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Original Article

Hypolipidemic and Renoprotective Effects of Methanolic Leaf Extract of *Aegle marmelos* in Streptozotocin-Induced Diabetic Rats: A Dose-Dependent Study

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ABSTRACT

Background: Diabetes mellitus is a chronic metabolic disorder commonly associated with dyslipidemia and progressive renal dysfunction, contributing to long-term complications. Leaves of *Aegle marmelos* (Bael), a traditional medicinal plant, contain phytochemicals with hypolipidemic and renoprotective activity. **Aim and Objectives:** To evaluate the dose-dependent hypolipidemic and renoprotective effects of a methanolic leaf extract of *Aegle marmelos* in streptozotocin-induced diabetic rats. **Materials and Methods:** Adult male Wistar rats were randomised into six groups (*n*=6 each): non-diabetic control, diabetic control, standard treatment (glimepiride + metformin), and three extract-treated group receiving 125,250, and 375 mg/kg *A. marmelos* once daily for 60 days after diabetes induction with streptozotocin (50 mg/kg, i.p.). The outcome assessors were blinded to group codes. The primary outcomes were serum urea and creatinine levels, and the secondary outcomes were Total Cholesterol (TC), LDL-Cholesterol (LDL-C), HDL- Cholesterol (HDL-C). Measurements were obtained at baseline (day 0) and day 60. The primary analysis compared groups at day 60 and assessed dose-response across the extract groups. **Results:** By day 60, extract-treated rats showed lower TC, LDL-C, urea, and creatinine and higher HDL-C than diabetic controls in a dose-dependent pattern. The 375 mg/kg group approached the standard therapy group on several endpoints. No treatment-related mortality was observed. **Conclusion:** The methanolic leaf extract of *A. marmelos* exhibited dose-dependent hypolipidemic and renoprotective effects in STZ-diabetic rats. These findings support further mechanistic evaluation and basic chemical standardisation for translational development.

Keywords: *Aegle marmelos*, Cholesterol, Diabetic nephropathy, Dyslipidemia, Streptozotocin, HDL, LDL.

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INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disorder characterized by sustained hyperglycemia resulting from impaired insulin secretion or reduced insulin sensitivity. This persistent hyperglycemic state disrupts carbohydrate, protein, and lipid metabolism. Globally, an estimated 589 million adults between the age 20-79 years were living with diabetes in 2024. This number is expected to rise to 853 million by 2050. Diabetes accounted for 3.4 million deaths, with over 80% of fatalities occurring in low- and middle- income countries (International Diabetes Federation, 2025). India is considered a global epicentre for diabetes, currently harbouring over 101 million individuals with diabetes and 136 million with prediabetes, according to the ICMR-INDIAB 2019-21 report (Anjana *et al.*, 2023). The high incidence in India is associated with factors such as fast-paced urban growth, inactive lifestyles, and genetic factors. Along with hyperglycemia, Diabetes Mellitus (DM) is associated with metabolic complications, including macrovascular and microvascular issues. Hyperglycemia induces oxidative stress and inflammation, contributing to dyslipidemia, characterised by elevated Triglyceride (TG) and Total Cholesterol (TC), reduced High Density Lipoprotein - Cholesterol (HDL-C), and increased atherogenic Low Density Lipoprotein - Cholesterol (LDL- C) (Mooradian, 2009; Giacco and Brownlee, 2010). This profile worsens cardiovascular and renal complications in diabetic patients.

The management of DM involves lifestyle modifications with pharmacotherapy. Pharmacotherapy includes Oral Hypoglycemic Agents (OHAs), which include biguanides (metformin), meglitinides (repaglinide), sulfonylureas (glimepiride), α-glucosidase inhibitors (voglibose), DPP-4

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inhibitors (sitagliptin), thiazolidinediones (pioglitazone), SGLT2 inhibitors (dapagliflozin) along with injectables like GLP-1 receptor agonists and insulin (American Diabetes Association Professional Practice Committee, 2025). However, there are also safety concerns with these agents. Each class has characteristic adverse-effect profiles like hypoglycemia with sulfonylureas, UTI with SGLT2 inhibitors, gastric intolerance with metformin. In the pursuit of safer and multi-targeted therapeutic options for diabetes management, phytopharmacology has gained increasing attention. Numerous medicinal plants have also emerged to be a promising alternative to conventional antidiabetic therapies, particularly for managing the metabolic and oxidative complications of diabetes. *Aegle marmelos* also known as bael, is widely used in traditional Ayurvedic medicinal plant. The leaves rich in flavonoids, coumarins, alkaloids, and terpenoids, recognized for antioxidant, anti-inflammatory, hypoglycemic, and hypolipidemic properties. Earlier *in vivo* studies suggest that *Aegle marmelos* leaf extracts can improve lipid indices and attenuate renal injury in diabetic rodents (Sharma *et al.*, 2007; Devi *et al.*, 2010; Bhatti *et al.*, 2013). *In vitro* findings support antioxidant and anti-inflammatory plausibility (Venkatesan *et al.*, 2024).

Despite the mounting preliminary finding, evidence for the dual hypolipidemic and renoprotective actions of *Aegle marmelos* in diabetes remains limited. Most prior studies used a single dose and evaluated either lipid or renal outcomes in isolation. We therefore investigated with a methanolic *A. marmelos* leaf extract produces dose- dependent improvements in lipid parameters i.e. Total Cholesterol (TC), Low Density Lipid Cholesterol (LDL-C) and High-Density Lipid Cholesterol (HDL-C) and renal markers (urea, creatinine) in streptozotocin-induced diabetic Wistar rats, benchmarked against metformin + glimepiride. This study aims to quantify graded effects across metabolic and renal endpoints within a single *in vivo* model to address this gap.

AIM AND OBJECTIVES

To evaluate the dose-response of methanolic *Aegle marmelos* leaf extract (125,250, 375 mg/kg; p.o., 60 days) on serum lipid (TC, LDL-C, HDL-C) and renal (urea, creatinine) markers in STZ-induced diabetic Wistar rats.

To compare day- 60 outcomes for the extract (375 mg/kg) with the active comparator (metformin + glimepiride) across same endpoints.

MATERIALS AND METHODS

The study was conducted in the Animal House at Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar, following approval from the Institutional Animal Ethics Committee, KIMS (IAEC No. 1730/PO/Re/13/CPCSEA). The study was conducted over 60 days. All procedure followed CPCSEA guidelines. Streptozotocin was obtained from HiMedia Laboratory (Pvt. Ltd., India). Necessary supplies, including glucometers and medications such as glimepiride, metformin, and mupirocin ointment were obtained from the KIMS Pharmacy.

Collection and preparation of plant extract

Fresh leaves of *Aegle marmelos* were procured locally and authenticated by a botanist at KIIT University, Bhubaneswar. Leaves were shade-dried at room temperature, grinded to coarse powder. Powdered leaves (100 g) were extracted with 400 mL of methanol in a Soxhlet apparatus for 6-8 hr (Figure 1). This extract was filtered and concentrated under reduced pressure using a rotary evaporator to yield a semi-solid mass with a 4.8% w/w yield. The extract was stored in an airtight container at 4°C until required for biological and phytochemical analysis.

Animals used and grouping of animals

36 healthy adult male albino Wistar rats weighing 180-200 g were used in the study. The rats were kept at acclimation for a week before initiation of the study. The standard conditions for keeping animals includes: Humidity at 30-60%, room temperature 25±2°C, and 12 hr of dark as well as 12 hr light were followed. Ad libitum food and water were provided to all rats. After confirming diabetes (section C), Rats were randomised using a computer-generated sequence prepared by an independent technician into six groups with 6 rats in each group. Group assignments were placed in Sequentially Numbered, Opaque, Sealed Envelopes (SNOSE) and opened only at allocation. Cages and sample tubes were labelled with anonymised codes. Animals from each group were distributed across cages to avoid cage effects. The grouping and intervention are planned as shown in Table 1.

Induction of experimental diabetes

Experimental diabetes was induced with Streptozotocin (STZ). Following an overnight fast (Group II-VI) rats were given a single intraperitoneal injection of freshly prepared STZ at a dose of 50 mg/kg body weight, diluted in a 0.9% saline solution. The vehicle control group (Group I) received normal saline only. To mitigate early hypoglycemia, all STZ-treated rats received a 5% glucose solution orally for 24-hr post-injection. 72 hr later, fasting blood glucose levels was measured using a glucometer. Rats with blood glucose levels ≥ 250 mg/dL were considered as diabetic and included in the study. No animals required exclusion.

Estimation of Biochemical Parameters

During the study, blood was collected from all animals on day 0 and again on day 60 to evaluate biochemical changes. Serum Total Cholesterol (TC) was estimated by CHOD POD (Cholesterol Oxidase-Peroxidase) enzymatic method. HDL- cholesterol (HDL-C) was measured using dextran sulphate precipitation technique. All lipid results are reported in mg/dL; internal quality controls were run with each batch. Serum urea and creatinine were measured on a semi- automated analyser (Photometer 5010,

Diasys India) using reagents from Erba Diagnostics (Mannheim, Germany), following the manufacturer's protocol. Results are reported in mg/dL. Assays were performed by blinded outcome assessors with internal quality control per run.

All biochemical analysis were performed at the central laboratory of KIMS, Bhubaneswar.

Acute Toxicity Studies

As per the Organization for Economic Cooperation and Development (OECD) guideline No. 423, the acute oral toxicity study was conducted. During the study, six albino Wistar rats were administered a high dose of extract of 2000 mg/kg per oral. These rats were observed for a period of 14 days, for clinical sign morbidity, mortality, with body weights recorded on day 0, 7, and 14. No mortality or treatment limiting signs were observed at 2000 mg/kg. Accordingly, efficacy doses of 125, 250, and 375 mg/kg p.o. were selected and considered safe for research.

Statistical Analysis

Data are presented as Mean±Standard Deviation (SD). Statistical comparisons between groups were tested using one-way ANOVA, followed by Tukey's *post hoc* test. Changes within groups from day 0 to day 60 were assessed using paired *t*-tests. All Statistical analysis were performed using socscistatistics.com. A $p<0.05$ was taken as statistically significant.

Animal Welfare and Monitoring

Throughout the study period, the animals were monitored twice daily for general health, grooming, food intake, and signs of distress. Humane endpoints, such as >20% body weight loss, severe lethargy, or signs of pain, were predefined; however, no adverse outcomes or mortality occurred. All animal handling procedures were performed by trained personnel. Investigators performing biochemical estimations were blinded to group allocation to reduce observer bias.

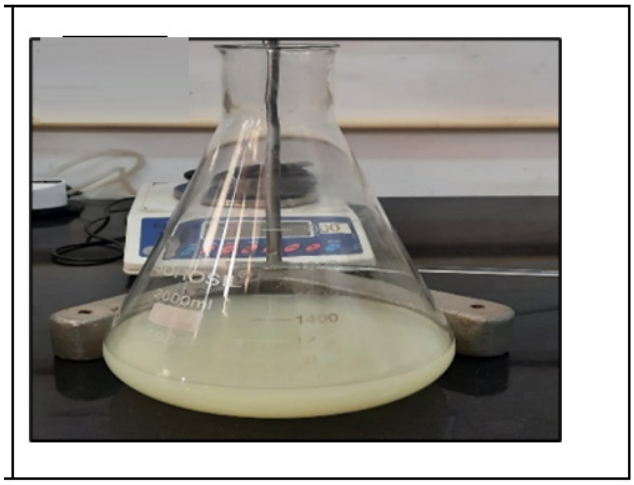

Figure 1: Preparation of *Aegle marmelos* extract. (A) Shade-dried *Aegle marmelos* (bael) leaves for extraction. (B) Methanolic extract in an Erlenmeyer flask.

RESULTS

As shown in Table 2, by day 60 the diabetic rats (Group II) exhibited a significant increase in TC and LDL-C, along with decrease in HDL-C levels by day 60, compared to their baseline values. In contrast, *Aegle marmelos* leaf extract group (Groups IV-VI) produced dose-dependent improvements in all lipid parameters, with highly significant differences versus diabetic control ($p<0.0001$). The highest dose (375 mg/kg; Group VI) exhibited lipid levels closely comparable to the standard treatment group (Group III).

As shown in Table 3, diabetic rats (Group II) demonstrated significantly elevated serum urea and creatinine levels on day 60 compared to baseline, indicating renal dysfunction associated with diabetic nephropathy. Oral administration of *A. marmelos* leaf extract (Group IV-VI) resulted in dose-dependent improvement in renal markers. Notably, Group VI (375 mg/kg) exhibited nearly normal renal parameters, comparable to those of the standard treatment group and significantly superior to those of the diabetic control group (Group II).

DISCUSSION

Antidiabetic pharmacotherapy remains the backbone of diabetes care, with agents like metformin, sulfonylureas, thiazolidinediones, DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 receptor agonists selected to match patient profile and treatment goals (Bailey, 2017). While these therapies improve glycemic control, their long-term use is often constrained by adverse events like gastrointestinal intolerance with metformin, hypoglycemia and weight gain with sulfonylureas, fluid retention with thiazolidinediones, or urinary infections with SGLT2 inhibitors (Maruthur *et al.*, 2016). Furthermore, these agents primarily target glucose lowering but offer limited protection against lipid abnormalities and renal deterioration, which are major contributors to diabetes related morbidity. This therapeutic gap has stimulated research in phytomedicines that may provide multi-targeted benefits.

Atherogenic dyslipidemia is a common metabolic disorder associated with diabetes. Individuals with diabetes present with elevated small dense LDL particles with concurrent reduction in HDL cholesterol is highly prevalent in diabetes and strongly associated with increased cardiovascular risks (Mooradian, 2009). These lipid abnormalities are mechanistically linked to oxidative stress and low-grade inflammation, both of which exacerbate vascular and renal damage. Diabetic nephropathy, the leading cause of end-stage renal disease worldwide, arises from hyperglycemia driven pathways such as advanced Glycation End-product (AGE) accumulation, mitochondrial dysfunction, and excessive Reactive Oxygen Species (ROS) generation (Giacco and Brownlee, 2010). Together, these processes accelerate lipid peroxidation, endothelial injury, and microvascular dysfunction,

underscoring the need for therapeutic strategies that address both dyslipidemia and renal impairment simultaneously.

As shown in Table 2, diabetic control rats (Group II) demonstrated a significant increase in serum TC and LDL-C, with a parallel decrease in HDL-C at day 60 compared with baseline, reflecting the classical diabetic dyslipidemia pattern. In contrast, treatment with *Aegle marmelos* leaf extract (Group IV-VI) produced dose dependent improvements across all lipid parameters. The highest dose (375 mg/kg; Group VI) achieved near normalisation of TC, LDL-C, and HDL-C levels, closely approximating vales in the standard therapy group (Group III). These findings suggest that *Aegle marmelos* exerts strong hypolipidemic actions, potentially mediated through inhibition of HMG-CoA reductase, modulation of hepatic lipid handling, and antioxidant effects. The results from this *in vivo* model reinforce earlier *in vitro* work, such as those by (Ahmad *et al*., 2021), who demonstrated antioxidant and antidiabetic activity of *A. marmelos* leaf extracts.

As shown in Table 3, diabetic rats (Group II) also exhibited a significant rise in serum urea and creatinine levels by day 60, consistent with renal dysfunction characteristic of diabetic nephropathy. *A. marmelos* leaf extract produces a graded reduction in these renal markers, with the 375 mg/kg dose restoring values close to normal and comparable to the standard therapy group. This nephroprotective effect may be explained by the ability of bioactive compound in *A. marmelos* to suppress pro-inflammatory cytokines such as TNF-α, inhibit inducible Superoxide Dismutase (SOD) and catalase. These outcomes corroborate with prior evidence from (Bhatti *et al*., 2013), who reported restoration of renal oxidative in STZ- diabetic rats treated with *A. marmelos.*

The methodological design of the present study adds novelty compared to earlier work. Whereas most previous studies investigated either lipid or renal outcomes at a single extract dose, we simultaneously evaluated both endpoints across three graded doses in a validated STZ- diabetic rat model. Randomisation, allocation concealment, and blinded outcome assessment strengthened internal validity and minimised bias. The 60 days treatment duration allowed assessment of sub- chronic effects, providing a translational insight into a potential long-term benefit. Thus, our finding extends a prior literature by demonstrating the dose-dependent dual efficacy of *A. marmelos* on lipid and renal outcomes in a single *in vivo* framework.

Table 1: Experimental groups, intervention and dosing in Streptozotocin (STZ)- induced diabetic Wistar rats.

Groups	Number of Rats	Description	Drug used
Group I	6	Vehicle Control	Normal saline
Group II	6	Diabetic Control	Streptozotocin (STZ)-induced
Group III	6	Treatment Control	Glimepiride (1mg/kg) + Metformin (500 mg/kg), p.o., once daily
Group IV	6	Extract- low dose	*A. marmelos* extract 125 mg/kg, p.o., once daily
Group V	6	Extract- medium dose	*A. marmelos* extract 250 mg/kg, p.o., once daily
Group VI	6	Extract- high dose	*A. marmelos* extract 375 mg/kg, p.o., once daily

Table 2: Effects of oral administration of methanolic leaf extract of *Aegle marmelos* on serum lipid profiles of STZ- induced diabetic rats at baseline (Day 0) and Day 60.

Group	Treatment	TC (mg/dL)		LDL-C (mg/dL)		HDL-C (mg/dL)	
		Day 0	Day 60	Day 0	Day 60	Day 0	Day 60
I	Vehicle control	91.83±2.79	96.78±3.07	40.5±2.67	39.64±1.56	57.56±2.88	56.44±2.65
II	Diabetic control	92.70±3.15	145.66±2.44***	39.88±3.21	68.87±2.32***	57.44±1.67	25.40±3.45***
III	Treatment control	94.23±2.54	106.40±1.87#	39.70±2.56	45.67±2.67#	57.89±2.06	50.30±2.44#
IV	Extract (125 mg/kg)	93.42±2.78	115.32±2.45#	40.80±3.15	57.34±3.05#	56.80±2.32	41.72±3.14#
V	Extract (250 mg/kg)	93.80±3.05	109.65±3.14#	40.32±2.77	48.70±2.88#	56.12±3.15	47.80±2.43#
VI	Extract (375 mg/kg)	92.83±2.56	97.34±2.75#	39.34±2.64	37.60±2.67#	57.30±2.77	57.80±3.60#

All values expressed as mean±SD. Between - group comparisons at Day 60 were conducted using one-way ANOVA followed by Tukey's *post hoc* test. Within group comparisons (Day 0 Day 60) paired *t*-test was conducted. *Indicates $p<0.05$ (significant), **$p<0.001$ (highly significant), ***$p<0.0001$ (extremely significant), when compared to day 0. # depicts $p<0.0001$- extremely significant, when compared with diabetic control at day 60.

Table 3: Effect of oral administration of *A. marmelos* methanolic leaf extract on the renal profiles of STZ- induced diabetic rats at baseline (Day 0) and Day 60.

Group	Treatment	Urea (mg/dL)		Creatinine (mg/dL)	
		Day 0	Day 60	Day 0	Day 60
I	Vehicle control	18.61±2.40	19.33±2.50	0.37±0.02	0.38±1.05
II	Diabetic control	19.23±3.10	32.90±2.38***	0.38±1.34	0.93±0.65***
III	Treatment control	18.87±2.50	21.64±2.40#	0.37±2.13	0.43±1.22#
IV	Extract (125 mg/kg)	18.70±2.33	25.80±3.24#	0.37±2.40	0.56±2.51#
V	Extract (250 mg/kg)	19.11±3.50	22.45±2.90#	0.38±1.02	0.45±1.35#
VI	Extract (375 mg/kg)	19.41±2.80	20.54±1.70#	0.38±1.87	0.39±2.34#

All values expressed as Mean±SD. Between-group comparisons at Day 60 were conducted using one-way ANOVA followed by Tukey's *post hoc* test. Within group comparisons (Day 0 Day 60) paired *t*-test was conducted. *Indicates $p<0.05$ (significant), **$p<0.001$ (highly significant), ***$p<0.0001$ (extremely significant), when compared to day 0. # depicts $p<0.0001$- extremely significant, when compared with diabetic control at day 60.

Aegle marmelos also known as Bael, has been integral to traditional ayurvedic medicine for centuries. The leaves, fruit, bark and roots contain flavonoids, coumarins, alkaloids, terpenoids and other phenolic with antioxidant and metabolic activities (Manandhar *et al.*, 2018). Along with these constituents, leaf extracts also show hypolipidemic and antioxidant effects in diabetic rodent models, and they also improve renal biochemical markers, supporting the dual signals observed here (Bhatti *et al.*, 2013; Ahmad *et al.*, 2021). Flavonoids can also modulate glucose handling (e.g., α-glucosidase inhibition) and oxidative stress, providing a plausible basis for lipid lowering and renal protection (Al- Ishaq *et al.*, 2019).

CONCLUSION

This study showed that the methanolic leaf extract of *Aegle marmelos* has a dose-dependent hypolipidemic and renoprotective effects in STZ-induced diabetic rats. The highest dose (375 mg/kg) yielding results comparable to standard oral hypoglycemic therapy. The extract improved lipid parameters (TC, LDL, and HDL) and renal function markers (urea and creatinine) due to phytoconstituents like flavonoids and phenolic compounds, which possess antioxidant and anti-inflammatory activities.

These findings support using *A. marmelos* as a supplementary intervention for diabetes management. Future research must assess long-term toxicity and safety of these compounds. Subsequent research should include pharmacokinetic profiling, drug interaction studies, and clinical trials to validate these findings in humans and explore integrating *A. marmelos* with established antidiabetic therapies.

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ABBREVIATIONS

DM: Diabetes Mellitus; **TC:** Total Cholesterol; **LDL-C:** Low Density Lipoprotein - Cholesterol; **HDL-C:** High Density Lipoprotein - Cholesterol; **TG:** Triglyceride; **OHAs:** Oral Hypoglycemic Agents; **DPP-4:** Dipeptidyl Peptidase-4; **SGLT2:** Sodium-Glucose Co-Transporter 2; **GLP-1:** Glucagon-Like Peptide-1; **STZ:** Streptozotocin; **i.p.:** intraperitoneal; **p.o.:** per oral; **KIMS:** Kalinga Institute of Medical Sciences; **IAEC:** Institutional Animal Ethics Committee; **CPCSEA:** Committee for the Purpose of Control and Supervision of Experiments on Animals; **CHOD POD:** Cholesterol Oxidase-Peroxidase; **OECD:** Organization for Economic Cooperation and Development; **SD:** Standard Deviation; **SNOSE:** Sequentially Numbered, Opaque, Sealed Envelopes; **AGE:** Advanced Glycation End-Product; **ROS:** Reactive Oxygen Species; **SOD:** Superoxide Dismutase.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL STATEMENT

The animal study was reviewed and approved by the Institutional Animal Ethics Committee of the Kalinga Institute of Medical Sciences (KIMS), Bhubaneswar (IAEC No. 1730/PO/Re/13/CPCSEA). All animal procedures were performed in accordance with the IAEC guidelines.

INFORMED CONSENT STATEMENT

This study did not involve human participants; therefore, informed consent was not required.

AUTHORS CONTRIBUTION

Dr Suman Supreeti: Concept, Design, manuscript preparation, manuscript editing and manuscript review; Dr Vartika Srivastava (Corresponding author): Definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis; Dr Chaitali Pattnayak:

Concept, design, definition of intellectual content, literature search, clinical studies, experimental studies; Dr Mangala Charan Das: Literature search, clinical studies, experimental studies and manuscript review; Dr Sougata Sarkar: Concept, design, experimental studies, data acquisition,s manuscript preparation, manuscript editing and manuscript review.

SUMMARY

A randomised 60 days Streptozotocin (STZ)-induced diabetic Wistar rats study assessed the dose-response of methanolic *Aegle marmelos* leaf extract relative to standard therapy. A metformin + glimepiride arm serves as the standard therapy. Doses tested were 125,250, and 375 mg/kg (p.o.). Primary outcomes serum lipids (TC, LDL-C, HDL-C) and renal markers (urea, creatinine) were accessed. Across doses, the extract improved both domains compared to diabetic controls. TC and LDL-C declined, while there was increase in HDL-C. Urea and creatinine also decreased. The 375 mg/kg dose showed the most consistent gain and approached the standard-therapy group on several endpoints. No treatments-related mortality was observed. Taken together, these findings support *Aegle marmelos* as a potential adjunct for dyslipidemia and early diabetic nephropathy in diabetes. Further work should standardise the extract, delineate mechanisms, and characterised pharmacokinetics.

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