Title : A Study of highly standardized aqueous extract of Terminalia chebula 250mg, 500mg versus Placebo in modifying cardiovascular risk with special reference to Endothelial dysfunction in patients with Type2 Diabetes Mellitus

Usharani Pingali, Chandrasekhar Nutalapati, Niranjan Koilagundla

Department of Clinical Pharmacology and Therapeutics,
Nizam's Institute of Medical Sciences (NIMS), Panjagutta, Hyderabad. Inda

Presenter Contact Details : Usharani Pingali, MD, DNB, FIPS, PGDipBioethics,
Professor and Head; Dept of Clinical Pharmacology and Therapeutics, NIMS.
Email ushapingali@yahoo.com; Phone: +919849574143; +91-40-23489211

Chandrasekhar Nutalapati – Senior resident, Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences (NIMS), Panjagutta, Hyderabad. India.

Niranjan Koilagundla - Senior resident, Department of Clinical Pharmacology and Therapeutics, Nizam's Institute of Medical Sciences (NIMS), Panjagutta, Hyderabad. India

ABSTRACT

Purpose: Cardiovascular disease is a major cause of morbidity and mortality among patients with diabetes mellitus (DM), and these patients account for a significant proportion of all patients with cardiovascular disease. Other risk factors are Hypertension, High LDL cholesterol, Low HDL cholesterol, oxidative stress. Endothelial dysfunction (ED) is one of the potential contributor to the pathogenesis of vascular disease in DM. Diabetes is associated with an increase risk of atherosclerosis including platelet hyper-reactivity increased inflammation, and endothelial dysfunction. Ayurvedic and many herbal drugs used for centuries in India. They possess potent antioxidant, anti-inflammatory and cardio-protective properties and are used by patients with increased risk of cardiovascular morbidity and mortality. Terminalia chebula (TC) is reported to possess antidiabetic, anti-oxidant, anti-inflammatory activity amongst others. *Terminalia chebula* fruit extract shows antioxidant effect by strongly inhibiting the in vivo lipid peroxidation in rat liver study. Lipid peroxides may be pro-inflammatory and can damage tissue directly (Bonta et al., 1980). Murali et al. reported that oral administration of Terminalia chebula extract once daily for two months reduced elevated blood glucose, and significantly reduced increases in glycosylated hemoglobin (HbA1c). However, very less information is available about the effects of *TC* in human diabetic patients. The present study was thus undertaken to evaluate the effect of TC 250mg, TC 500mg versus Placebo on endothelial function in patients with type 2 diabetes.

Methodology: Patients of either gender, aged 30-65 years, with fasting plasma glucose of 110-126 mg/dL, glycosylated haemoglobin (HbA1c) between 6.5 % and 8% and on stable dose of anti-diabetic medication (metformin 1500-2500 mg/day) for the past 8 weeks prior to the screening visit; and having endothelial dysfunction defined as ≤ 6% change in reflection index (RI) on post salbutamol challenge test were included in the study. Patients

with severe uncontrolled hyperglyceamia, uncontrolled hypertension, cardiac arrhythmia, impaired hepatic or renal function, any other serious disease requiring active treatment and treatment with any other food supplements, were excluded.
All the eligible subjects were randomized to receive either treatment for 12 weeks – group1-one capsule of Terminalia chebula 250mg, group 2-one capsule 500mg twice daily; group 3-one capsule of Placebo twice daily.
Subjects were reviewed for followup at 4, 8 and 12 weeks of therapy. At each visit they were evaluated for efficacy and safety. Pharmacodynamic evaluation for endothelial function was conducted at baseline and end of treatment. Salbutamol challenge test employing digital volume plethysmography was used to assess endothelial function. Blood samples were collected for biomarkers (Nitric oxide MDA, Glutathione, hsCRP) and Serum lipid profile, before and at end of treatment. Safety lab investigations for hematological, hepatic and renal biochemical parameters were conducted before and at the end of the study. Any ADR reported was recorded in the case report form. Compliance assessed by pill count method. ANOVA ,"t" Test and Tukey's posthoc tests were used for statistical analysis by Prism Graphpad**.**

Results: Of 74 subjects screened, 60 eligible subjects completed the study, twenty in each group. Significant reduction in mean RI was noted with TC 250mg (−2.38±0.82% to −4.93±1.87% ; p<0.001) and TC 500mg (−2.35%±0.85% to −6.14%±1.01%;p<0.001) suggesting improvement in endothelial function compared to baseline and placebo (-2.11±1.61 to -1.01±2.05%). On further analysis, it was found that change in RI with *TC* 500 mg was significantly better compared to 250 mg ($p < 0.001$).

Significant improvement noted in biomarkers of oxidative stress and systemic inflammation with TC 250 and 500mg compared to baseline and placebo. The mean percent change in biomarker was analysed for each treatment. It was observed that the mean increase in nitric oxide was 10.64 ± 6.16% for *TC* 250 mg and 16.52 ± 5.19% for *TC* 500 mg compared to baseline while Glutathione was 9.25% and 17.97% respectively for *TC* 250 mg, *TC* 500 mg compared to baseline. Mean percentage reduction in malondialdehyde was 6.83% with *TC* 250 mg and 11.20% with *TC* 500 mg. Similarly, *TC* 250 mg and *TC* 500 mg produced a mean percentage decrease in hsCRP of 9.25% and 26.47% respectively, compared to baseline. There was no significant change in any of the parameters with placebo.

Treatment with *TC* 250 mg and 500 mg significantly reduced total cholesterol ($p<0.001$), low-density lipoprotein cholesterol (LDL-C, $p<0.01$), and triglycerides ($p<0.001$) levels compared with baseline. There was an increase in high-density lipoprotein cholesterol (HDL-C, $p<0.001$) levels seen with TC 500mg compared with baseline.

All treatments were well tolerated with no serious adverse event. Two patients on *TC* 250 mg and one patient on *TC* 500 mg complained of dyspepsia. Mild headache reported by three patients oin placebo. All ADRs resolved with symptomatic treatment. None of the patients discontinued the study prematurely because of these adverse events.

Conclusion: Both TC250 and 500mg significantly improved endothelial function, serum lipid profile and reduced biomarkers of oxidative stress suggesting improvement in endothelial function in diabetic patients. No significant alterations were observed in safety lab parameters. Terminalia chebula 500mg twice daily produced more pronounced response on

pharmacodynamic parameters of endothelial function and biomarkers of oxidative stress as evidenced by significant reduction in mean RI index and improvement in nitric oxide, Glutathione and hsCRP compared to TC 250mg and placebo. It is suggested that further studies maybe undertaken in larger number of patients for exploring the beneficial effects of these formulations.

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