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RESEARCH ARTICLE

Effect of an aqueous extract of *Terminalia chebula* on endothelial dysfunction, systemic inflammation, and lipid profile in type 2 diabetes mellitus: A randomized double-blind, placebo-controlled clinical study

Usharani Pingali | Deepasree Sukumaran | Chandrasekhar Nutalapati

Department of Clinical Pharmacology & Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad, India

Correspondence
Chandrasekhar Nutalapati, Department of Clinical Pharmacology & Therapeutics, Nizam's Institute of Medical Sciences, Panjagutta, Hyderabad, Telangana, 500082, India.
Email: csnpru@gmail.com

Endothelial dysfunction is a crucial complication in type 2 diabetic patients, related to cardiovascular risk. *Terminalia chebula* (TC), a traditional ayurvedic herb, is known for its antioxidant and antihyperlipidemic activity. A prospective, randomized, double-blind, placebo-controlled clinical study was undertaken to evaluate the effects of an aqueous extract of *T. chebula* 250 and 500 mg versus placebo on endothelial dysfunction and biomarkers of oxidative stress in type 2 diabetic patients. A total of 60 eligible patients were randomized to receive either *T. chebula* 250 mg, *T. chebula* 500 mg, or placebo twice daily for 12 weeks. The subjects were assessed based on the endothelial function, the levels of nitric oxide, malondialdehyde, glutathione, high sensitivity C-reactive protein, glycosylated hemoglobin, and lipid profile at baseline and after 12 weeks of treatment. Treatment with *T. chebula* 250 mg and *T. chebula* 500 mg for 12 weeks significantly improved the endothelial function (reflection index) compared to placebo (absolute changes: - *T. chebula* 250: −2.55 ± 1.82% vs. *T. chebula* 500: −5.21 ± 2.41% vs. placebo: 1.40 ± 2.11%). Other cardiovascular risk indicators were also significantly ameliorated in the treatment groups compared to placebo. In conclusion, *T. chebula* (especially, 500 mg BID dose) significantly minimized the cardiovascular risk factors in patients with type 2 diabetes compared to placebo.

KEYWORDS
endothelial dysfunction, lipid profile, oxidative stress, *Terminalia chebula*, type 2 diabetes

1 | INTRODUCTION

Diabetes mellitus (DM) is a prevalent risk factor influencing the morbidity and mortality of cardiovascular disease (CVD) in patients with diabetes (Yamagishi, Nakamura, Matsui, Ueda, & Imaizumi, 2007). Atherosclerotic CVD is frequently preceded by type 2 DM (T2DM) as a principal health complication because international diabetes federation estimated that 592 million (1 in 10 persons) global population will suffer from DM by 2035 (Aguiree et al., 2013), and T2DM demonstrated a disproportionately higher prevalence compared to type 1 DM (Wild, Roglic, Green, Sicree, & King, 2004). In the United States, CVD related deaths are 1.7 times more prevalent among adult men and women (>18 years) with DM compared to those without DM because of multiple reports of stroke and myocardial infarction (Centers for Disease Control and Prevention, 2014). The relative risk for CVD morbidity and mortality with diabetes ranges from 1 to 3 in men and from 2 to 5 in women, compared to those without DM (Rivellese, Riccardi, & Vaccaro, 2010).

Endothelial dysfunction (EnD) is crucially linked to the development of micro- and macrovascular complications in type 2 diabetes

(Takata et al., 2008). The condition is frequently associated with CVD morbidities, including atherosclerosis, hypertension, coronary artery disease, chronic heart failure, and peripheral artery disease. EnD typically demonstrates a reduced endothelial function, which is translated into reduced vasodilation, proinflammatory condition, and atherosclerotic state (Endemann & Schiffrin, 2004). The oxidative stress-induced apoptosis of the endothelial cells is frequently mediated by p38 mitogen-activated protein kinase and/or by c-Jun N-terminal kinase, both of which are activated by kinase cascades initiated by apoptosis-signaling kinase 1 (Pober, Min, & Bradley, 2009). In diabetic patients, the hyperglycemic condition produces oxidative stress via different mechanisms, including polyol pathway activity, glucose autoxidation, protein kinase C activation, and advanced glycation end product (AGE) formation, and these hyperglycemia-induced metabolic pathways are significantly implicated in the pathogenesis of EnD (De Vriese, Verbeuren, Van De Voorde, Lameire, & Vanhoutte, 2000).

The demand for nutraceuticals is continuously growing in western countries. Different traditional medicines, including traditional Chinese medicine, Ayurveda, Unani, etc. are considered as nutraceuticals and health supplements. However, the nutraceutical industry is not rigorously regulated. So, the need for the manufacturer of the nutraceutical to prove efficacy, safety, and quality of a marketed product is less strongly enforced than in the pharmaceutical sector. Due to the general lack of clinical evidence for many products, false claims of efficacy, concerns about quality, and issues of serious illness, the nutraceutical industry is highly criticized (Williamson, Liu, & Izzo, 2020). The randomized clinical trial of nutraceuticals is the best method for establishing the efficacy, safety, and quality of a nutraceutical ingredient.

Terminalia chebula Retz. (Family: Combretaceae) (also known as black myrobalan in English) is widely distributed in India and Southern Asia (Afshari, Sadeghnia, & Mollazadeh, 2016). The *T. chebula* fruits are used in traditional Unani, Ayurvedic, and homeopathic medicines since antiquity, owing to their diverse phytoconstituents, such as polyphenols, terpenes, anthocyanins, flavonoids, alkaloids, and glycosides (Afshari et al., 2016). In many Ayurvedic formulations, *T. chebula* fruits are incorporated for treating different diseases, such as chronic ulcers, leukorrhea, pyorrhea, fungal infections of the skin, geriatric diseases, memory-booster, and brain tonic (Afshari et al., 2016). Besides, *T. chebula* has been frequently recommended in the treatments of various conditions, including cancer, CVDs, paralysis, leprosy, ulcers, gout, arthritis, epilepsy, cough, fever, diarrhea, gastroenteritis, skin disorders, urinary tract infection, and wound infections (Lee et al., 2011). *T. chebula* treatment can diminish athermatous plaque formation in the aortas of rabbits compared to the control group (Shaila, Udupa, & Udupa, 1998). Lee et al. reported that chebulic acid, isolated from *T. chebula*, could restrict the progression of AGE-induced endothelial cell dysfunction in vitro (Lee, Koo, Suh, Kim, & Lee, 2010). The same research group later reported that a *T. chebula* methanolic extract, containing 2.7% chebulic acid, could prevent AGE formation and thus endothelial cell dysfunction in vitro (Lee et al., 2011). In one of our previous study, a proprietary standardized aqueous extract of *T. chebula* (AyuFlex, Natreon Inc., NJ) significantly improved the endothelial function and reduced the biomarkers of oxidative stress and systemic inflammation in patients with metabolic syndrome (Kishore, Kishan, Ramakanth, Chandrasekhar, & Pingali, 2016).

This prospective, randomized, double-blind, placebo-controlled clinical study was aimed at evaluating the effect of a proprietary standardized aqueous extract of *T. chebula* (AyuFlex) at the doses of 250 and 500 mg twice daily on the endothelial function, systemic inflammation and lipid profile in T2DM patients.

2 | MATERIALS AND METHODS

This 12-week prospective clinical trial was conducted using a random-assignment, parallel-group, single-center, double-blind, placebo-controlled design between May 2013 to November 2013 at the Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences, Hyderabad. The protocol of the study was not modified after the trial's commencement.

2.1 | Enrollment of study subjects

Seventy-four subjects were selected from the interested outpatients visiting the outpatient department of the Nizam's Institute of Medical Sciences, Hyderabad. At the study center, the participants were provided an information package containing informed consent form, background information of the study, description of the intended care as per study protocol, information sheet regarding study participation, and contact information for study enrolment.

Patients of either sex, aged between 30 to 65 years with fasting plasma glucose levels of 110–126 mg/dL, glycosylated hemoglobin (HbA1c) levels between 8.0%, under the anti-diabetic treatment (metformin 1,500–2,500 mg/day) for the past 8 weeks before the screening visit, who were diagnosed with EnD defined as ≤6% change in reflection index (RI) on post salbutamol challenge test, who understood the risks and benefits of the protocol and willfully provided written informed consent, were included in the study. Patients with severe uncontrolled hyperglycemia, uncontrolled hypertension, cardiac arrhythmia, impaired hepatic or renal function, history of malignancy or stroke, smoking, chronic alcoholism, any other serious disease requiring active treatment and treatment with any other herbal supplements, were excluded from the study.

2.2 | Ethical consideration

The study was conducted following the Declaration of Helsinki (World Medical Association, 2013) and 'Guidelines for Clinical Trials on Pharmaceutical Products in India – Good Clinical Practice Guidelines issued by the Central Drugs Standard Control Organization, Ministry of Health, and Government of India. Institutional Review Board approval was received from the study center at the Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical

Sciences, Hyderabad. Ethics Committee notifications as per Good Clinical Practice Guidelines, issued by Central Drugs Standard Control Organization and Ethical Guidelines for Biomedical Research on Human Subjects, issued by the Indian Council of Medical Research, were followed. The ethical committee approval number was No. EC/NIMS/1376/2012 (No. ESGS/NIMS/IRB/11/2010 Dt. November 18, 2010). Informed consent was obtained from each patient before study enrollment.

2.3 | Investigational products

The investigational product, AyuFlex, a standardized aqueous extract of the fruits of *T. chebula* (containing low molecular weight hydrolysable tannins, with chebulinic acid, chebulagic acid, gallic acid, ellagic acid, and flavonoids as bioactives) in the capsule dosage form, was received from Natreon Inc, New Brunswick, NJ. The matching placebo capsules, containing microcrystalline cellulose (49.7% w/w), lactose (49.5% w/w), and magnesium stearate (0.69% w/w) as excipients, were also supplied by Natreon Inc.

2.4 | Randomization and blinding

After screening, the eligible subjects were randomized through a computer-based predetermined randomized formation (GraphPad Prism version 4) in a 1:1:1 ratio using unstratified blocks of the same length, and those subjects were assigned to one of the three treatment groups. As a double-blind study, the randomization and group assignment process were concealed both from doctors and subjects. All the study medications were formulated as hard gelatin capsules having identical size, shape, color, texture, and weight, and they were packed in identical (both appearance and weight) and tamper-proof containers. The bottles containing the test products contained sequentially designated numbers and were dispensed by the pharmacist to the subjects as per the randomly allocated sequence. During data collection, the research coordinators, the study investigators, and the attending care personnel were prohibited to access the randomization codes and allocations. Unblinding was allowed only after completion of the entire data collection process or in case of serious adverse events. The randomization codes were covered in aluminum foil and placed in a separate, sealed envelope for each patient. After the completion of the study period, the allocations were unblinded to tabulate the data, but the identity of the study groups was undisclosed to the data analysts. The data were double entered and blinded to the statisticians.

2.5 | Interventions

All randomized subjects received either one capsule of *T. chebula* 250 mg (TC250) (batch # FOM-250-032013) twice daily or one capsule of *T. chebula* 500 mg (TC500) (batch # FOM-500-032413) twice daily or one placebo capsule (batch # PLA-071313) twice daily.

2.6 | The efficacy variables

The primary efficacy measure was the endothelial function as reflected by RI % after 12 weeks in all treatment groups. Secondary efficacy parameters were the levels of serum nitric oxide (NO), biomarkers of oxidative stress [malondialdehyde (MDA) and glutathione (GSH)], high sensitivity C-reactive protein (hsCRP), lipid profile [total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), very LDL-cholesterol (VLDL-C)], and HbA1c after 12 weeks in all treatment groups.

2.7 | Assessment of endothelial function

Endothelial function was assessed using the salbutamol challenge test employing digital volume plethysmography, following the methods of Chowienczyk et al. (1999)) and Naidu, Sridhar, Rani, and Mateen (2007). The patients were inspected at the supine position after resting for 5 minutes. A digital volume pulse (DVP) was recorded using a photo-plethysmograph (Pulse Trace PCA2, PT200, Micro Medical, Kent, UK) transmitting infra-red light at 940 nm, placed on the index finger of the right hand. The signal from the plethysmograph was digitized using a 12-bit analog to a digital converter with a sampling frequency of 100 Hz. DVP waveforms were recorded over 20 second period, and the height of the late systolic/early diastolic portion of the DVP was expressed as a percentage of the amplitude of the DVP to yield the RI, following the procedure of Millasseau, Kelly, Ritter, and Chowienczyk (2002). After the DVP recording, three measurements of RI were calculated, and the mean value was determined. The patients were then administered with 400 μg of salbutamol by inhalation. After 15 minutes, three more measurements of RI were recorded, and the difference in mean RI before and after administration of salbutamol was used for assessing endothelial function. A change in ≤6% of RI post salbutamol administration was considered as EnD.

2.8 | Biomarker evaluation

MDA (Vidyasagar et al., 2004), NO (Miranda, Espey, & Wink, 2001) and GSH (Ellman, 1959) levels were estimated spectrophotometrically, and hsCRP by ELISA method. After overnight fasting of 12 hrs, the samples were collected after the last dose of medication for determining lipid profile (TC, HDL-C, LDL-C, TG, VLDL-C) and HbA1c by appropriate standard techniques.

2.9 | Follow up visits

The subjects were recalled for follow-up visits at 4 weeks, 8, and 12 weeks of therapy for evaluating the efficacy and safety of the interventions. Endothelial function was evaluated at baseline and after

12 weeks of treatment. Blood samples were collected for evaluating the oxidative stress markers (MDA, NO, GSH), hs-CRP, lipid profiles (TC, HDL-C, LDL-C, TG, VLDL-C), and HbA1c at baseline and after 12 weeks.

2.10 | Safety evaluation

The patients underwent a complete physical examination and laboratory investigations for safety parameters, including hematological, hepatic, and renal biochemical parameters at baseline and after 12 weeks by appropriate standard techniques. At each visit, the subjects were asked to report any adverse drug reactions for records in the case report form.

2.11 | Compliance verification

The compliance with study medications was verified by the pill-count method. Compliance was considered good, fair or poor, if a patient received >80%, between 60% and 80%, or <60% of the dispensed medication.

2.12 | Sample size determination

To detect a change of more than 6% in endothelial function with a 5% margin of alpha error, power of 80% and assuming a dropout rate of 10% and a screen failure of 5% a total of 74 subjects would be screened to get a sample size of 63 subjects in all the groups.

2.13 | Statistical analysis

Quantitative data were expressed as means with standard deviations (SD); categorical and discrete data were expressed as numbers. All statistical analyzes were performed using IBM SPSS version 23. The posttest (after 12 weeks) values of the three groups were compared using analysis of covariance keeping the baseline values as covariates following Bonferroni's posthoc analysis. In all analyzes, differences were considered statistically significant when the probability of chance occurrence was less than 5% (i.e., $p < .05$), while trends were identified as values of $0.06 \leq p \leq .10$. The effect size was determined using partial eta-squared (η_p^2) with 0.01 considered to be small, 0.06 to be medium, and >0.14 to be large.

3 | RESULTS

A total of 74 subjects were screened and 60 eligible subjects completed the study. Twenty subjects each in *T. chebula* 250 mg, *T. chebula* 500 mg, and placebo groups completed the study, as evident in the CONSORT diagram (Figure 1). At baseline, demographic and physical parameters were similar in all three groups (Table 1).

3.1 | Endothelial function (RI %)

A significant treatment effect was observed in RI % ($F = 61.9$, $p < .001$; $\eta_p^2 = 0.689$) over the study duration (Table 2). Between-group analysis showed significant differences for TC250 versus placebo ($p < .001$), TC500 versus placebo ($p < .001$), and TC250 versus TC500 ($p < .001$).

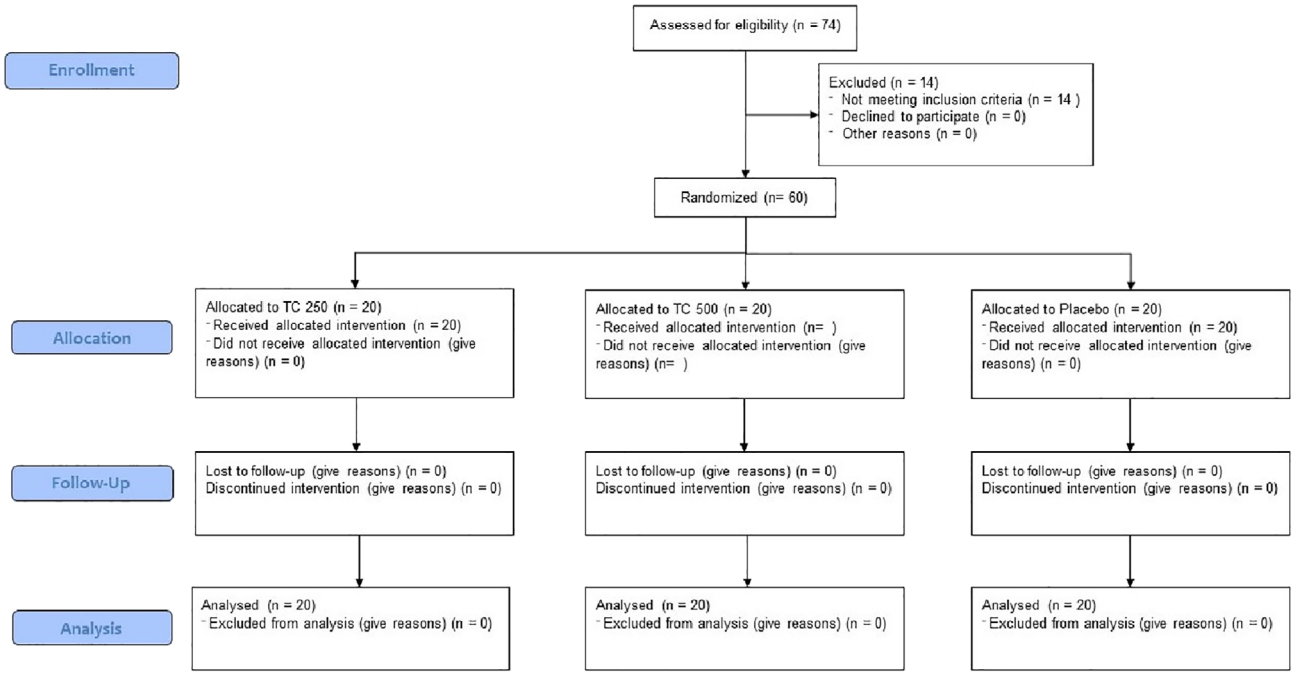

FIGURE 1 CONSORT flow diagram [Colour figure can be viewed at wileyonlinelibrary.com]

3.2 | Endothelial marker

A significant treatment effect was also noticed in serum NO levels (F = 23.5, p < .001; η_p^2 = 0.466) along the treatment groups (Table 3). The sub-group analysis showed significant differences for TC250 versus placebo (p < .001), TC500 versus placebo (p < .001), and TC250 versus TC500 (p = .009).

3.3 | Oxidative stress markers

The serum GSH levels displayed a significant treatment effect (F = 19.6, p < .001; η_p^2 = 0.412) along the treatment groups (Table 3). Significant sub-group differences were observed for TC250 versus placebo (p = .011), TC500 versus placebo (p < .001), and TC250 versus TC500 (p = .006).

Twelve weeks therapy of *T. chebula* produced a significant treatment effect for serum MDA levels (F = 7.85, p = .001; η_p^2 = 0.219) (Table 3). Supplementation with *T. chebula* 500 mg exhibited a significant difference (p = .001) compared to the placebo group.

3.4 | Inflammation marker

The inflammation marker, hsCRP levels, demonstrated a significant overall treatment effect (F = 12.02, p < .001; η_p^2 = .3) (Table 3); *T. chebula* 500 mg twice daily displayed significantly lower post-test hsCRP levels compared to the placebo (p < .001) and TC250 (p = .009) groups.

3.5 | Lipid profiles

Supplementation with *T. chebula* produced significant treatment effects in the lipid profiles of the subjects, demonstrating a significant overall treatment effect in TC levels (F = 23.14, p < .001; η_p^2 = 0.452) over the study duration (Table 4). The sub-group analysis showed significant differences in TC levels in the post-test results, that is, TC250 versus placebo (p < .001) and TC500 versus placebo (p < .001).

Serum HDL-C levels were increased significantly (F = 12.06, p < .001; η_p^2 = 0.301) along the treatment groups (Table 4). Both TC250 (p = .010) and TC500 (p < .001) groups exhibited significant increases in post-test serum HDL-C levels compared to the placebo group.

A significant treatment effect was also noticed in serum LDL-C levels (F = 12.38, p < .001; η_p^2 = 0.307) along the treatment groups (Table 4). *T. chebula* 250 mg (p = .003) and 500 mg (p < .001) twice daily significantly reduced the post-test serum LDL-C levels compared to the placebo group.

A similar trend has been observed in serum TG levels, showing a significant treatment effect (F = 38.04, p < .001; η_p^2 = 0.576) by the study groups, and the sub-group analysis exhibited significant differences in the post-test TG levels among the groups [TC250 vs. placebo (p < .001), TC500 vs. placebo (p < .001), and TC250 vs. TC500 (p = .016)] (Table 4).

Also, the serum VLDL-C levels demonstrated a significant treatment effect (F = 5.86, p = .005; η_p^2 = 0.173) over the study duration (Table 4). Supplementation with *T. chebula* 500 mg (p = .004) significantly reduced the post-test serum VLDL-C levels compared to the placebo group.

3.6 | Effect on glycosylated hemoglobin A1c (HbA1c %)

Serum HbA1c levels demonstrated a significant treatment effect (F = 10.41, p < .001; η_p^2 = 0.271) over the study duration (Table 5). The post-test serum HbA1c levels were significantly different among the groups [TC500 vs. placebo (p < .001); TC250 vs. TC500 (p = .002)].

3.7 | Safety evaluation

No significant changes were observed in vital, hematological, renal, and hepatic functions with all groups (Table 6). All subjects tolerated the therapy well. No serious adverse events were recorded in the study. Two patients in TC 250, one patient in TC 250 complaint of dyspepsia and three patients in placebo group complaint of mild headache. However, no subjects in any of the groups dropped out of the study owing to adverse events.

TABLE 1 Demographic characteristics of all study groups

Parameter	TC 250	TC 500	Placebo
Total no	20	20	20
Age in Yrs	53.85 ± 5.07	53.85 ± 4.80	55.30 ± 5.66
Gender (M/F)	13/7	12/8	14/6
Bodyweight (kg)	67.20 ± 5.66	64.05 ± 2.60	64.05 ± 3.30
BMI (kg/m^2)	24.35 ± 2.00	23.79 ± 1.20	24.14 ± 1.43

Note: Values Presented as Mean ± Standard Deviation.

TABLE 2 Effect of the treatments on endothelial function (RI)

				P values			
Parameter RI (%)	TC250 (n = 20)	TC500 (n = 20)	Placebo (n = 20)	Overall	TC250 vs. placebo	TC500 vs. placebo	TC250 vs. TC500
Baseline	−2.38 ± 0.822	−3.36 ± 1.39	−2.41 ± 1.08	—	—	—	—
Post-test	−4.93 ± 1.87	−8.57 ± 1.94	−1.01 ± 2.05	<.001	<.001	<.001	<.001

Note: Values presented as Mean ± SD. p values were obtained using analysis of covariance followed by Bonferroni's posthoc analysis. Differences were considered significant at p < .05

TABLE 3 Effect of the treatments on the endothelial marker (NO), and biomarkers of oxidative stress (GSH, MDA) and inflammation (hsCRP)

				P values			
Parameter	TC250 (*n* = 20)	TC500 (*n* = 20)	Placebo (*n* = 20)	Overall	TC250 vs. placebo	TC500 vs. placebo	TC250 vs. TC500
NO (μM/L)							
Baseline	30.47 ± 3.65	30.93 ± 2.28	35.87 ± 4.87	–	–	–	–
Post-test	33.63 ± 3.74	36.03 ± 3.03	34.93 ± 4.21	<.001	<.001	<.001	.009
GSH(μM/L)							
Baseline	387.40 ± 44.7	388.55 ± 47.62	381.01 ± 55.4	–	–	–	–
Post-test	422.5 ± 48.14	454.95 ± 47.87	387.77 ± 56.87	<.001	.011	<.001	.006
MDA (nM/ml)							
Baseline	3.42 ± 0.61	3.29 ± 0.67	3.34 ± 0.52	–	–	–	–
Post-test	3.18 ± 0.64	2.92 ± 0.67	3.35 ± 0.37	.001	.059	.001	.404
hsCRP (mg/L)							
Baseline	1.34 ± 0.40	1.51 ± 0.59	1.42 ± 0.86	–	–	–	–
Post-test	1.18 ± 0.25	1.00 ± 0.09	1.39 ± 0.82	<.001	.264	<.001	.009

Note: Values presented as Mean ± SD. *p* values were obtained using analysis of covariance followed by Bonferroni's posthoc analysis. Differences were considered significant at $p < .05$.

TABLE 4 Effect of the treatments on lipid profile

				P values			
Parameter	TC250 (*n* = 20)	TC500 (*n* = 20)	Placebo (*n* = 20)	Overall	TC250 vs. placebo	TC500 vs. placebo	TC250 vs. TC500
Total cholesterol (mg/dl)							
Baseline	173.1 ± 20.3	183.75 ± 30.0	191.05 ± 25.21	–	–	–	–
Post-test	160.8 ± 22.9	164.8 ± 23.15	198.85 ± 23.7	<.001	<.001	<.001	1.000
HDL-C (mg/dl)							
Baseline	44.0 ± 5.57	37.75 ± 3.88	38.25 ± 5.13	–	–	–	–
Post-test	45.05 ± 5.08	41.95 ± 4.25	37.04 ± 5.0	<.001	.010	<.001	.681
LDL-C (mg/dl)							
Baseline	118.2 ± 22.2	116.5 ± 24.35	121.20 ± 29.37	–	–	–	–
Post-test	110.4 ± 22.5	101.75 ± 18.4	130.70 ± 30.1	<.001	.003	<.001	.492
Triglycerides (mg/dl)							
Baseline	174.5 ± 28.8	172.85 ± 36.91	175.20 ± 28.32	–	–	–	–
Post-test	146.8 ± 34.0	129.40 ± 28.63	176.90 ± 27.4	<.001	<.001	<.001	0.016
VLDL-C (mg/dl)							
Baseline	35.95 ± 4.39	31.85 ± 6.92	27.70 ± 4.01	–	–	–	–
Post-test	31.7 ± 5.8	27.05 ± 8.26	28.85 ± 5.05	.005	.067	.004	1.000

Note: Values presented as Mean ± SD. *p* values were obtained using analysis of covariance followed by Bonferroni's posthoc analysis. Differences were considered significant at $p < .05$.

TABLE 5 Effect of treatments on Glycosylated Hemoglobin A1c (HbA1c %)

				P values			
Parameter HbA1c (%)	TC250 (*n* = 20)	TC500 (*n* = 20)	Placebo (*n* = 20)	Overall	TC250 vs. placebo	TC500 vs. placebo	TC250 vs. TC500
Baseline	7.49 ± 0.32	7.17 ± 0.33	7.63 ± 0.23	–	–	–	–
Post-test	7.36 ± 0.31	6.98 ± 0.20	7.51 ± 0.18	<.001	.535	<.001	.002

Note: Values Presented as Mean ± SD. *p* values were obtained using analysis of covariance followed by Bonferroni's posthoc analysis. Differences were considered significant at $p < .05$.

TABLE 6 Effect of the treatments on the safety parameters

	TC 250 (n = 20)		TC 500 (n = 20)		Placebo (n = 20)	
Parameters	**Baseline**	**Post treatment**	**Baseline**	**Post treatment**	**Baseline**	**Post treatment**
Heart rate (bpm)	69.65 ± 2.50	70.10 ± 2.05	68.80 ± 1.36	68.70 ± 1.66	71.90 ± 4.55	71.65 ± 3.54
Systolic BP (mmHg)	122.70 ± 2.18	121.90 ± 2.71	121.40 ± 3.44	120.90 ± 3.40	122.20 ± 3.37	122.20 ± 2.67
Diastolic BP(mmHg)	80.70 ± 2.36	79.00 ± 2.29	78.40 ± 3.59	77.20 ± 2.19	80.20 ± 2.75	79.70 ± 2.99
Fasting plasma glucose (FPG mg/dl)	120.15 ± 4.44	118.35 ± 3.31	121.75 ± 2.92	118.60 ± 4.83	122.65 ± 2.96	124.10 ± 3.21
Hemoglobin (gm/dl)	12.46 ± 0.63	12.42 ± 0.57	12.47 ± 0.62	12.38 ± 0.60	12.67 ± 0.67	12.53 ± 0.66
WBC count (/mm^3)	7,190 ± 458.72	7,175 ± 485.45	7,250 ± 465.10	7,220 ± 521.74	7,195 ± 506.25	7,220 ± 495.88
Platelet count (lakh/ mm^3)	2.18 ± 0.18	2.18 ± 0.19	2.09 ± 0.22	2.11 ± 0.20	2.18 ± 0.25	2.19 ± 0.26
Blood urea (mg/dl)	22.35 ± 3.57	21.95 ± 3.28	22.65 ± 3.30	21.85 ± 2.68	25.55 ± 3.85	27.10 ± 3.61
S. Creatinine (mg/dl)	1.04 ± 0.07	1.05 ± 0.06	1.06 ± 0.06	1.03 ± 0.09	1.05 ± 0.06	1.05 ± 0.06
AST (SGOT) (U/L)	23.10 ± 4.40	22.40 ± 3.68	22.50 ± 4.36	23.30 ± 3.84	24.50 ± 3.68	25.45 ± 4.08
ALT (SGPT) (U/L)	25.10 ± 3.24	26.25 ± 3.24	24.20 ± 4.27	23.70 ± 3.47	24.30 ± 3.64	26.15 ± 2.56
ALP (U/L)	175.4 ± 22.51	176.6 ± 25.27	174.50 ± 22.67	173.6 ± 22.51	171.6 ± 21.34	176.8 ± 21.74
Total bilirubin (mg/dl)	0.21 ± 0.08	0.19 ± 0.08	0.25 ± 0.06	0.024 ± 0.05	0.20 ± 0.06	0.21 ± 0.17

Note: Values presented as Mean ± SD. No significant changes in vital, hematological, renal and hepatic functions with all treatments.

4 | DISCUSSION

In the present prospective, randomized, double-blind clinical study, we evaluated the efficacy of a standardized aqueous extract of *T. chebula* at the dosage of 250 mg and 500 mg twice daily against EnD among the T2DM patients and compared it with the placebo group. We also investigated the efficacy of the extract in restoring levels of NO, the oxidative stress markers (GSH and MDA), inflammation (hsCRP) markers and lowering the lipid profiles (TC, HDL-C, LDL-C, TG, and VLDL-C) and HbA1c level.

A detailed analysis of the results revealed that *T. chebula* at the dosage of 250 mg ($p < .001$) and 500 mg ($p < .001$) significantly improved the endothelial function (RI%) compared to the placebo group. In fact, the higher dose (500 mg) ($p < .001$) of *T. chebula* exhibited a significantly better therapeutic effect than its lower dose (250 mg), suggesting that the extract functioned in a dose-dependent manner. The results of the present study agreed with one of our previous studies, where *T. chebula* at the dosage of 250 and 500 mg twice daily improved the endothelial function significantly in patients with metabolic syndrome (Kishore et al., 2016) compared to the placebo group. In two separate in vitro studies, Lee et al demonstrated that chebulic acid, from *T. chebula*, inhibited the progression of AGE-induced endothelial cell dysfunction(Lee et al., 2010), and a *T. chebula* methanolic extract, containing 2.7% chebulic acid, prevented the formation of AGEs and endothelial cell dysfunction (Lee et al., 2011).

NO is an endothelium-derived relaxing factor and a key marker of vascular health with antiplatelet, antithrombotic, and anti-inflammatory properties (Loscalzo & Jin, 2010). The endothelial vasodilatory process is majorly hampered due to a reduced NO generation (Endemann & Schiffrin, 2004). In our study, treatment with *T. chebula* 250 mg ($p < .001$) and 500 mg ($p < .001$) significantly improved the NO level compared to placebo in T2DM patients; *T. chebula* 500 mg ($p = .009$) exhibited significantly better therapeutic effect than *T. chebula* 250 mg, implying a dose-dependent mechanism. The results of our previous study agreed with this finding where *T. chebula* 250 and 500 mg improved the NO levels dose-dependently in patients with metabolic syndrome (Kishore et al., 2016).

MDA and GSH indicate the severity of oxidative stress in tissue (Pingali, Nutalapati, & Illendulla, 2020). Excessive oxidative stress causes injury or apoptosis of the endothelial cells and develops EnD (Pober et al., 2009). In our study, a higher dose of *T. chebula* (500 mg) ameliorated the oxidative stress by significantly reducing the serum MDA level ($p = .001$) and markedly elevating the serum GSH level ($p < .001$) in T2DM patients compared to placebo. This outcome is supported by our previous study, where serum MDA and GSH levels were restored by *T. chebula* supplementation (Kishore et al., 2016). Many in vivo studies in various animal models have established that the antioxidant phytoconstituents of *T. chebula*, such as polyphenols, terpenes, anthocyanins, and flavonoids, can significantly restore the MDA and GSH levels in different tissues (Afshari et al., 2016; Jadon, Bhadauria, & Shukla, 2007; Kim, Hong, Koo, Kim, & Lee, 2011; Lee et al., 2005; Mahesh, Bhuvana, & Begum, 2009).

C-reactive protein levels in serum are elevated due to acute infections, inflammatory conditions, and trauma. The hsCRP level is measured for predicting CVD risks (Kamath, Xavier, Sigamani, & Pais, 2015). In the present study, *T. chebula* supplementation at the dose of 500 mg twice daily significantly reduced the serum hsCRP level ($p < .001$) in T2DM patients compared to placebo. Our previous study exhibited a similar result, where both 250 mg and 500 mg dose of *T. chebula* twice daily significantly reduced the serum hsCRP level in a dose-dependent manner in patients with metabolic syndrome compared to placebo ($p < .001$; $p < .001$) (Kishore et al., 2016). In a

randomized double-blind clinical, a polyherbal formulation, containing *T. chebula*, significantly reduced the serum hsCRP level compared to the baseline value in an obese adolescent population (Shivakumar, Ilango, Dubey, Subhasree, & Agrawal, 2015). However, the administration of *Triphala*, containing *T. chebula*, *Terminalia bellerica*, and *P. emblica*, failed to exhibit a significant reduction in the serum hsCRP level compared to placebo in hypolipidemic adults receiving atorvastatin (Ekanayaka, Rupasinha, Sooriyarachchi, & Goonaratna, 2017).

Hyperlipidemia is a major cardiovascular risk factor in patients with T2DM (Laakso, 1999). Coronary artery disease can be controlled by reducing hypercholesterolemia by intensive interventions, including dieting, exercise, and anti-hypercholesterolemic and anti-inflammatory drugs (Genest, 2000). In our study, *T. chebula* at the doses of 250 and 500 mg significantly reduced the levels of total cholesterol ($p < .001$; $p < .001$), LDL-C ($p = .003$; $p < .001$), triglyceride ($p < .001$; $p < .001$) and VLDL-C [$p = .067$ (not-significant); $p = .004$], as well as significantly increased the HDL-C level ($p = .010$; $p < .001$) compared to placebo among T2DM patients. The results of the present study followed a similar trend to our previous study, where, *T. chebula* significantly reduced the levels of total cholesterol, LDL-C, triglyceride, and VLDL-C, as well as significantly increased the HDL-C level compared to the baseline values among metabolic syndrome patients (Kishore et al., 2016). In another randomized clinical trial, Lopez et al. reported that *T. chebula* significantly reduced the total cholesterol levels from day 14 to day 84 among healthy overweight patients, though no significant effect was noted on the other lipid parameters (Lopez et al., 2017). Many in vivo animal studies have also evaluated the lipid-lowering effects of *T. chebula*; a consistent trend of total cholesterol, LDL-C, triglyceride, and VLDL-C levels' reduction and HDL-C level's enhancement was reported in hyperlipidemic animals (Anjum et al., 2014; Maruthappan & Shree, 2010; Murali et al., 2007; A. Singh, Srivastav, & Pandey, 2018).

HbA1c is recognized as an accurate index of long-term blood glucose regulation, and HbA1c is acutely responsive to blood glucose changes (Goldstein, Peth, England, Hess, & Da Costa, 1980). In the present study, *T. chebula* at a dose of 500 mg twice daily for 12 weeks significantly reduced the HbA1c level ($p < .001$) in the blood of the T2DM patients compared to placebo. In line with our results, different in vivo animal studies have reported that *T. chebula* can significantly reduce the HbA1c level in streptozotocin-induced diabetic rats (Kumar, Arulselvan, Kumar, & Subramanian, 2006; Murali et al., 2007; Senthilkumar & Subramanian, 2008). In a randomized clinical trial among the T2DM patients, a polyherbal formulation, containing *T. chebula*, significantly reduced the HbA1c level compared to the control group (Awasthi et al., 2015). Treatment with *Triphala*, containing *T. chebula*, *T. bellerica*, and *P. emblica*, demonstrated a significant reduction in the HbA1c level compared to the baseline values in T2DM patients (N. Singh et al., 2015).

The active treatment of *T. chebula* at the dose of 250 and 500 mg twice daily for 12 weeks demonstrated modest and statistically significant improvement in the parameters of EnD and biomarkers. The effect was much more with *T. chebula* 500 mg. Since T2DM are is associated with cardiovascular morbidity, in view of our positive findings, we postulate that the add-on treatment with *T. chebula* may significantly decrease cardiovascular morbidity by improving EnD, systemic inflammation, and lipid profile.

The major limitation of the present study design is the relatively small sample size. A study with a larger population involving a wider cross-section of the subjects with regard to age groups, occupation, and socioeconomic background would provide more conclusive results.

5 | CONCLUSION

The outcomes of our present study indicate that a 12-week supplementation of a proprietary standardized aqueous extract of *T. chebula* (AyuFlex) can significantly ameliorate the EnD among the T2DM patients by significantly improving the production of NO (the endothelial vasorelaxant), reducing the oxidative stress (evident by a significant reduction of serum MDA levels and a significant improvement of serum GSH levels) and reducing the inflammation marker hsCRP levels in the blood. *T. chebula* also minimized the risks of CVDs and hyperglycemia by modulating the blood lipid levels and the HbA1c level. The principal phytoconstituents of *T. chebula*, chebulagic acid and chebulinic acid, might be responsible for its action against EnD. These data suggest that an aqueous extract of *T. chebula* could be utilized as a primary ingredient in the therapeutic formulations focusing on the rejuvenation of cardiovascular health.

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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

ORCID

Usharani Pingali https://orcid.org/0000-0002-9300-8022
Chandrasekhar Nutalapati https://orcid.org/0000-0002-0529-2706

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