Randomized placebo-controlled trial of Guggulu Ghanavati in Hyperlipidemia

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Abstract:
Hyperlipidemia is term used to denote raised serum levels of cholesterol or triglycerides or both. The lipid hypothesis proposed by Rudolph Virchow in 1856 suggested that blood lipid accumulation in arterial walls caused atherosclerosis. There is no precise term for hyperlipidemia in the Ayurvedic classics. Yet various scholars have tried use distinct nomenclature for hyperlipidemia, e.g., Rasagata Sneha Vriddhi, Rasa Raktagata Sneha Vriddhi, Dhamani Pratichayah, Medovriddhi, Medoroga or Medodosha, Ama Medo Dhatu, etc. A detailed study of hyperlipidemia reveals its similarity to Asthayi Medo Dhatu Vriddhi with regard to the pathophysiology. Also, this excessively increased Asthayi Medo Dhatu is Ama in nature, due to which it is retained in the body for a longer time, resulting in further complications. From the Ayurvedic point of view hyperlipidemia is a result of Santarpana. Acharya Charaka has stated that regular administration of Guggulu as a formulation can cure all the Santaranjanya Vyadhis or diseases due to overnutrition. [7] Considering the lack of definite Ayurveda comprehension of hyperlipidemia, as well as the role of hyperlipidemia in the causation life-threatening diseases, we carried out this study to evaluate the efficacy of Guggulu Ghanavati in the management of hyperlipidemia.

Keywords:
Hyperlipedemis, Dyslipemia, hypertriglyceremia, Hypercholesteremia, Dhamani-Pratichaya, Dhamanigata, Medovrudhi, Hrudroga

Introduction
The growing challenges of modernization have resulted in human beings readjusting their customary behavior by modifying their dietary and lifestyle preferences. Fast foods, lack of exercise, stress, and various addictions are some of the factors which are adversely impacting the lifestyle of man in the 21st century. This has resulted in a discrepancy between the external environment and man's internal mechanism, leading to a multitude of diseases, mainly due to impaired metabolism; these are popularly referred to as lifestyle diseases. Hyperlipidemia is one such disorder. It has been identified as a potential risk factor for many diseases, including cardiovascular diseases, the metabolic syndrome, and hypertension. Hyperlipidemia is defined as the presence of raised or abnormal levels of lipids and/or lipoproteins in the blood. [1]
Hyperlipidemia has drawn worldwide interest for its ability to participate in the pathology of atherosclerotic diseases like coronary heart disease (CHD), which is an important cause of morbidity and mortality the world over. In 1913, a study by Anitschkow showed that feeding rabbits cholesterol could induce symptoms similar to atherosclerosis, suggesting a role for cholesterol in atherogenesis. [3] Since then raised levels of cholesterol and triglycerides have been identified as the prime modifiable risk factors in atherosclerotic disease. Globally, raised cholesterol is estimated to be responsible for 18% of cerebrovascular disease and 56% of ischemic heart disease. Overall, these diseases accounts for about 4.4 million deaths (7.9% of the total) and 40.4 million disability adjusted life years (DALYs) (2.8% of the total). [4] Raised total cholesterol, being a risk factor for ischemic heart disease and stroke, is a major cause of the disease burden in both the developed and developing world. [5] Also, after controlling for LDL and HDL cholesterol, increased serum levels of triglycerides have been shown to be an independent risk factor for coronary heart disease. [6]

**Materials and Methods**

Patients fulfilling the criteria and attending the OPD and IPD of the Dept. of Kayachikitsa, K.D.M.G.S Ayurvedic College, Chalisgaon, Dist- Jalgaon were selected for the present study irrespective of age, sex, religion, etc. A detailed proforma was specially designed encompassing all the aspects of the disease to collect the data.

**Diagnostic criteria**

Patients were diagnosed on the basis of the lipid profile. Lipid profile showing any one or more of the following criteria was considered diagnostic of hyperlipidemia. [8]

- Serum cholesterol 201 mg/dl or more
- Serum Triglycerides 151 mg/dl or more
- Serum LDL 131 mg/dl or more
- Serum VLDL 41 mg/dl or more

**Inclusion criteria**

Patients fulfilling the following general and diagnostic criteria were selected for the present study.

- Patient's age more than 20 years and below 60 years
- Body Mass Index (BMI) <40

**Exclusion criteria**

Patients having history of serious cardiac disorders like myocardial infarction, cardiac failure, etc.

- Patients having any major illness, insulin-dependent diabetes mellitus, diabetes mellitus that was poorly controlled or newly diagnosed or if the patient was taking some new therapy or recently adjusted therapy
- Patients having a history of untreated thyroid disorder
- Hyperlipidemia due to drugs (e.g., glucocorticoids)
- Pregnant females and lactating mothers
- Renal insufficiency

**Concomitant medication**

Known lipid-lowering drugs like statins or fibrates were stopped during the study.

**Investigations**

Routine hematological examination was done before treatment to rule out any pathological conditions.

Biochemical examination - Complete lipid profile, fasting blood glucose, serum creatinine, and blood urea was checked before and after treatment.

Apolipoprotein B was investigated as a
biomarker for hyperlipidemia in selected patients.

**Study design**
This was a placebo-controlled randomized clinical study. Informed consent was taken from all the patients before including them in the trial.

**Drugs and posology**
The selected patients were randomly allocated into two groups as follows:

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
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<tbody>
<tr>
<td>Drug</td>
<td>Guggulu Ghanvati</td>
<td>Placebo</td>
</tr>
<tr>
<td>Dose</td>
<td>500 mg*2 TID</td>
<td>500 mg*2 TID</td>
</tr>
<tr>
<td>Duration</td>
<td>30 Days</td>
<td>30 Days</td>
</tr>
<tr>
<td>Anupan</td>
<td>Lukewarm water</td>
<td>Lukewarm water</td>
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<tr>
<td>Kala</td>
<td>Before Meals</td>
<td>Before Meals</td>
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</table>

**Contents of Guggul Ghanvati**
Guggulu (Combifera mukul)

**Pathya apathya (dietary advice)**
All the registered patients were advised to follow specific dietary changes and exercise patterns.

**Assessment of therapy**

**Criteria for assessment**
The patients were examined weekly and a suitable scoring pattern was designed comprising of objective signs to assess any changes in the patients. After completion of 1 month of treatment, the efficacy of the therapy was assessed on the basis of the following subjective as well as objective criteria.

**Subjective criteria:** Symptomatic evaluation of all the patients was undertaken for which a multidimensional scoring pattern was adopted. The patients were assessed twice, before and after the therapy, to assess the severity of the symptoms. The severity was scored according to the criteria shown below and the percentage relief was calculated to assess the efficacy of the therapy.

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<tbody>
<tr>
<td>Absence Symptoms</td>
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<tr>
<td>Mild degree of Symptoms</td>
<td>1</td>
</tr>
<tr>
<td>Modrate Degree of Symptoms</td>
<td>2</td>
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<tr>
<td>Severe Degree of Symptoms</td>
<td>3</td>
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A detailed scoring pattern was prepared and used for the main signs and symptoms, such as Chala Sphika Udara Stana, Alasya/Utsahahani, Kshudra Swasa (Ayasa Swasa), Daurbalya (Alpa Vyayama), Nidraadhiyka, Swedadhikya, Daurgandhya, Snigdhanga, Ati Pipasa, Ati Kshudha (Ati Kshudha was decided on the basis of Ruchi, Abhyavaharana Shakti, and Jarana Shakti), Anga Gaurava (heaviness of body), Sandhishhoolaa, and Gatra Sada.

The assessment was done before starting the treatment and after 30 days of treatment (i.e., the completion of the treatment) and the improvement was assessed on the basis of the percentage relief obtained and statistical evaluations.

**Objective criteria:** The following objective criteria were assessed:

Biochemical test: Complete lipid profile, including serum cholesterol, serum triglycerides, serum HDL, serum LDL, and serum VLDL was done before and after treatment. Since the plasma levels of apolipoprotein B are known to reflect the total numbers of atherogenic particles, [9] it was used as a biomarker for hyperlipidemia and was assessed in selected patients before and after treatment.

Body fat percentage: Body fat percentage was measured in selected patients using the Omron Body Fat
Monitor (Model HBF-306, Omron Healthcare Co. Ltd., Japan). Body fat percentage refers to the percentage of the body fat mass (weight of the fat) in relation to the total body weight. [10] The weight of the body that is exclusive of fat is referred to as the fat-free body mass.

Body fat percentage = \{Body fat mass (kg) / Body weight (kg)\} × 100

Body fat mass = Body weight (kg) - Fat free mass (kg)

Body circumference measurements: Measurement of the girth of the following areas, where adipose tissue is generally found to be more, was taken:

- Chest: In normal expansion, at the level of the nipples
- Waist: At the level of the umbilicus
- Pelvis: At the level of the anterior superior iliac spine
- Hip: At the level of the highest point of distension of the buttocks
- Mid-arm: Middle of the arm between the shoulder joint and the elbow joint
- Mid-thigh: Middle of the thigh between the hip joint and the knee joint
- Mid-calf: Middle of the calf between the knee joint and the ankle joint
- In case of girth measurements, the mean values were taken before and after treatment.

Skin-fold thickness: The effectiveness of therapy on body fat was assessed by measuring the skin-fold thickness using Vernier calipers before and after treatment; measurement was taken in the following areas:

- Skin-fold thickness over the middle portion of the biceps muscle
- Skin-fold thickness over the middle portion of the triceps muscle
- Skin-fold thickness over the abdomen

Body mass index (BMI): The body mass index (BMI) or Quetelet index, a measurement that compares a person's weight and height, was also assessed.

**Statistical analysis**
The data was mainly analyzed using Student's paired t test. The obtained results were interpreted as:

- Insignificant: p<0.5
- Significant: p<0.01
- Highly Significant: p<0.001

The overall effect of the therapy was judged based on assessment of the lipid profile, for which a specialized scoring pattern was devised. Lipid profile was given a total score of 100, with each of the parameters of the lipid profile, i.e., serum cholesterol, serum triglycerides, serum HDL, serum LDL, and serum VLDL, given a score of 20. The range for the lipid profile was decided as per the American Journal of Lifestyle Medicine [8] and accordingly the scoring pattern was set.

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<tr>
<th>Sr.</th>
<th>Cholesterol score</th>
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<tr>
<td>&gt;240 mg/dl</td>
<td>0</td>
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<tr>
<td>200-219mg/dl</td>
<td>10</td>
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<tr>
<td>&lt;200 mg/dl</td>
<td>20</td>
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<tr>
<td>&lt;150 mg/dl</td>
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<tr>
<td>150-199mg/dl</td>
<td>5</td>
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<tr>
<td>200-499mg/dl</td>
<td>10</td>
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<tr>
<td>&gt;500 mg/dl</td>
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<th>HDL score</th>
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<tr>
<td>&lt;40 mg/dl</td>
<td>0</td>
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<tr>
<td>40-60 mg/dl</td>
<td>10</td>
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<tr>
<td>&gt;60 mg/dl</td>
<td>20</td>
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<th>LDL score</th>
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<tr>
<td>&gt;190 mg/dl</td>
<td>0</td>
</tr>
<tr>
<td>160-189mg/dl</td>
<td>5</td>
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<tr>
<td>130-159mg/dl</td>
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The scores taken after treatment were subtracted from the scores taken before treatment. The result if found negative was considered to be deterioration of condition. Thus, the total effect of the therapies was graded as following:

- Complete remission: 75-100%
- Marked improvement: 50-75%
- Moderate improvement: 25-50%
- Mild improvement: 0-25%
- Unchanged: 0
- Worsened: <0

**Observations**

The study was conducted on 61 patients. Among the patients, 47.54% were in the age-group of 40-50 years; 59.02% were females, 83.60% were married, and 86.89% were Hindu by religion.

The Dashvidha Pariksha revealed that 32.79% of the patients had Kaphapradhana Pittanubandhi Sharir Prakriti, 49.18% had Tamasic Manas Prakriti, 65.57% were Madhyama Sara, 52.46% were Madhyama Satva, and 65.57% were Madhyama Samhanana. The majority of the patients had Pravara Premana, characterized by body weight between 71-80 kg (36.06%), BMI greater than 25 kg/m² (81.96%), waist circumference greater than 102 cm in male patients (32%) and greater than 88 cm in female patients (66.67%), waist-to-hip ratio greater than 0.9 in male patients (96%) and waist-to-hip ratio greater than 0.85 in female patients (55.56%). Among the male patients 86.67% had body fat percentage greater than 25%, and among the female patients 95.45% had body fat percentage greater than 32%. Most of the patients had Pravara Abhyavahara Shakti (50.82%), Pravara Jarana Shakti (47.54%), Tikshnagni (49.18%), and Madhyama Koshta (67.21%). In Nidanas, Ahara was found to be dominant in Madhura Rasa(57.38%), Guru Guna(73.77%) and Snigdha Guna (63.93%). Adhyashana (73.77%) and Vishamashana (33.70%) were found to be the dominant dietary habits. Consumption of fried foods (70.49%) and bakery products (42.62%) was also found to be common. In Vihara, Divaswapa (75.41%) and Avyayama (70.49%) was found to most commonly, whereas in Manas Nidana Atichinta (45.90%) was dominant. Most of the patients (62.30%) had insidious onset of disease; 57.37% had had disease for less than 1 year, and 63.30% had negative family history of hyperlipidaemia. Most of the females (58.33%) had attained menopause. The majority of the patients showed symptoms of Bharavridddhi (68.85%), Angagaurava (63.93%), and Daurbalya (50.82%), and there was associated obesity in 81.96%. Dushti of Kapha Dosha was present in 88.52%, Medo Dhatu in 90.16%, Rasa Dhatu in 47.54%, and Sweda in 73.77%.

**Effect of therapy**

Effect on symptoms: In the Guggul Ghanvati group, there was relief of symptoms like Anga Gaurava (100%), GatRasada (95.31%), Atipipasa (90.58%), Kshudra Shvasa (89.36%), Alasya (85%), Sandhishoola (84.29%), Nidradhikya (83.61%), Daurbalya (70.97%), Snigdhangata (55.56%), Daurgandhya (55.17%), Swedadhikya (41.45%), Angachalatva (22.45%), and Atikshudha (18.18%). The relief in Alasya, Kshudra Shwasa, Daurbalya, and Atipipasa was statistically significant (P≤.05). On
Sandhishoola, GatRasada, Angagaurava, and Nidradhikya the relief was statistically highly significant (P ≤ .01). Statistically significant results were also obtained in relief of Snigdhangata (P ≤ .02) and Jarana (P ≤ .05).

In the placebo control group, relief was found in Atikshudha (105.06%), Ksudra Shvasa (73.33%), Anga Gaurava (65.38%), GatRasada (62.5%), Alasya (58.33%), Snigdhangata (35.48%), and Daurbalya (34.48%); relief was also seen in Nidradhikya (33.33%), Atipipasa (33.33%), Sandhishoola (29.95%), Swedadhikya (29.03%), Daurgandhya (20%), and Angachalatva (2.56%).

**Effect on body parameters**

Guggul Ghanvati reduced body weight in 2.57% of the subjects, BMI in 2.65%, and body fat percentage in 7.75%. All the results were statistically highly significant (P < .001). In the placebo control group reduction in body weight was seen in 1.52% and reduction of BMI in 1.52%; these changes were found to be statistically significant (P < .05). There was an increase in the body fat percentage in 0.27%, but this was not statistically significant (P > .5) [Figure 1].

**Effect on body circumferences**

Guggul Ghanvati reduced the mid-arm circumference in 5.35% of the patients, chest circumference in 2.49%, abdomen circumference in 5.23%, hip circumference in 4.04%, and pelvis circumference in 3.64%. The results were found to be statistically highly significant (P < .001). It was also seen to reduce the mid-thigh (3.66%) and mid-calf circumferences (1.24%); this was found to be statistically significant (P < .05). In the placebo control group there was reduction in the circumferences of mid-arm (3.98%), chest (2.52%), and pelvis (2.20%). The results were found to be statistically highly significant (P < .001). There was also reduction of the circumferences of the abdomen (3.67%), hip (2.69%), mid-thigh (3.76%), and mid-calf (1.44 %), which were all found to be statistically significant (P < .05) [Figure 2].

**Effect on skin-fold thickness**

Guggul Ghanvati reduced biceps skin-fold thickness in 18.11%, triceps skin-fold thickness in 18.8%, and abdominal skin-fold thickness in 18.52% of patients. These results were found to be statistically highly significant (P < .001). In the placebo control group there was reduction of biceps skin-fold thickness in 9.37%, triceps skin-fold thickness in 9.33%, and abdominal skin-fold thickness in 7.68%; These changes were statistically significant (P < .05) [Figure 3].
Effect on lipid profile
On statistical evaluation by paired 't' test, Guggul Ghanvati Group was seen to decrease S.Cholesterol (3.28%), S. Triglycerides (11.1%), S.HDL (2.06%), S.LDL (1.98%), S.VLDL (11.50%) and increase S. Apolipoprotein B (1.14%). However the effect was found to be statistically insignificant. Placebo Control Group was seen to decrease S.Cholesterol (7.82 %), S.Triglycerides (3.93 %), S. VLDL (3.93 %), S.HDL (6.45 %), S.LDL (9.78 %) and S. Apolipoprotein B (13.35%). However the results were found to be statistically insignificant. In the placebo control group, serum cholesterol decreased in 7.82% of subjects, serum triglycerides in 3.93%, serum VLDL in 3.93%, serum HDL in 6.45%, serum LDL in 9.78%, and serum apolipoprotein B in 13.35%. However, the results were found to be statistically insignificant [Figure 4].

Overall effect of therapy
In group A (Guggul Ghanvati), 28 patients completed the full course of treatment; 12 patients (42.86%) showed mild improvement, 4 patients (14.28%) showed moderate improvement, 7 (25%) patients were unchanged, and the condition of 5 patients (17.86%) worsened. In group B (placebo group), 22 patients completed the entire course of therapy, out of which 10 patients (45.45%) showed mild improvement, 1 patient (4.54%) showed moderate improvement, 5 (22.72%) patients remained unchanged, and the condition of 6 (27.27%) patients worsened [Figure 6].
Adverse events
During the study only one adverse event was noted. In the Guggul Ghanvati group, a 55-year-old female patient complained of mild calf muscle cramps.

Discussion
Thus, Guggul Ghanvati is a true drug possessing pharmacological activity. All the patients in both the groups followed strict dietary restrictions as well as lifestyle changes. Therefore, the difference between the two groups can be attributed to the pharmacological efficacy of the drug (along with some benefit from the dietary and lifestyle changes). The above findings are consistent with the Ama Pachana, Lekhana, and Upashoshana properties of the drug, which result in the reduction of Anga Gaurava, GatRasada, Alasya, Nidradhikya, Snigdhangata, Angachalatva, and Swedadhikya. Reduction in Anga Gaurava, Anga Chalatva, Kshudra Shvasa, and Sandhishoola can also be attributed to the loss of body weight caused by the administration of Guggul Ghanvati. Atikshudha was seen to decrease to a greater extent in the placebo group. Placebo provides psychological relief in patients hence some symptoms of the disease are seen to decrease as a result of it.

Guggul Ghanvati was also seen to be mild successful in reversing the dyslipidaemic changes in the patients, which may be needs long duration of the therapy. Serum cholesterol was found to rise in some patients on starting drug therapy and dietary restrictions. This may be because of excessive endogenous production of cholesterol in the body in response to the decreased dietary supply. Serum triglycerides showed a better response to Guggul Ghanvati than serum cholesterol; the response however was not significant, which may be due to the fact that the stored triglyceride in our body is changed every 2-3 weeks due to its constant synthesis and utilization, whereas it takes a longer duration to work on cholesterol. Guggul Ghanvati showed better results on other objective parameters related to obesity (i.e., body weight, BMI, body fat percentage, body circumferences, and skinfold thickness), which shows its depletory action on Sthayi Medo Dhatu.

In this study we also observed that the patients who shed their excess weight during the course of study showed better improvement in their lipid profiles as compared to the patients whose weight remained constant. Thus, a relationship can be established between obesity and hyperlipidemia, which is in accordance with the Poshya Poshaka Meda Dhatu relationship described in Ayurveda.

Thus, Guggul Ghanvati was seen to reduce the levels of 'bad' cholesterol (serum LDL) and increase the levels of 'good' cholesterol (serum HDL), thereby correcting dyslipidemia. HDL is known to have protective action against atherosclerosis and to reduce the risk for cardiovascular disease.

Probable mode of action of Guggul Ghanvati
The total effect of the Guggul Ghanvati is Tridosha Shamaka, especially Kapha Vata
Shamaka. It is Tikta, Kashaya, and Katu in Rasa; Laghu and Ruksha in Guna; and Katu in Vipaka; and thus pacifies the vitiated Kapha Dosha, which is dominant in the pathogenesis of hyperlipidemia. It also depletes the excessively produced Rasa, Mamsa, Meda, Vasa, Sweda, and Kleda, which are all similar in attributes to Kapha Dosha. It should be noted here that one of the ways of synthesis of Kapha Dosha in the body is as a Mala of Rasa Dhatu. Similarly, Sweda is the Mala of Meda Dhatu. Thus, it is known to act against the Santarpanottha pathogenesis of hyperlipidemia. Hyperlipidaemia has the vitiation of Kapha Dosha and Rasa, Mamsa, Meda, Vasa, Sweda, and Kleda, which as Dushyas. Involvement of the same Doshas and Dushyas is seen in the pathology of the diseases like Medoroga, Prameha and Kushtha. Hence Guggul Ghanvati which is indicated in Santarpanajanya diseases like Medoroga, Prameha and Kushtha can be used in the treatment of Hyperlipidaemia. Guggul Ghanvati relieve the body of excess of Kapha, Meda, Kleda, Vasa, and Sweda by diminishing their Drava Guna also augmentation of the digestive fire, leading to proper formation of the Rasadi Dhatus and digest the Ama Dosha present at the Jatharagni level as well as the Medodhatvagni level. Guggul is Rasayana in nature, leading to the formation of optimal Dhatus, and thereby protect the body from injury due to vitiated Doshas.

**Conclusion**

Hyperlipidemia can be treated on the principles of Apatarpana and by following the line of treatment of Sthaulya or Prameha since all the three arise due to Medo Dushti. Guggul Ghanvati showed a better result on all the subjective and objective parameters than placebo. Dietary and lifestyle changes are supportive to therapy in hyperlipidaemia and obesity.

**References**

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