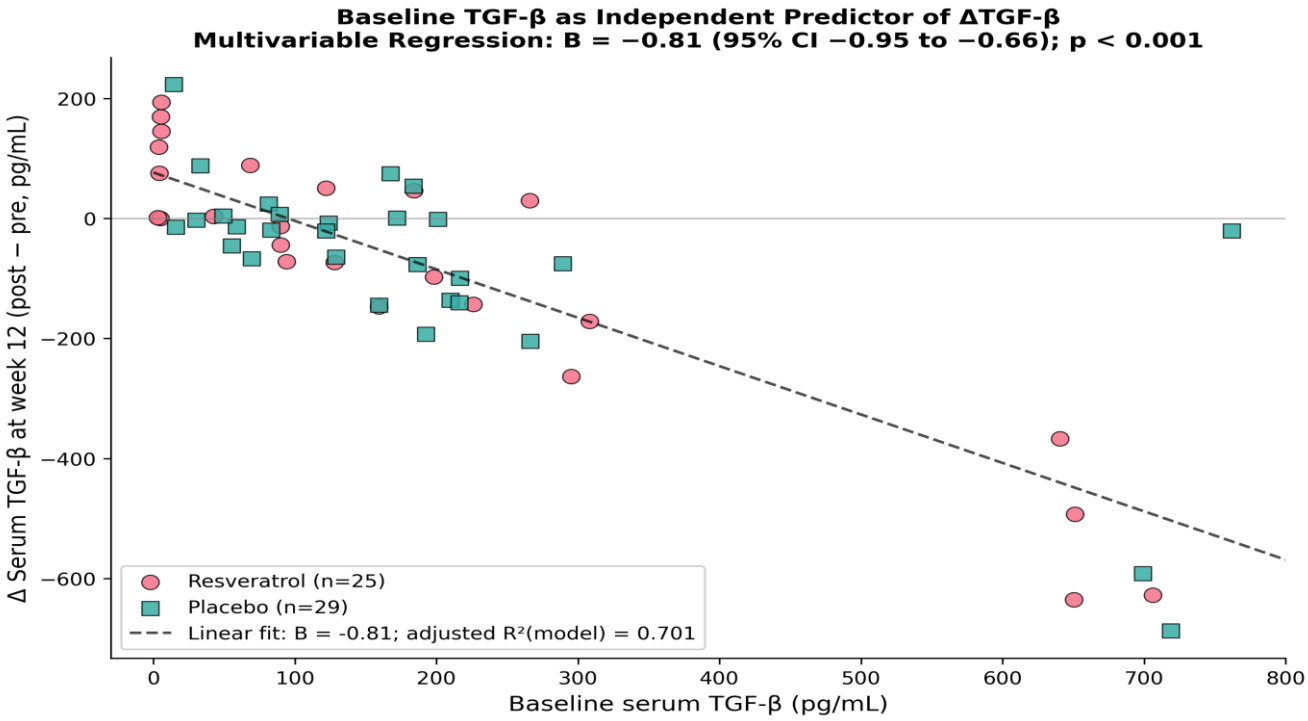

Figure 3. Scatter plot of baseline serum TGF-β versus the change in serum TGF-β at week 12 by treatment arm. The dashed line shows the linear fit; baseline TGF-β was the dominant independent predictor of ΔTGF-β in multivariable regression (B = −0.81; 95% CI −0.95 to −0.66; p<0.001).

The intervention was well tolerated, with mild gastrointestinal symptoms reported at frequencies similar to placebo and no serious adverse events. The cohort is representative of contemporary DKD presenting at a tertiary referral hospital in Indonesia. The near-equal gender distribution, mean age in the mid-fifties, median diabetes duration of 6.5 years, and predominantly overweight body mass index (mean 27.26 kg/m²) align with epidemiological data showing that DKD becomes prevalent in middle age and is amplified by adiposity-driven low-grade inflammation and oxidative stress.[1,3] The high background use of insulin (80.8%), ARB (72.2%), and statins (77.8%) also reflects intensive standard-of-care therapy, which raises the methodological bar for any add-on intervention to demonstrate measurable benefit on top of an already optimized regimen.[12,13] The predominance of A2 albuminuria with smaller A3 representation, and the wide eGFR distribution (G1–G4), illustrate the heterogeneity of clinical DKD and is important when interpreting biomarker dynamics over a short window.[11]

TGF-β1 occupies a central and largely conserved position in the molecular pathology of DKD: in mesangial cells, podocytes, and tubular epithelial cells, hyperglycaemia and angiotensin II signaling activate TGF-β with downstream Smad2/3 phosphorylation and accelerated synthesis of collagen and fibronectin, driving glomerulosclerosis and tubulointerstitial fibrosis.[5,6] Population studies link circulating TGF-β1 with kidney disease and incident microalbuminuria,[7,8] and serum TGF-β1 has been shown to discriminate DKD severity and correlate with cystatin C in cross-sectional analyses.[8] In the present trial, the within-group decrease in serum TGF-β was statistically significant in the resveratrol arm (p=0.008) but not in placebo (p=0.428). The between-group difference in change did not reach significance

(p=0.303), reflecting wide inter-individual variation and outlier influence on a single end-of-study measurement. This pattern is consistent with the multivariable result that baseline TGF-β explained 70% of the variance in change—those starting high regressed more, irrespective of treatment, although treatment may add a directional contribution that the present sample is underpowered to detect at the between-group Δ level. Mechanistically, resveratrol-mediated activation of SIRT1/AMPK and suppression of NF-κB and TGF-β/Smad transcripts in pre-clinical DKD models, together with restoration of autophagy via SIRT1/SphK1 signaling, provide a coherent biological substrate for the observed within-group decline.[14,15,18]

Albuminuria emerged as the most responsive endpoint. The resveratrol arm decreased the median UACR from 94.1 to 89.8 mg/g (p=0.017), whereas the placebo arm rose from 81.9 to 112 mg/g (p=0.029), producing a highly significant between-group difference in change (p<0.001). Multivariable regression independently confirmed assignment to resveratrol as a predictor of UACR reduction (B = −394.12 mg/g; 95% CI −659.53 to −128.71; p=0.004; adjusted R^2 = 0.129), with the magnitude reflecting the wide baseline range of UACR rather than a uniform proportional reduction.[20] The directional contrast with placebo is biologically plausible: in untreated DKD, the natural history is progressive worsening of albuminuria driven by hyperfiltration, podocyte injury, and endothelial dysfunction, all of which can be modulated by polyphenol-mediated reductions in oxidative stress, ROS production, and TGF-β signaling.[5,7,15,16] Our findings replicate the magnitude and direction reported by Sattarinezhad et al, who demonstrated UACR reduction with resveratrol 500 mg/day on top of losartan in T2DM with albuminuria.[20] By extension, the strict between-group separation we observed—decline on active treatment versus rise on placebo—argues against regression-to-the-mean as the sole driver and supports a true pharmacological effect.

Both arms showed numerical declines in median eGFR over 12 weeks, with neither change reaching conventional significance and no between-group difference (Δ p=0.567). Several mechanistic and methodological factors contribute to this null finding. First, eGFR is dominated in the short term by haemodynamic factors and is influenced by serum creatinine variability, hydration status, dietary protein, and lean mass, all of which can mask small structural effects.[11] Second, in DKD with preserved baseline eGFR, the early phase of disease is often characterised by hyperfiltration; corrections of hyperfiltration can paradoxically appear as a numerical decrease in eGFR even when long-term renal-survival benefits are accruing—a well-described pattern with SGLT2 inhibitors and renin–angiotensin blockade.[12,13] Third, fibrotic remodelling—the substrate for any sustained eGFR change—evolves over many months to years, far beyond the 12-week observation window of this trial. Consistent with this interpretation, the most current systematic review and dose–response meta-analysis of clinical resveratrol trials concluded that eGFR improvements are most evident in non-diabetic populations and at intervention durations exceeding 8 weeks, with greater consistency the longer the trial.[24] In our multivariable model, baseline eGFR stage (rather than treatment) was the only significant predictor of ΔeGFR (B = −4.76 per stage increment; p=0.021), reinforcing the dominance of baseline status over a short-term pharmacological signal.

Our results both replicate and extend the existing clinical literature on resveratrol in kidney disease. Sattarinezhad et al, in the only previous RCT specifically in diabetic nephropathy (n=60), reported a similar UACR reduction with no eGFR change after 90 days of 500 mg/day, confirming that the clinical signal is reproducible across dosing regimens and bioavailability strategies.[20] Saldanha et al's crossover trial of 500 mg/day for 4 weeks in non-dialysis CKD (n=20) found no significant changes in Nrf2 or NF-κB expression, consistent with the proposition that 4 weeks may be insufficient to capture biological effects

in CKD.[21] Lin et al's three-arm trial in peritoneal dialysis (n=64) demonstrated improvements in net ultrafiltration with 150 mg or 450 mg/day for 12 weeks—relevant for establishing the safety and tolerability of doses bracketing ours—and Alvarenga et al's CKD G3–G4 crossover trial of 500 mg/day did not reduce uremic toxin levels but provided important safety data.[22,23] Our use of a low-dose phospholipid-formulated resveratrol with a defined antifibrotic biomarker (serum TGF-β) addresses key gaps these prior studies left open: low-dose efficacy and TGF-β-axis modulation in vivo. The animal-model dose–response meta-analysis of Liu et al likewise reports more reliable benefit at low doses (≤15 mg/kg/day or 100–200 mg/kg/day in murine models), supporting the clinical relevance of our 50 mg/day total dose with a high-bioavailability carrier.[17]

Taken together, the within-group reduction in serum TGF-β, the between-group decline in UACR, and the unchanged short-term eGFR fit a coherent model in which resveratrol acts at multiple converging nodes: SIRT1/AMPK activation increases mitochondrial biogenesis and antioxidant capacity, restores autophagy, and dampens NF-κB-driven inflammation; downstream, TGF-β/Smad transcriptional activity is suppressed, reducing fibrogenic gene expression and stabilizing the glomerular filtration barrier with consequent reduction of albuminuria.[14-16,18,19] In DKD specifically, podocyte autophagy preservation has emerged as a particularly attractive target because podocyte loss is the proximate cause of irreversible nephron loss, and resveratrol has been shown to enhance podocyte autophagy and suppress apoptosis in glucose-stressed models.[18] The fact that biomarker (TGF-β) and clinical surrogate (UACR) responded in the same direction—but eGFR did not—mirrors the well-recognised hierarchy of response: molecular and biochemical changes precede measurable clinical change, which precedes structural change.[5,17,20]

From a systems-biology perspective, the convergence of stress-oxidative, inflammatory, and metabolic insults on the TGF-β/Smad axis explains why a polyphenol with multi-target activity may add value in addition to single-pathway pharmacotherapies. Hyperglycaemia drives the polyol, hexosamine, and protein kinase C pathways and increases advanced glycation end-product (AGE) formation; AGEs engage the receptor RAGE and amplify reactive oxygen species (ROS) production through NADPH oxidase 4 (NOX4) in mesangial cells and podocytes, which in turn activates p38 and JNK mitogen-activated protein kinases and phosphorylates Smad2/3, even in the absence of fresh ligand stimulation.[5,6,16] Resveratrol, by activating AMPK and SIRT1, simultaneously suppresses NOX4 expression, deacetylates and inhibits NF-κB p65, and elevates the transcription of antioxidant enzymes including superoxide dismutase, catalase, and glutathione peroxidase via the Nrf2/ARE pathway.[14-16] Pre-clinical studies further document upregulation of adiponectin receptors AdipoR1/AdipoR2 in diabetic glomeruli following resveratrol treatment, integrating the metabolic axis with the antifibrotic effect.[15] Each of these intermediate steps offers a plausible reason why a low molar concentration of an orally absorbed phospholipid-formulated stilbene can yield measurable in vivo signals on TGF-β and on the protein-leak phenotype of glomerular injury, even in patients already taking renin–angiotensin blockade and statins.

Additionally, the renal endothelial component is increasingly recognised as a co-determinant of albuminuria. The glycocalyx layer of glomerular endothelial cells contributes to the size- and charge-selectivity of the filtration barrier; in diabetes, glycocalyx degradation by heparanase and matrix metalloproteinases occurs early, often before podocyte injury becomes histologically obvious.[5] Polyphenols, including resveratrol, modulate endothelial nitric oxide synthase (eNOS) coupling, restore nitric oxide bioavailability, and dampen endothelin-1 expression in endothelial cells, thereby reducing intra-glomerular pressure and mechanical stress on the filtration barrier.[14] These endothelial effects can act synergistically with podocyte protection to deliver the

early UACR signal we observed without requiring overt structural change in the nephron.

Resveratrol was well tolerated. The frequency of mild gastrointestinal complaints (bloating: 14.8% versus 11.1% on placebo) is consistent with the published safety record of trans-resveratrol up to 1 g/day, where transient gastrointestinal symptoms predominate without serious adverse events at doses below the gram range.[19,24] No biochemical abnormalities required treatment discontinuation, and there were no episodes of hyperkalaemia or acute kidney injury attributable to the intervention. The dosing schedule (25 mg twice daily) leveraged a phospholipid-formulated preparation to enhance bioavailability, which is particularly relevant given the rapid first-pass metabolism of free resveratrol.[19]

These results support the role of low-dose resveratrol as a safe adjunct to standard DKD care that yields measurable reductions in albuminuria over 12 weeks. UACR is an established surrogate for the risk of progression to end-stage kidney disease, cardiovascular events, and mortality, and any sustained reduction in albuminuria—particularly when achieved on top of optimized renin–angiotensin and statin therapy—is clinically meaningful.[9,10,12] Concomitantly reducing serum TGF-β within-group, while not yet powered to demonstrate a between-group effect, is biologically encouraging and supports continued mechanistic investigation. The intervention is inexpensive, orally administered, and broadly compatible with the contemporary DKD therapeutic armamentarium, including SGLT2 inhibitors, GLP-1 receptor agonists, and finerenone, although direct combination data are not yet available.[12,13]

In Indonesian and broader low- and middle-income contexts, the practical accessibility of resveratrol becomes especially salient. SGLT2 inhibitors and finerenone substantially reduce the risk of major adverse renal events and slow eGFR decline in DKD; however, real-world uptake remains constrained by cost, prescriber familiarity, and concerns about euglycaemic ketoacidosis or hyperkalaemia.[12,13] An adjunctive nutraceutical such as resveratrol with a favourable safety profile and a documented antifibrotic biomarker signal could therefore complement, rather than replace, evidence-based pharmacotherapy. Moreover, the predominantly albuminuric phenotype enrolled in this trial is the subgroup most likely to derive incremental benefit from anti-fibrotic add-ons, because albuminuria reflects active glomerular and podocyte injury that is responsive to anti-inflammatory and SIRT1/AMPK-modulating interventions; the non-albuminuric phenotype, in which vascular and tubulointerstitial mechanisms predominate, may respond less robustly and warrants separate investigation.[7,11]

From a policy and pragmatic-care standpoint, integrating resveratrol into a DKD management bundle would require attention to three issues: standardisation of the formulation (the lecithin-based phospholipid carrier used here is not interchangeable with crystalline trans-resveratrol); robust pharmacovigilance for drug-interaction risk via cytochrome P450 modulation, particularly with statins, calcium-channel blockers, and warfarin; and clear patient education on the adjunctive—not substitutive—nature of the intervention.[14,19] Within these constraints, the present trial supports clinicians considering resveratrol as a second-line adjunct in patients with persistent A2 or A3 albuminuria despite optimised standard care, while awaiting confirmatory data from larger trials.

Strengths of the study include the rigorous double-blind, placebo-controlled design with concealed allocation and identical-appearing capsules; pre-specified primary outcomes that combine a profibrotic biomarker (serum TGF-β) with a clinical surrogate (UACR) and a fundamental renal-function metric (eGFR); inclusion of multivariable adjustment that confirms the independence of the resveratrol effect on UACR; and integration of CONSORT reporting standards.[26] The use of a defined phospholipid-formulated low-dose preparation with regulatory registration improves reproducibility. Limitations include the single-centre setting in a tertiary Indonesian hospital, which may limit generalizability;

the modest sample size, which limits power to detect between-group differences in TGF-β; the 12-week duration, which is too short to detect meaningful structural eGFR change; and the absence of urinary TGF-β1 measurement, which would complement the systemic biomarker. We did not measure plasma resveratrol or its metabolites, so we cannot directly verify systemic exposure or build dose–response relationships within the cohort. We also did not collect detailed adherence biomarkers beyond pill count and family-supervised dosing logs. Future trials should be multi-centre, larger, and longer, ideally with serial biomarker measurements and urinary TGF-β1, and should test combinations with SGLT2 inhibitors or finerenone to evaluate additive or synergistic effects.[12,13]

Several research priorities emerge from this work. First, multicentre randomized controlled trials of at least 12-month duration are needed to determine whether the early UACR signal observed here translates into hard renal endpoints—doubling of serum creatinine, sustained 30–40% eGFR decline, or onset of kidney failure—as defined by KDIGO progression criteria.[11] Second, dose-finding studies should compare the 50 mg/day phospholipid-formulated regimen used here with higher daily doses (100–250 mg) and with crystalline trans-resveratrol at the same molar exposure, while measuring plasma resveratrol and its glucuronide and sulphate metabolites to characterise pharmacokinetics in DKD specifically. Third, trials should incorporate urinary TGF-β1, urinary kidney injury molecule-1 (KIM-1), and urinary monocyte chemoattractant protein-1 (MCP-1) alongside serum TGF-β to capture the local renal expression of the fibrogenic and inflammatory programmes that systemic biomarkers approximate only indirectly.[5,7,8] Fourth, mechanistic substudies could quantify peripheral SIRT1 activity, AMPK phosphorylation in peripheral blood mononuclear cells, and circulating advanced glycation end-products as biomarkers of treatment engagement. Fifth, factorial trials testing resveratrol against and in combination with SGLT2 inhibitors and finerenone would clarify whether multi-pathway modulation yields additive or synergistic anti-fibrotic effects in clinical DKD.[12,13] Finally, sub-phenotyping by albuminuric versus non-albuminuric DKD, by baseline eGFR stage, and by inflammatory profile may identify the patient subgroup most likely to benefit—a personalised-medicine question that warrants dedicated investigation.[7,11]

5. Conclusion

Adjuvant low-dose resveratrol (25 mg twice daily) for 12 weeks, added to contemporary standard care in adults with diabetic kidney disease, was associated with significant within-group reductions in serum TGF-β and urinary albumin-to-creatinine ratio, and produced a robust between-group difference in change in UACR favouring the active arm. Glomerular filtration rate did not change significantly over the 12-week window. The intervention was well tolerated, with no serious adverse events and a frequency of mild gastrointestinal symptoms similar to placebo. These findings support a biologically coherent antifibrotic and anti-albuminuric signal that warrants confirmation in larger, longer, multi-centre trials with serial biomarker measurement and exploration of combinations with established nephroprotective therapies.

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