



A randomized double blind placebo controlled trial of guatteria gaumeri mother tincture in the management of hyperlipidemia

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ABSTRACT

Aim: Guatteria gaumeri has antioxidant, anti-inflammatory, and anti-diabetic activities. In the present randomized double-blind placebo-controlled trial is the efficacy of guatteria gaumeri mother tincture in hyperlipidemia. Hyperlipidemia patients meeting the inclusion criteria were randomly assigned to the treatment and placebo. **Methods:** 30 patients in the treatment group took guatteria gaumeri mother tincture; whereas the patients in the placebo group took placebo mother tincture for 12 weeks. The lipid profiles of the patients were evaluated at baseline, and after 6 and 12 weeks of the clinical trial. **Results:** The final results showed that guatteria gaumeri mother tincture significantly p-value 0.05 and improved LDL, HDL, cholesterol, compared to the placebo group. The guatteria gaumeri showed an inhibitory effect on hepatic enzymes and possible liver toxicity. No serious side effect was reported for guatteria gaumeri mother tincture administration. Therefore, guatteria gaumeri mother tincture could be considered as a supplement for the treatment of dyslipidemia.

Key words:

Randomized double blind placebo controlled trial, hyperlipidemia, guatteria gaumeri.

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INTRODUCTION

Guatteria gaumeri Greenm; synonymy *G. leiophylla* Safford belongs to the Anonaceae family and has been used as a popular remedy for dissolution of calculi in traditional medicine [1-3]. Preliminary studies have shown that an aqueous infusion prepared from the bark of this plant, given orally to normal dogs, produces a decrease in serum levels of cholesterol. Guatteria gaumeri bark contains significant amounts of alpha asarone, but not its carcinogenic isomer beta asarone and other related transpropenylbenzene compounds. Guatteria gaumeri helps in regulating cardiac disorders [4-6], hyperlipidemia and hypertension. Hypercholesterolaemia, is a metabolic condition of increased circulating cholesterol in the blood is among the most commonly known risk factors of coronary heart disease. After the arrival of VLDL into the circulation system it will be changed over into IDL by the activity of lipoprotein lipase and hepatic lipase, where phospholipids and apolipoproteins moved back to HDL7. Besides, after the hydrolysis by hepatic lipase, IDL will be changed over to LDL and misfortune more apolipoproteins [8-11]. Fringe cholesterol is come back to the liver by invert cholesterol transport pathway utilizing HDLs which are initially orchestrated by the liver what's more, discharged into the blood. In the blood, HDL cholesterol is esterifies by LCAT to cholesterol ester what's more, moved to VLDL and chylomicrons to return to the liver through LDL receptor. Cholesterol ester are moved to LDL particles by CETP and

afterward exposed to LDL-receptors interceded endocytosis. At long last, cholesterol esters are hydrolyzed to cholesterol and removed from the body as bile corrosive [12-14]. Extremely high doses (60 mg/kg) of pure alpha asarone extracted from lancewood caused significant maternal harm when fed to pregnant mice. Guatteria gaumeri mother tincture main component is alpha-asarone, which has been isolated by different extraction procedures and subsequently synthesized, as well as 16 analogs, derivatives of 4-propenyl-1, 2-dimethoxybenzenes 5-substituted [15,16].

MATERIAL AND METHODS

PREPARATION OF GUATTERIA GAUMERI MOTHER TINCTURE

Guatteria gaumeri mother tincture was obtained from Sri Ganganagar Pharmacy, Ganganagar, Rajasthan, India. The guatteria gaumeri mother tincture¹⁴ was kept at room temperature in darkness until use.

PREPARATION OF MOTHER TINCTURE BOTTLES

Extraction of guatteria gaumeri mother tincture [14] was purchased and stored as mentioned above. Guatteria gaumeri mother tincture and placebo were prepared into bottle in Department of homoeopathy pharmacy, Sri Ganganagar Homoeopathic Medical College, Hospital and Research Center, Sri Ganganagar. The guatteria gaumeri mother tincture bottle was identified at the department of homoeopathy Pharmacy,

Sri Ganganagar Homoeopathic Medical College, Hospital and Research Center, Sri Ganganagar. The placebo mother tincture bottle was filled with neutral and inert additive substance whereas; each *Guatteria gaumeri* mother tincture bottle was filled with 200µl/kg body weight mother tincture (recommended dose given for rats in 20 µl/100 g body weight) & per orally in de ionized water (180 µl) as vehicle for administration. There were no in clinical studies on the anti hyperlipidemic effect of *Guatteria gaumeri* mother tincture. In the abovementioned works, administration of *Guatteria gaumeri* mother tincture was safe and effective.

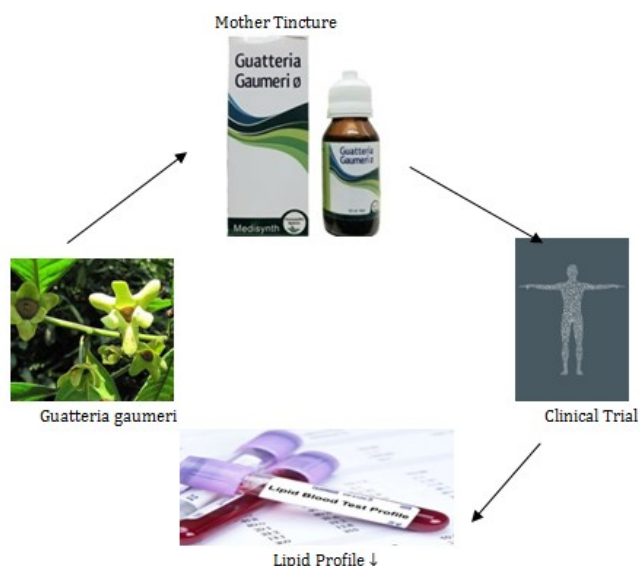


Fig 01: Graphical Abstract

STUDY DESIGN

The randomized double blind placebo controlled trial was fully conducted in accordance with the Ethical Committee of the Sri Ganganagar Homoeopathic Medical College, Hospital and Research Center, Ganganagar and written informed consent was obtained from all patients before their inclusion in the randomized double blind placebo controlled trial. The trial was randomized double blind placebo controlled trial, three months, clinical trial which was carried out on 30 hyperlipidemic outpatients of Sri Ganganagar Homoeopathic Medical College, Hospital and Research Center, Sri Ganganagar, Rajasthan, India. The authors applied inclusion and exclusion criteria for patients to improve the quality of the results in this trial.

INCLUSION CRITERIA

Male and female outpatients aged 25 to 65 years; incidence of hyperlipidemia with at least one of the following factors: cholesterol level >200 mg/dl or TG level higher than 150 mg/dl or LDL-C level higher than 130mg/dL or HDL-C level <40 mg/dl.

EXCLUSION CRITERIA

The patients who had a history of chronic or metabolic diseases such as diabetes, Ischemic heart disease, hypertension, tachycardia, peripheral vascular disease, coronary artery disease, thyroid dysfunction, hospitalized, cannot follow therapeutic lifestyle modification and pregnancy. In addition, the exclusion criterion was a recent change in dosage of antilipemic agents such as hydroxymethylglutaryl coenzyme A (HMG-COA) reductive inhibitor, or adding hypoglycemic agents such as first and second generation sulfonylureas or

supplements or drugs known to affect the blood lipids, presence of side effects and unwillingness to participate in randomized double blind placebo controlled trial.

Other exclusion criteria were: LDL level more than 190 in patients who need medical treatment (for healthy people or with one risk factor); LDL ≥ 160 in patients who need drug treatment (for those with two or more risk factors of the following:

- Smoking.
- Hypertension.
- Low HDL level (less than 40).
- History of coronary artery disease at an early age in the household (less than 55 years in males and in females under age 65 years old), 5. Age above 65 years old).

SAMPLE SIZE

To have a power of 90%, a two sided test was used, with a significance level of 0.05, and a 20% minimum detectable mean difference changes for LDL-C and SD 20.5% between treatment and placebo group. Finally, minimum sample size of 30 patients for each arm was calculated. Because of expected dropout, we considered 15 patients in each group.

The patients were randomized double blind placebo controlled trial divided into the treatment (15 patients) treatment group and the placebo (15 patients) groups. Finally, 30 patients successfully completed a randomized double blind placebo controlled trial.

INTERVENTIONS

Participants were randomized double blind placebo controlled trial to 2 intervention groups of 15 patients. The patients in the treatment group were taking asparagus racemosus mother tincture, for 12 weeks; whereas the patients in placebo group were taking placebo (mother tincture) for 12 weeks. Participants did not receive any other hypocholesterolemic drugs during the randomized double blind placebo controlled trial. The patient’s compliance and medication adherence were confirmed through checking with the patient and his/her caregiver along with a mother tincture count at each visit.

OUTCOME MEASURES

Lipid profile (Cholesterol, TG, HDL and LDL), blood pressure (SBP and DBP), BMI index and liver enzymes (ALT, AST, ALP) were measured at baseline, 6 weeks and 3 months after intervention in treatment and placebo group.

MASKING

The enrolled participants were assigned using a stratified randomization and all of them received asparagus racemosus mother tincture or placebo mother tincture, which were prepared in the same way. For randomization, a randomized code number was obtained from Microsoft Excel for each pillbox (treatment and control groups). All mother tincture bottles had similar colour, shape, size, texture and odour. The mother tincture bottles were stored in a dark container and coded by a pharmacist. The participants and those assessing outcomes were blinded until all participants finished the protocol.

SAFETY

The patients were requested to inform investigators about any adverse events or complaints for all illnesses, and hospitalizations that occurred during the trial. The symptoms were checked and recorded at the beginning and at each visit by general physician, cardiologist. Also, possible side effects were checked and recorded via telephone call every week and the general physician/homoeopathy physician was responsible for continuing or discontinuing the drugs.

STATISTICAL ANALYSIS

Baseline characteristics were analyzed using independent t-test or χ^2 tests. The significant differences at various time points were assessed by repeated measures of ANOVA. The variables were reported as mean and standard deviation (Mean \pm SD). P value less than 0.05 was considered statistically significant.

Table 01: Demographic data of the patients in both study groups (M \pm SD)

Variable	Control group	Test group	P _{value}
Age	0.30 \pm 0.70	0.41 \pm 0.70	0.27
Years	0.5 \pm 0.71	0.5 \pm 0.71	0.4
Gender (M/F)	0.93 \pm 0.70	1.06 \pm 0.79	0.315
Marital status (M/UM)	0.86 \pm 0.83	1.13 \pm 0.83	0.194
Education (Diploma/UG/PG)	0.73 \pm 0.88	1.26 \pm 0.88	0.054
Smoing	0.66 \pm 0.72	1.33 \pm 0.81	0.212

Male (M), Female (F), Married (M), Unmarried (UM), under graduate (UG), post graduate (PG)

Table 2: The measurements of lipid profile between two groups (M \pm SD)

Variable	Control group	Test group	T _{value}	P _{value}
CH				
At base line	210.2 \pm 0.7	210.4 \pm 0.9	0.641	0.261
After 6 weeks	209.9 \pm 0.9	179.4 \pm 1.5	63.13	0.0001
After 12 weeks	209.2 \pm 1.0	139.4 \pm 1.3	159.93	0.00001
TG				
At base line	159.3 \pm 0.9	159.4 \pm 0.7	0.211	0.421
After 6 weeks	201.7 \pm 0.3	170.8 \pm 1.0	21.48	0.0001
After 12 weeks	201.6 \pm 0.6	120.0 \pm 0.5	130.95	0.00001
LDL				
At base line	149.3 \pm 0.8	139.9 \pm 37.2	0.196	0.105
After 6 weeks	149.0 \pm 0.7	130.2 \pm 2.0	33.43	0.0001
After 12 weeks	148.6 \pm 0.9	99.9 \pm 0.8	148.56	0.00001
HDL				
At base line	33.1 \pm 1.8	32.9 \pm 2.2	0.08	0.464
After 6 weeks	31.5 \pm 1.5	37.1 \pm 2.2	9.16	0.0001
After 12 weeks	31.3 \pm 1.7	49.85 \pm 2.1	24.72	0.00001

RESULTS

Among 30 type 2 hyperlipidemia patients with mean \pm SD, age group cases were observed 0.30 \pm 0.78 in control group and 0.41 \pm 0.70 in a test group, P_{value} showed 0.27. Patient years mean \pm SD were 0.5 \pm 0.71 in control group and test group was 0.5 \pm 0.71, P_{value} showed 0.4. Patient gender mean \pm SD were 0.93 \pm 0.70 in control group and test group was 1.06 \pm 0.79, P_{value} showed 0.315. Patient marital statuses mean \pm SD were 0.86 \pm 0.83 in control group and test group was 1.13 \pm 0.83, P_{value} showed 0.194. Patient education mean \pm SD were 0.73 \pm 0.88 in control group and test group was 1.26 \pm 0.88, P_{value} showed 0.054. Patient smokers mean \pm SD were 0.66 \pm 0.72 in control group and test group was 1.33 \pm 0.81, P_{value} showed 0.212 (Table 1).In 30 hyperlipidemia patient mean \pm SD of cholesterol is 210.2 \pm 0.7 in control group, 210.4 \pm 0.9 in test

group, P_{value} is 0.261, T_{value} is 0.641 at baseline. After 6 weeks of the cholesterol mean and standard deviation values are 209.9 \pm 0.9 in control group, 179.4 \pm 1.5 in test group, T_{value} is 63.13, P_{value} is 0.0001. After 12 weeks mean \pm SD values 209.2 \pm 1.0 in control group, 139.4 \pm 1.3 in test group, P_{value} is 0.00001, T_{value} is 159.93. P_{value} is very signification in cholesterol variable. Triglycerides (TG) base line mean \pm SD values are 159.3 \pm 0.9 in control group, 159.4 \pm 0.7 in test group, P_{value} is 0.421, T_{value} is 0.211. After 6 weeks mean \pm SD values were 201.7 \pm 0.3 in control group, 170.8 \pm 1.0 in test group, T_{value} is 21.48, P_{value} is 0.0001. After 12 weeks mean \pm SD values were 201.6 \pm 0.6 in control group, 120.0 \pm 0.5 in test group, T_{value} is 130.95, P_{value} is 0.00001. In low density lipoprotein (LDL) base line values were 149.3 \pm 0.8 in control group, 139.9 \pm 37.2 in test group, T_{value} is 0.196, P_{value} is 0.105. After 6

weeks mean \pm SD values were 149.0 ± 0.7 in control group, 130.2 ± 2.0 in test group, P_{value} 0.0001, T_{value} is 33.43. After 12 weeks mean \pm SD values were 148.6 ± 0.9 in control group, 99.9 ± 0.8 in test group, P_{value} is 0.00001, T_{value} is 148.56. High density lipoprotein (HDL) base line mean \pm SD values were 33.1 ± 1.8 in control group, 32.9 ± 2.2 in test group, P_{value} 0.464, and T_{value} is 0.08. After 6 weeks mean \pm SD values were 31.5 ± 1.5 in control group, 37.1 ± 2.2 in test group, P_{value} is 0.0001, T_{value} is 9.16. After 12 weeks mean \pm SD value is 31.3 ± 1.7 in control group, 49.85 ± 2.1 in test group, P_{value} is 0.00001, T_{value} is 24.72 (Table 02).

DISCUSSION

According to our data and previous research does not have a serious side effect in therapeutic doses. Also, in this randomized double blind placebo controlled trial we observed that the serum level of liver enzymes likes ALT, AST and ALKP were P_{value} significant in test group. Some studies showed that green leaf *guatteria gaumeri* contains alpha-asarone and the amino and metoxi analogs.

Crude extract and purified aqueous fraction of *guatteria gaumeri* have been demonstrated for its antioxidant effect. Juarez, SQnchez Res Bndiz studies showed that this plant, given orally to normal dogs, produces a decrease in serum levels of cholesterol. The lipid lowering effects of *guatteria gaumeri* extract in hypercholesteremic rats was demonstrated and the investigation revealed that primary reason of antihypercholesterolemic effect was increased excretion of cholesterol, neutral sterols, bile acid and increase in hepatic bile acid content. Increased HMG-CoA reductase activity in hypercholesteremic rats upon treatment with *guatteria gaumeri* root powder was powder.

Interestingly, normocholesteremic animals under asparagus racemosus treatment, exhibited no significant variations either in excretion of cholesterol, neutral sterols, bile acid, hepatic cholesterol and bile acid content. Significant increase in plasma HDL-C levels with a concurrent decline in the plasma cholesterol level and an improvement in the atherogenic index of hypercholesterolemic test animals clearly indicated the beneficial role of root administration in hypercholesteremic animals. The reduction in the levels of HDL-C is an indicative of high risk of cardiovascular disease, so improvement in its levels gives cardioprotective activity. *Guatteria gaumeri* after daily dosing per os of 80 mg/kg of alpha-asarone and the amino and metoxi analogs for seven days to hypercholesterolemic male rats, cholesterol decreased 57.3, 37.5 and 46.9% and triglycerides diminished 42.5, 67.6 and 17.2% respectively. Some of the other analogises showed also important hypolipidemic activity. Similarly alpha asarone decreased 80.6% the weight of gallstones in hamsters. Studies using adult rat hepatocytes suggest that at least part of the hypolipidemic effect of alpha asarone could be due to a decrease in the secretion of lipids. Alpha asarone did not produce any toxic effect after oral administration to rats of 10 or 50 mg/kg for 28 days, or genotoxicity by the dominant lethal test.

CONCLUSION

The results obtained in this randomized double blind placebo controlled trial therefore suggest that the hypocholesteremic effect of *guatteria gaumeri* could be mediated through an increased bile acid synthesis for elimination of body cholesterol. Further studies performed in the human and in several experimental animals have confirmed the

hypocholesterolemic properties of this plant remedy. The chemical analysis of ethanolic extracts of *guatteria gaumeri* has revealed the presence of asarone, a compound with reputed hypocholesterolemic properties. The increased hepatic antioxidant activities in *guatteria gaumeri* homoeopathic mother tincture administered people indicate that alpha-asarone which has been isolated by different extraction procedures and subsequently synthesized, as well as 16 analogs, derivatives of 4-propenyl-1,2-dimethoxybenzenes 5-substituted is obtained in *guatteria gaumeri* homoeopathic mother tincture mother tincture could contribute to amelioration of the hyperlipidemic conditions. However, further researches are required to clarify the mechanism of this effect. No side effects issues were reported in the randomized double blind placebo controlled trial.

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