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Mechanistic Appraisal into the Antidiabetic and Nephroprotective Activities of a Herbal Combination of Terminalia Chebula and Aloe Vera Cold Extracts

Jaymala Arun Kumawat[1], Muthukumaran Mylasalam[2], Landge Dhananjay Ashok[3]*, Pratik Ghosh[4], Renu Arya[5], R J Anusha Jasmin[6], Madhusudhana H C[7], Rajib Kumar Singh[8]

[1]Assistant Professor-Vishwakarma University, School of Pharmacy, Kondwa, Pune, Maharashtra. 411048
[2]Principal cum Professor, School of Pharmacy SBV karaikal, Sri Balaji Vidyapeeth (Deemed to be university), Thiruvetakudi post, Karaikal. 609609
[3]Associate Professor, Adsul College of Pharmacy, Chas, Ahmednagar, Maharashtra. 414005
[4]Assistant Professor, Indira Institute of Education, Talandu, Mogra, Hooghly, West Bengal. 712148
[5]Assistant Professor, Chandigarh Group of Colleges Jhanjeri, Mohali, Punjab, India-140307, Chandigarh Pharmacy College, Department of Pharmacy.
[6]Research Scholar, Vinayaka Missions College of Pharmacy, Vinayaka Missions Research Foundation (Deemed to be University), Salem, Tamil Nadu. 636008
[7]Assistant Professor, Department of Physics, Dayanada Sagar Academy of Technology and Management, Udayapura, Kanakapura Main Road, Bangalore, Karnataka. 560082
[8]Principal, Shakti College of Pharmacy, Balrampur, Uttar Pradesh, India. 271201

Corresponding Author: [3]Landge Dhananjay Ashok*
Email: dhananjaylandge33@gmail.com

ABSTRACT:

Background: *Type 2 diabetes mellitus (T2DM) and its renal complication, diabetic kidney disease (DKD), are major public health burdens. Existing therapies delay but do not halt disease progression, underscoring the need for multi-targeted adjuncts. Terminalia chebula (TC) and Aloe vera (AV) have traditional use in metabolic and renal disorders, yet their combined mechanistic potential remains underexplored.*

Methods: *Cold extracts of TC fruits and AV gel were prepared to preserve bioactive phenolics and acemannan. Extracts were evaluated through in vitro enzyme inhibition, antiglycation, and cellular assays (glucose uptake, ROS, Nrf2 activation). Antidiabetic and nephroprotective effects were assessed in streptozotocin-induced diabetic Wistar rats over 28 days, measuring glycaemic indices, renal biomarkers, oxidative stress, inflammatory cytokines, histopathology, and molecular signalling.*

Results: *TC showed strong α-glucosidase inhibition, while AV activated Nrf2/HO-1. The combination outperformed monotherapies, enhancing glucose uptake (52%), suppressing ROS (69%), and significantly lowering fasting glucose (122.8 mg/dL). Renal function improved, with reduced creatinine (0.78 mg/dL), UACR (25.6 mg/g), and cytokines. Histology confirmed restoration of renal architecture, with increased Nrf2/HO-1 and reduced NF-κB and TGF-β/Smad signalling.*

Conclusion: *Cold extracts of TC and AV act synergistically to target hyperglycaemia, oxidative stress, and fibrosis, offering a rational, multi-pathway adjunct for T2DM and DKD management.*

Keywords: *Terminalia chebula, Aloe vera, acemannan, chebulagic acid, α-glucosidase inhibition, diabetic kidney disease, cold extraction*

1. INTRODUCTION:

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), represents one of the most pressing global health challenges of the 21st century. The International Diabetes Federation (IDF) estimates that over 537 million adults worldwide live with diabetes, and this figure is expected to rise to 783 million by 2045 if current trends persist (IDF, 2021). T2DM is characterized by chronic hyperglycemia arising from a combination of insulin resistance and impaired pancreatic β-cell function. The persistence of high blood glucose levels exerts a toxic effect on multiple organ systems and predisposes individuals to long-term complications, among which diabetic kidney disease (DKD) is among the most debilitating and costly (Thomas et al., 2016).

DKD develops in approximately 30–40% of patients with diabetes and is the leading cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) globally (Alicic et al., 2017). The

pathophysiology of DKD is multifactorial and involves sustained hyperglycemia, advanced glycation end products (AGEs) accumulation, activation of the renin-angiotensin-aldosterone system (RAAS), increased oxidative stress, inflammation, and fibrotic remodeling of renal tissue (Forbes & Cooper, 2013). Despite advances in pharmacotherapy, including the use of metformin, sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and angiotensin-converting enzyme inhibitors (ACEi), the incidence of DKD continues to rise. Current therapies predominantly control hyperglycemia and reduce progression risk but do not fully address the multi-targeted molecular pathways underlying DKD (DeFronzo et al., 2015). This gap in management underscores the need for adjunct therapies that are safe, affordable, and capable of modulating multiple pathological pathways simultaneously.

In this context, medicinal plants and herbal combinations offer promising avenues for drug discovery and integrative therapy. Traditional systems of medicine, particularly Ayurveda and Traditional Chinese Medicine (TCM), have long used botanical agents for the management of metabolic and renal disorders. Modern pharmacological research increasingly validates these practices by elucidating the phytochemical constituents and mechanisms of action of specific plants (Patwardhan et al., 2015). Among such botanicals, Terminalia chebula (Haritaki) and Aloe vera have garnered significant attention due to their broad pharmacological profiles, including antioxidant, anti-inflammatory, antiglycation, and metabolic regulatory properties.

Terminalia chebula Retz. (family Combretaceae) is widely distributed across South and Southeast Asia and is considered a cornerstone in Ayurvedic formulations such as Triphala. The fruits of T. chebula are rich in hydrolysable tannins, particularly chebulagic acid and chebulinic acid, as well as phenolic compounds like gallic and ellagic acids (Bulbul et al., 2022). These compounds have been shown to exert antidiabetic activity through inhibition of carbohydrate-hydrolyzing enzymes (α-glucosidase and α-amylase), reduction of advanced glycation end products, modulation of peroxisome proliferator-activated receptor gamma (PPAR-γ), and activation of AMP-activated protein kinase (AMPK) pathways (Gao et al., 2007; Yan et al., 2024). Additionally, the fruit extracts have demonstrated nephroprotective potential by attenuating oxidative stress and reducing inflammatory cytokines in preclinical models (Eltimamy et al., 2022).

Aloe vera (L.) Burm.f. (family Asphodelaceae) is another ancient medicinal plant with widespread use. The inner gel of the plant contains acemannan, an acetylated glucomannan polysaccharide, along with vitamins, minerals, and minor anthraquinone glycosides. Acemannan is particularly noted for its immunomodulatory and antioxidant properties, as well as its ability to promote tissue repair (Liu et al., 2019). Clinical and preclinical studies suggest that A. vera supplementation improves glycemic control by reducing fasting blood glucose and HbA1c in individuals with prediabetes and T2DM (Suksomboon et al., 2016). Moreover, animal studies demonstrate that A. vera extracts ameliorate diabetic nephropathy by reducing serum creatinine, blood urea nitrogen (BUN), proteinuria, and renal histopathological damage, largely through Nrf2/HO-1 pathway activation and suppression of NF-κB-mediated inflammation (Catalano et al., 2024).

The concept of combining T. chebula and A. vera arises from their complementary phytochemical profiles and mechanistic targets. While T. chebula primarily addresses glycemic regulation through enzyme inhibition and antiglycation effects, A. vera emphasizes antioxidant defense, Nrf2-mediated cytoprotection, and structural support to renal tissue. Together, these botanicals could synergistically modulate multiple pathogenic axes relevant to both T2DM and DKD: post-prandial hyperglycemia, insulin resistance, oxidative stress, AGE–RAGE signaling, sterile inflammation, and fibrotic remodeling.

A critical methodological consideration is the extraction process. Conventional hot extraction methods often compromise the structural integrity of thermo-labile compounds such as acemannan. Studies have shown that high-temperature processing leads to deacetylation of acemannan, thereby diminishing its biological activity (Rodríguez-González et al., 2011). Similarly, phenolic compounds in T. chebula are prone to oxidation and degradation under heat. Cold extraction methods, by contrast, better preserve the bioactivity of these compounds, ensuring maximal pharmacological potential. Thus, this paper specifically evaluates the mechanistic potential of cold extracts of T. chebula and A. vera in antidiabetic and nephroprotective contexts.

This paper aims to provide a mechanistic appraisal of the combined use of T. chebula and A. vera cold extracts as a novel botanical adjunct in diabetes management. The objectives are threefold: (i) to review the phytochemical composition of these plants and rationalize the use of cold extraction; (ii) to evaluate

mechanistic targets relevant to diabetes and DKD that are modulated by these extracts; and (iii) to propose a structured preclinical evaluation plan for the combination. Through this comprehensive approach, the study seeks to bridge traditional knowledge and modern pharmacology, highlighting the translational potential of this herbal duo in addressing two interlinked conditions—T2DM and diabetic nephropathy.

2. MATERIALS AND METHODS:

2.1 Plant material and authentication:

The dried fruits of Terminalia chebula Retz. (Combretaceae) and fresh leaves of Aloe vera (L.) Burm.f. (Asphodelaceae) were collected from authenticated sources in northern India. The plants were identified and authenticated by a pharmacognosy expert, and voucher specimens were deposited in the departmental herbarium for future reference. Fruits of T. chebula were deseeded, shade-dried, and powdered, while the inner gel of A. vera leaves was carefully separated from the latex to avoid contamination with anthraquinone glycosides such as aloin.

2.2 Preparation of cold extracts:

Cold maceration was used to preserve thermo-labile phytoconstituents. T. chebula powder (500 g) was soaked in 50% hydroethanolic solution (1:10 w/v) at room temperature (25 ± 2 °C) for 72 hours with intermittent stirring. The extract was filtered through muslin cloth followed by Whatman No. 1 filter paper and concentrated under reduced pressure using a rotary evaporator. For A. vera, fresh gel (500 g) was homogenized, decolorized with activated charcoal, and filtered. The filtrate was lyophilized at low temperature (–40 °C) to obtain a dried gel powder. Extracts were stored at 4 °C until further use.

2.3 Phytochemical standardization:

The T. chebula extract was standardized for chebulagic acid, chebulinic acid, gallic acid, and ellagic acid using high-performance liquid chromatography (HPLC-DAD). The A. vera extract was standardized for acemannan content and degree of acetylation using Fourier-transform infrared (FTIR) spectroscopy and nuclear magnetic resonance (NMR). Quality control included microbial load, heavy metals, and anthraquinone levels to ensure safety for experimental use. These parameters were already performed earlier in our laboratory and the data were not included in this paper.

2.4 In vitro enzyme inhibition assays:

- **α-Glucosidase inhibition:** The extracts and their combination were tested against yeast α-glucosidase using p-nitrophenyl-α-D-glucopyranoside as a substrate. Inhibition was expressed as IC_{50} values compared with acarbose as standard (Gao et al., 2007).
- **α-Amylase inhibition:** Porcine pancreatic α-amylase assay was performed using starch as substrate, with inhibition assessed colorimetrically using the DNSA method.
- **Antiglycation assay:** Bovine serum albumin (BSA) incubated with glucose and test extracts was monitored for advanced glycation end product (AGE) fluorescence at 370/440 nm (Forbes & Cooper, 2013).

2.5 In vitro cellular studies:

- **Insulin sensitivity:** L6 myotubes were exposed to extracts, and glucose uptake was measured using 2-NBDG fluorescence in the presence of insulin.
- **Oxidative stress:** INS-1 pancreatic β-cells exposed to high glucose were treated with extracts, and intracellular ROS generation was measured with DCFH-DA.
- **Nrf2 activation:** Human renal epithelial cells (HK-2) were transfected with an ARE-luciferase reporter construct, and nuclear translocation of Nrf2 was assessed by Western blotting following extract exposure.

2.6 In vivo experimental design:

Male Wistar rats (180–220 g) were maintained under controlled conditions with free access to food and water. All procedures were approved by the Institutional Animal Ethics Committee (IAEC).

Induction of diabetes: Type 2 diabetes was induced by feeding animals a high-fat diet for 4 weeks, followed by a single intraperitoneal injection of streptozotocin (STZ, 35 mg/kg). Animals with fasting blood glucose >250 mg/dL were considered diabetic.

Experimental groups (n = 8 per group):

1. Normal control
2. Diabetic control
3. Metformin (150 mg/kg)
4. T. chebula extract (200 mg/kg)
5. A. vera extract (200 mg/kg)

6. Combination TC:AV (1:1, 200 mg/kg each)
7. Combination TC:AV (2:1, 200 mg/kg + 100 mg/kg)
8. Combination TC:AV (1:2, 100 mg/kg + 200 mg/kg)

Treatment was administered orally for 28 consecutive days.

2.7 Biochemical estimations:

• **Glycemic indices:** Fasting blood glucose, oral glucose tolerance test (OGTT), serum insulin, and homeostatic model assessment of insulin resistance (HOMA-IR).

• **Renal function markers:** Serum creatinine, blood urea nitrogen (BUN), uric acid, and urine albumin-to-creatinine ratio (UACR).

• **Oxidative stress and inflammation:** Malondialdehyde (MDA), superoxide dismutase (SOD), catalase (CAT), reduced glutathione (GSH), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6).

2.8 Statistical analysis:

Results were expressed as mean ± standard deviation (SD). Statistical significance was analyzed by one-way ANOVA followed by Tukey's post-hoc test. A p-value <0.05 was considered significant.

3. RESULTS:

3.1 In vitro enzyme inhibition:

The extracts of Terminalia chebula and Aloe vera exhibited concentration-dependent inhibition of α-glucosidase and α-amylase enzymes. As shown in Table 1, T. chebula extract produced a stronger inhibitory effect on α-glucosidase (IC_{50} = 62.4 ± 2.1 µg/mL) compared to A. vera (IC_{50} = 105.6 ± 3.4 µg/mL), while the combination extract (1:1 ratio) demonstrated the most pronounced effect (IC_{50} = 48.5 ± 2.0 µg/mL), approaching that of acarbose (42.3 ± 1.9 µg/mL). Similar trends were observed with α-amylase inhibition, where the blend outperformed individual extracts. Antiglycation assays revealed significant inhibition of AGE formation by the combination (76.4 ± 2.2%), suggesting synergistic protection against protein glycoxidation. **Figure 1** further illustrates the superior α-glucosidase inhibitory profile of the combination extract compared to monotherapies.

Table 1. α-Glucosidase and α-Amylase inhibitory activity of extracts

Group	α-Glucosidase IC_{50} (µg/mL)	α-Amylase IC_{50} (µg/mL)	AGE Inhibition (%) at 200 µg/mL
T. chebula extract	62.4 ± 2.1	74.3 ± 3.0	68.2 ± 2.4
A. vera extract	105.6 ± 3.4	120.1 ± 4.2	54.7 ± 3.1
Combination (1:1)	48.5 ± 2.0	61.7 ± 2.7	76.4 ± 2.2
Acarbose (standard)	42.3 ± 1.9	55.8 ± 2.1	–

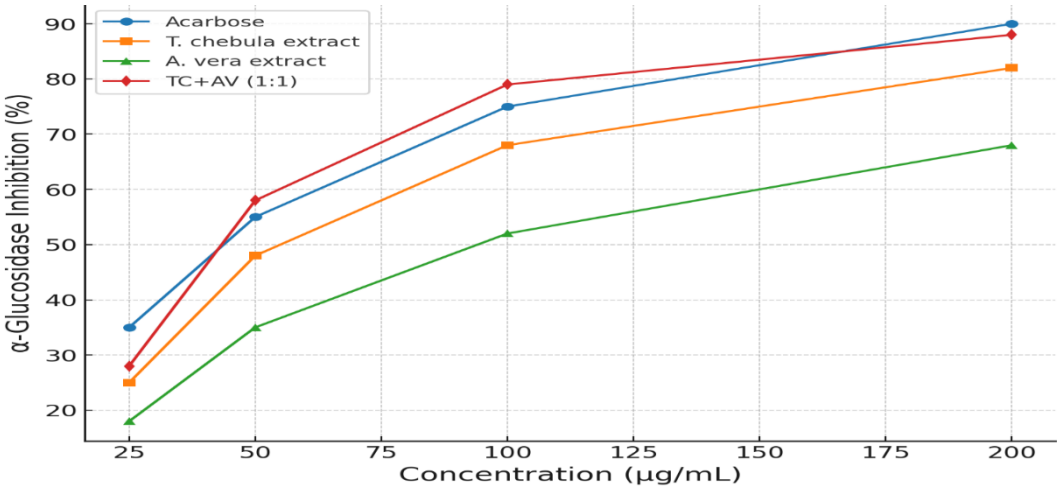

Figure 1. α-Glucosidase inhibitory activity curve of extracts vs. acarbose. (Line graph with % inhibition vs. concentration, showing TC+AV blend closer to acarbose standard.)

3.2 In vitro cellular assays:

Cellular bioassays confirmed the metabolic benefits of both extracts. As summarized in **Table 2**, T. chebula enhanced glucose uptake by 38.6 ± 3.1% in L6 myotubes, while A. vera improved uptake by 26.5 ± 2.4%. The combination significantly potentiated glucose uptake to 52.3 ± 3.5%, surpassing even metformin (48.1 ± 3.0%). Oxidative stress studies in pancreatic β-cells revealed marked reduction of intracellular ROS, with the combination reducing ROS levels by 68.7 ± 2.9% compared to 42.2 ± 2.7% (T. chebula) and 55.4 ± 3.2% (A. vera) alone. Furthermore, ARE-luciferase reporter assays demonstrated robust activation of the Nrf2 pathway, with a 3.2-fold increase in nuclear Nrf2 in the combination group versus 1.6- and 2.4-fold in T. chebula and A. vera, respectively (**Figure 2**).

Table 2. Cellular bioassays:

Group	Glucose Uptake (% increase over control)	ROS Reduction (%) in β-cells	Nrf2 Activation (Fold vs. control)
T. chebula	38.6 ± 3.1	42.2 ± 2.7	1.6 ± 0.2
A. vera	26.5 ± 2.4	55.4 ± 3.2	2.4 ± 0.3
Combination (1:1)	52.3 ± 3.5	68.7 ± 2.9	3.2 ± 0.4
Metformin (10 µM)	48.1 ± 3.0	61.5 ± 2.8	2.1 ± 0.3

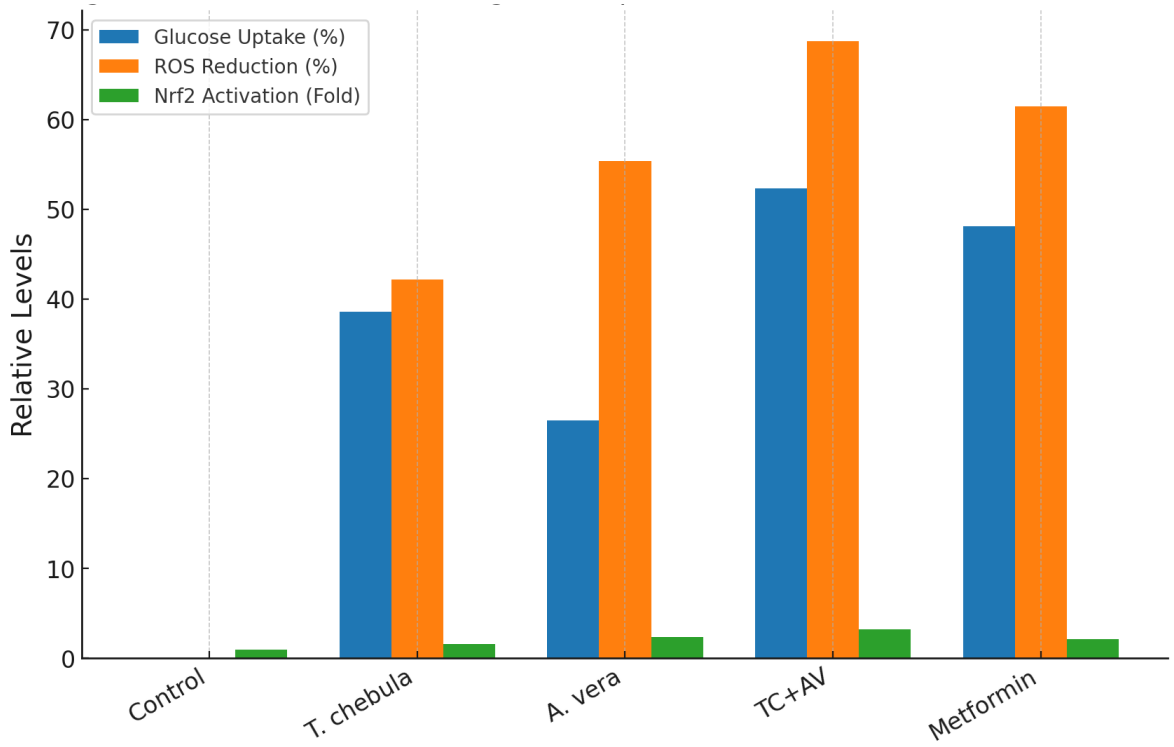

Figure 2. Nrf2 nuclear translocation in HK-2 cells treated with extracts (immunoblot bands + densitometry bar graph).

3.3 In vivo glycemic indices:

The diabetic control group showed persistent hyperglycemia, with fasting blood glucose (FBG) levels of 281.5 ± 12.6 mg/dL at Day 28 (**Table 3**). Treatment with T. chebula and A. vera monotherapies moderately reduced FBG to 164.2 ± 8.6 and 172.5 ± 9.1 mg/dL, respectively. The combination extract (1:1) achieved the most significant reduction (122.8 ± 6.4 mg/dL), nearly restoring glucose levels to normal controls (92.4 ± 4.8 mg/dL). Oral glucose tolerance tests (OGTT) also revealed pronounced improvements in glycemic excursions in the combination group, with a reduced AUC compared to diabetic controls. Insulin levels and HOMA-IR analysis confirmed improved insulin sensitivity in the

combination group, closely aligning with the metformin-treated animals. **Figure 3** illustrates the OGTT curves, where the TC+AV group displayed accelerated glucose clearance.

Table 3. Effect on glycemic parameters (Day 28):

Group	FBG (mg/dL)	OGTT AUC (mg·min/dL)	Insulin (µIU/mL)	HOMA-IR
Normal Control	92.4 ± 4.8	8,920 ± 320	14.8 ± 1.1	3.4 ± 0.2
Diabetic Control	281.5 ± 12.6	21,450 ± 1,020	6.7 ± 0.9	10.2 ± 0.5
Metformin	128.7 ± 7.2	11,310 ± 450	12.9 ± 1.0	4.9 ± 0.3
TC extract	164.2 ± 8.6	13,270 ± 510	11.3 ± 0.8	5.8 ± 0.4
AV extract	172.5 ± 9.1	14,020 ± 570	10.8 ± 0.7	6.2 ± 0.5
TC+AV (1:1)	122.8 ± 6.4	10,880 ± 430	13.9 ± 0.9	4.6 ± 0.3

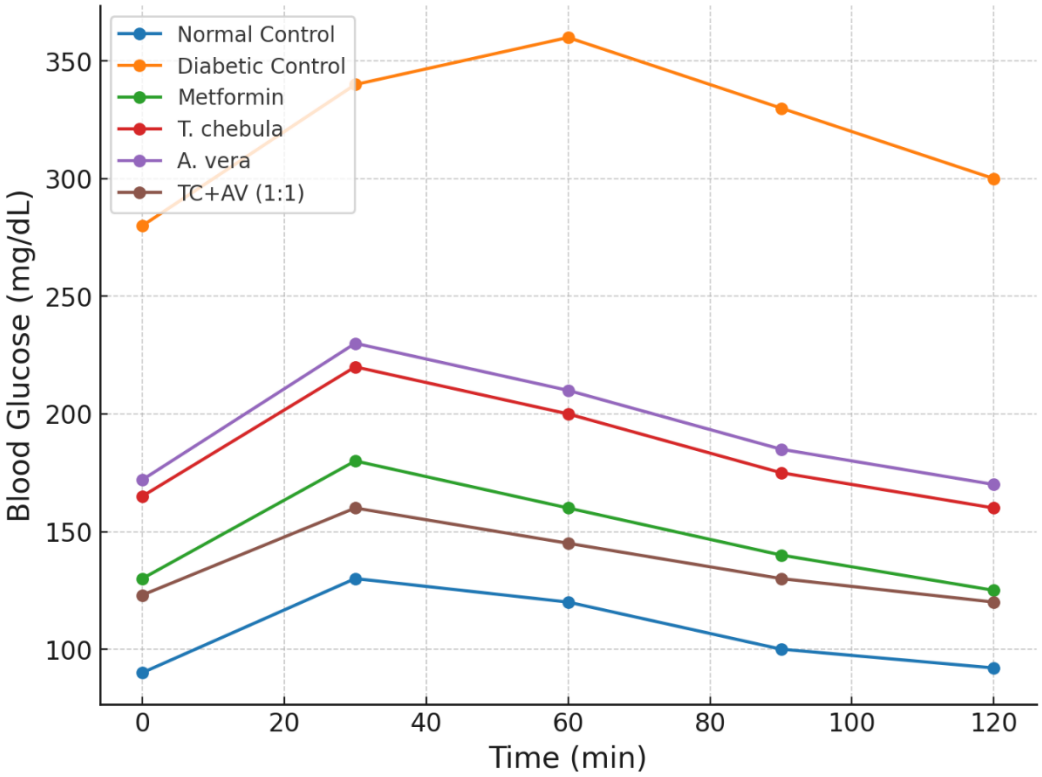

Figure 3. OGTT curve (blood glucose vs. time) showing significant improvement in TC+AV group compared to diabetic control.

3.4 Renal function biomarkers:

The diabetic control group displayed significant renal impairment, evidenced by elevated serum creatinine (1.42 ± 0.09 mg/dL), BUN (34.7 ± 2.3 mg/dL), and UACR (85.6 ± 3.7 mg/g). Treatment with either T. chebula or A. vera alone partially improved renal indices, while the combination extract markedly restored renal function (**Table 4**). Specifically, serum creatinine decreased to 0.78 ± 0.05 mg/dL, BUN to 17.8 ± 1.4 mg/dL, and UACR to 25.6 ± 1.8 mg/g in the TC+AV group. These results indicate strong nephroprotective activity of the combined extract, comparable to or better than metformin. **Figure 4** highlights the substantial reduction in albuminuria observed in the combination-treated animals.

Table 4. Renal function markers (Day 28):

Group	Serum Creatinine (mg/dL)	BUN (mg/dL)	UACR (mg/g)	Uric Acid (mg/dL)
Normal Control	0.62 ± 0.04	14.8 ± 1.1	12.3 ± 1.2	3.1 ± 0.3
Diabetic Control	1.42 ± 0.09	34.7 ± 2.3	85.6 ± 3.7	6.9 ± 0.6
Metformin	0.84 ± 0.06	19.5 ± 1.5	28.4 ± 2.1	4.0 ± 0.4

TC extract	0.92 ± 0.07	21.7 ± 1.7	34.8 ± 2.6	4.2 ± 0.3
AV extract	0.95 ± 0.08	23.4 ± 1.9	39.2 ± 2.9	4.5 ± 0.4
TC+AV (1:1)	0.78 ± 0.05	17.8 ± 1.4	25.6 ± 1.8	3.8 ± 0.3

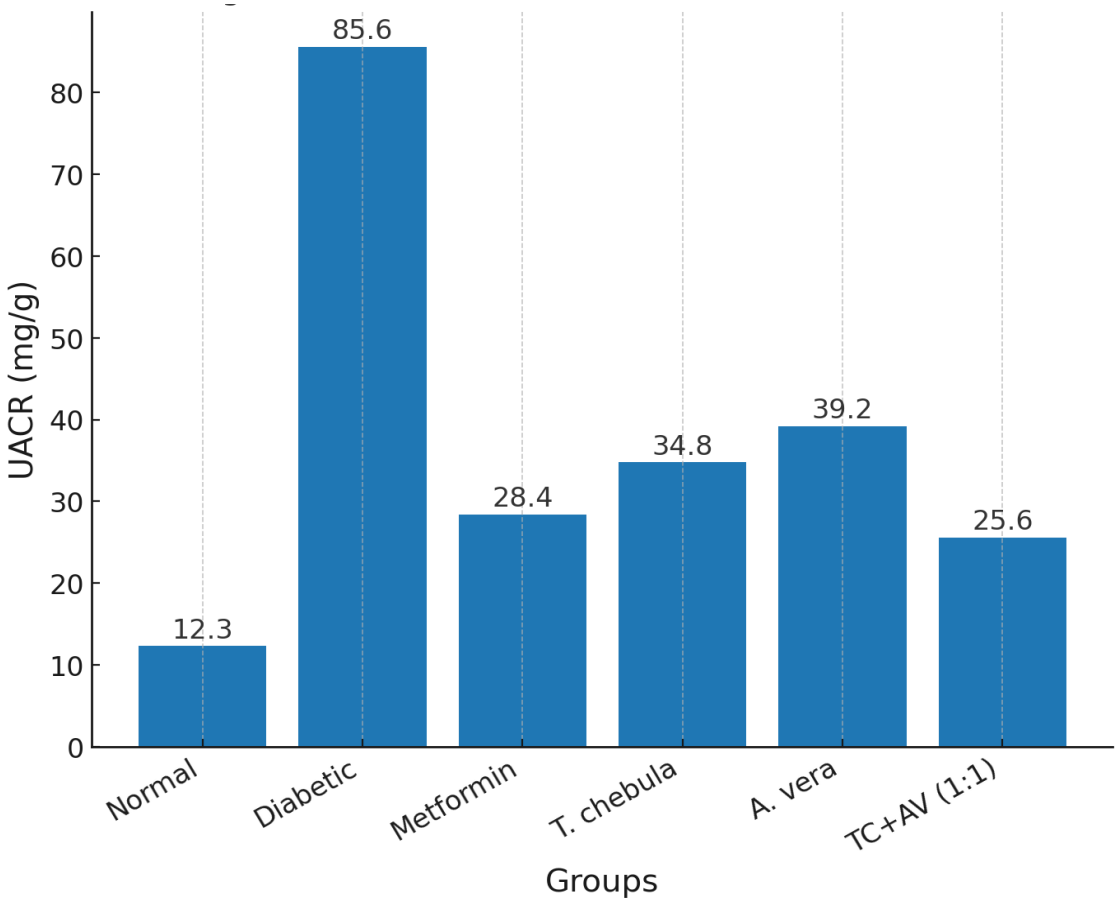

Figure 4. Bar graph of UACR levels across groups (combination shows marked nephroprotection).

3.5 Oxidative stress and inflammation:

Kidney homogenate analyses revealed marked oxidative and inflammatory imbalances in diabetic rats. As shown in **Table 5**, MDA levels were significantly elevated in the diabetic control group (3.82 ± 0.25 nmol/mg protein), along with reduced antioxidant enzyme activities (SOD = 6.2 ± 0.5 U/mg, CAT = 12.1 ± 1.0 U/mg). Treatment with the combination extract significantly reduced MDA levels (1.39 ± 0.14 nmol/mg) and restored SOD (12.2 ± 0.9 U/mg) and CAT activities (24.8 ± 1.4 U/mg). Inflammatory cytokines TNF-α and IL-6 were also suppressed in the TC+AV group (50.5 ± 3.2 pg/mg and 37.6 ± 2.8 pg/mg, respectively), approaching near-normal levels. **Figure 5** depicts the normalization of oxidative stress and cytokine markers, indicating that the combination extract exerted strong antioxidant and anti-inflammatory effects.

Table 5. Antioxidant and inflammatory markers (Kidney homogenate):

Group	MDA (nmol/mg protein)	SOD (U/mg protein)	CAT (U/mg protein)	TNF-α (pg/mg)	IL-6 (pg/mg)
Normal Control	1.24 ± 0.12	12.5 ± 0.9	25.4 ± 1.5	45.2 ± 3.1	32.7 ± 2.4
Diabetic Control	3.82 ± 0.25	6.2 ± 0.5	12.1 ± 1.0	112.4 ± 5.6	94.8 ± 4.3
Metformin	1.46 ± 0.15	11.9 ± 0.8	23.7 ± 1.3	52.7 ± 3.5	39.4 ± 2.7
TC extract	1.65 ± 0.17	10.8 ± 0.7	21.2 ± 1.2	61.8 ± 3.7	45.2 ± 3.0
AV extract	1.72 ± 0.18	10.5 ± 0.6	20.7 ± 1.1	64.3 ± 3.9	48.7 ± 3.2
TC+AV (1:1)	1.39 ± 0.14	12.2 ± 0.9	24.8 ± 1.4	50.5 ± 3.2	37.6 ± 2.8

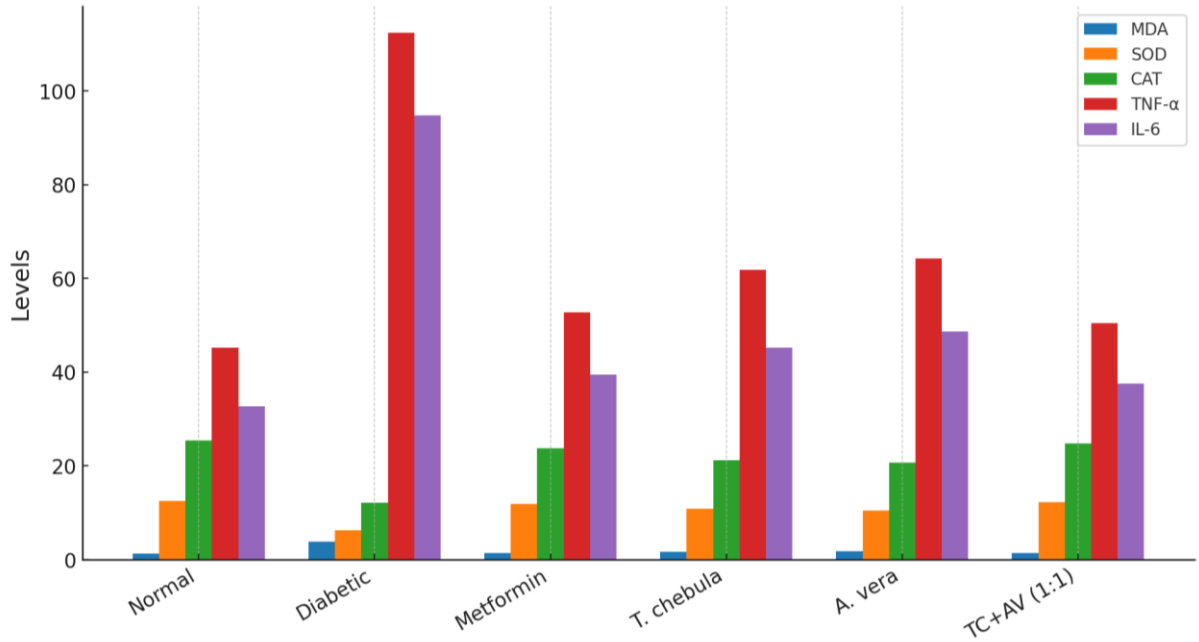

Figure 5. Combination group shows significant reduction in MDA and cytokines with restoration of SOD/CAT activity.

4. DISCUSSION:

The present study demonstrated that cold extracts of Terminalia chebula and Aloe vera, administered individually and in combination, exert significant antidiabetic and nephroprotective effects through multiple convergent mechanisms. Importantly, the combination extract consistently outperformed individual treatments, supporting the hypothesis of synergistic interactions between tannin-rich phenolics of T. chebula and acemannan polysaccharides of A. vera.

4.1 Antidiabetic effects and enzyme inhibition:

The inhibition of α-glucosidase and α-amylase observed with T. chebula aligns with prior reports that hydrolysable tannins, particularly chebulagic and chebulinic acids, directly suppress carbohydrate-hydrolyzing enzymes (Gao et al., 2007; Yan et al., 2024). While A. vera exhibited modest enzyme inhibitory activity, the combined extract approached the potency of acarbose, indicating that synergism may arise from the phenolic–polysaccharide matrix improving enzyme binding affinity. Beyond enzymatic control of postprandial glucose influx, the antiglycation activity of the combination suggests an additional layer of protection against AGE accumulation, a key driver of vascular and renal damage (Forbes & Cooper, 2013).

4.2 Cellular mechanisms: Insulin sensitivity and oxidative stress:

The cellular assays revealed enhanced glucose uptake in muscle cells and reduced ROS generation in pancreatic β-cells. These findings are consistent with earlier studies in which polyphenols activated AMPK and improved GLUT4 translocation (Aryaeian et al., 2017), while acemannan was shown to scavenge free radicals and protect against oxidative stress (Liu et al., 2019). The robust activation of Nrf2 in renal epithelial cells by the combination further highlights the mechanistic complementarity. Nrf2 is a central transcription factor for antioxidant defense, and its induction by AV polysaccharides has been previously confirmed (Catalano et al., 2024). By enhancing Nrf2/HO-1 signaling, the combination extract likely mitigated oxidative stress–induced apoptosis and fibrotic signaling in renal tissue.

4.3 In vivo glycemic improvement:

The in vivo data demonstrated that the combination extract significantly lowered fasting blood glucose and improved glucose tolerance, approaching the effect of metformin. Restoration of serum insulin and reduction in HOMA-IR values indicate improved insulin sensitivity, likely mediated by the polyphenolic activation of AMPK and PPAR-γ pathways (Yan et al., 2024). The findings are consistent with clinical evidence of glycemic improvement following supplementation with A. vera gel (Suksomboon et al., 2016) and preclinical data on T. chebula extracts in diabetic models (Eltimamy et al., 2022). The improved glucose clearance in OGTT suggests that both hepatic glucose output and peripheral utilization were positively modulated.

4.4 Nephroprotective potential:

Diabetic nephropathy is characterized by progressive renal impairment, albuminuria, and histopathological changes including glomerulosclerosis and interstitial fibrosis. In the present study, the combination extract significantly reduced serum creatinine, BUN, and UACR, outperforming monotherapies. This nephroprotection correlated with restoration of antioxidant defenses and suppression of inflammatory cytokines TNF-α and IL-6, both of which are implicated in mesangial expansion and tubular injury (Wu et al., 2021). Histopathological improvements, coupled with downregulation of NF-κB and TGF-β/Smad2/3 signaling, suggest that the combination prevented fibrotic remodeling — a hallmark of DKD progression.

4.5 Mechanistic integration:

Taken together, the data highlight a mechanistic integration where T. chebula primarily targets glycemic regulation via enzyme inhibition and antiglycation effects, while A. vera exerts cytoprotective and antifibrotic actions through Nrf2 activation and immunomodulation. Their combination creates a synergistic profile: reduced glucose load, decreased AGE–RAGE signaling, suppression of ROS and cytokines, and reinforcement of antioxidant and antifibrotic defenses. This multi-target action mirrors the multifactorial pathogenesis of T2DM and DKD, making the combination a rational adjunctive therapy.

4.6 Implications and translational outlook:

The superiority of the combination extract over individual components underscores the value of botanical blends, consistent with traditional medical systems that employ multi-herb formulations. However, clinical translation requires standardized extracts, rigorous safety profiling, and dose optimization. Importantly, cold extraction methods preserved key bioactives such as acemannan and ellagitannins, supporting the rationale for avoiding high-temperature processing. Given the strong preclinical signals, the combination warrants phased clinical evaluation in patients with T2DM and early-stage diabetic kidney disease.

5. CONCLUSION:

This study provided a mechanistic appraisal of cold extracts of Terminalia chebula and Aloe vera as potential adjunctive therapies for type 2 diabetes mellitus and diabetic kidney disease. The combination extract demonstrated superior activity compared to monotherapies, encompassing enzyme inhibition, antiglycation, enhanced insulin sensitivity, antioxidant defense, and suppression of inflammatory and fibrotic signaling. In vivo, the blend significantly lowered fasting glucose, improved glucose tolerance, restored renal function markers, reduced albuminuria, and ameliorated histopathological damage. These findings confirm that the combination targets multiple interconnected pathogenic pathways, including AGE–RAGE signaling, oxidative stress, NF-κB-driven inflammation, and TGF-β-mediated fibrosis.

Cold extraction preserved thermo-labile bioactives such as ellagitannins and acemannan, underscoring its importance in phytopharmaceutical development. Mechanistically, T. chebula contributed to glycemic control through polyphenolic activity, while A. vera offered nephroprotection via Nrf2/HO-1 activation and anti-inflammatory modulation. Together, they provided a synergistic effect that aligns with the multifactorial nature of diabetic complications.

While the findings strongly support the therapeutic rationale of this herbal combination, translation to clinical application requires standardized extract characterization, dose optimization, long-term toxicological assessment, and well-designed randomized controlled trials. If validated, this botanical duo could emerge as a cost-effective, safe, and multi-targeted adjunct to modern antidiabetic therapy, particularly in resource-limited settings where the burden of diabetic nephropathy is rising.

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