A RANDOMIZED, DOUBLE BLIND STUDY TO EVALUATE THE PHARMACOLOGICAL EFFECT OF A POLYHERBAL DRUG (LIPOTAB) IN MANAGING DYSLIPIDEMIA

Yasmeen Shamsi¹, Harendra Kumar²

¹Department of Kulliyat, Faculty of Medicine (Unani), Jamia Hamdard University, New Delhi
²Department of Rehabilitation Sciences, Faculty of Allied Health Sciences, Jamia Hamdard University, New Delhi

E-mail of Corresponding Author: yshamsi@jamiahamdard.ac.in

ABSTRACT

Cardiovascular disease (CVD) is the number one cause of death worldwide. Cardiovascular disease occurs usually due to atherosclerosis of large and medium sized arteries and dyslipidemia has been found to be one of the most important contributing factors. Lowering lipids through dietary intervention or pharmacological therapy has been shown to decrease the incidence of atherosclerotic events. Lipotab is a polypharmaceutical herbal drug, which has shown lipid lowering, antioxidant, anti-inflammatory and vasorelaxant activities in various animal models. To evaluate the efficacy and safety of Lipotab in dyslipidemic human subjects a randomized double blind placebo controlled clinical study was conducted in Clinical Research Unit, Majeedia Hospital, Jamia Hamdard University, New Delhi. Twelve week Lipotab treatment, was discovered significantly effective than placebo in improving lipid profile of the study subjects. The results of the present study suggest that Lipotab is a safe and efficacious drug in treating dyslipidemia. This polypharmaceutical herbal drug can be valuable in prevention of atherosclerosis and cardiovascular disease by antiplatelet, fibrinolytic, antioxidant and cholesterol lowering activities of its various ingredients.
**Keywords:** Dyslipidemia, Herbal drug, Allium sativum, Curcuma longa, Cardiovascular disease

**INTRODUCTION**
Cardiovascular disease (CVD) is the number one cause of death worldwide (1, 2). About two-thirds of the estimated 14.3 million annual cardiovascular disease deaths occur in the developing world (3). CVD covers a wide array of disorders, including diseases of the cardiac muscle and of the vascular system supplying the heart, brain, and other vital organs (4). Acute coronary events (heart attacks) and cerebrovascular events (strokes) often occur suddenly, and are often fatal (5). CVD usually occurs as a result of atherosclerosis of large and medium sized arteries and dyslipidemia has been found to be one of the most important contributing factors for atherosclerosis (6).

Dyslipidemia is a disorder of lipoprotein metabolism; it may manifest with the elevated levels of serum total cholesterol (TC), low-density lipoprotein (LDL), triglycerides, and a decrease in the high density lipoprotein (HDL) concentration (7). Atherosclerosis is usually characterized by both increased LDL-cholesterol and increased triglycerides (TG) levels and often accompanied by low HDL-cholesterol levels (8, 12). However, elevated low-density lipoprotein cholesterol (LDL) is thought to be the best indicator of atherosclerosis risk (9, 10, 11, 13). Lowering lipids through dietary intervention or pharmacological therapy has been shown to decrease the incidence of atherosclerotic events (14). A plant based diet rich in fruit, vegetables, and legumes and low in saturated fat along with regular aerobic exercise programme is an effective prescription for a person with elevated risk of cardiovascular disease (15). Drug therapy for cholesterol reduction includes statins, bile acid resins, nicotinic acid and fibrates (15). A number of medicinal plants possess antihyperlipidemic activity, literature suggests that the lipid lowering action of herbs is mediated through, inhibition of hepatic cholesterol biosynthesis and reduction of lipid absorption in the intestine (16). These herbs may be useful in reducing the risk of cardiovascular disease.

Liptab is a polypharmaceutical herbal drug consisting of Allium sativum, Curcuma longa and Nepeta hindostan.

**Pharmacological study of Lipotab and its Individual Ingredients:**
The results of a study examining the endothelium modulated effects of polypharmaceutical drug Lipotab and its individual ingredients in isolated aortic rings of rat suggested a direct vasorelaxant effect of the drug on the vascular smooth muscle (17).

In another study evaluating the effect of Lipotab on isoprenaline (ISO) induced left ventricular (LV) remodeling and heart failure (HF) in Wistar albino rats, the results indicated that Lipotab prevents ISO-induced LV remodeling and consequent HF in rats through its antioxidant and anti-inflammatory activity (18).

The pharmacological studies showed that supplementation with Allium sativum in cholesterol fed rabbit produced lowering in total, free, ester cholesterol and phospholipids resulting in a lower degree of atherosclerosis (19).

The alcoholic extract of Nepeta hindostana (whole plant) showed cardiac stimulant activity on normal and hypodynamic heart of frog and rabbit. The alcoholic extract provided significant protection from isoproterenol-induced experimental myocardial necrosis (myocardial infarction) in rats (20).

The protective effects on the cardiovascular system of Curcuma longa include lowering cholesterol and triglyceride levels, decreasing susceptibility of low density lipoprotein (LDL) to lipid peroxidation (21) and inhibiting platelet aggregation (22). Water and fat-soluble extracts
of Curcuma longa and its curcumin component exhibited strong antioxidant activity, comparable to vitamins C and E (23). A study of ischemia in the feline heart demonstrated that curcumin pretreatment decreased ischemia-induced changes in the heart (24).

The aim of the present study was to evaluate the efficacy and safety of Lipotab tablet in dyslipidemic human subjects.

**MATERIAL AND METHODS**

**Study Drug:**
The study drug Lipotab (500 mg) tablet is a polyherbal drug which contains dried powder of Nepeta hindostana whole plant (200 mg), Allium sativum bulb (150 mg) and Curcuma longa rhizome (150 mg). Both Lipotab and placebo were supplied by Hamdard Wakf Laboratories, New Delhi, India.

**Study Design:**
This was a randomized, double blind, placebo controlled study, conducted in Clinical Research Unit of Hamdard National Foundation at Majeedia Hospital, Jamia Hamdard, New Delhi, during the year 2001-2004.

**Participants:**

**Inclusion Criteria:**
Subjects (men and women) aged 25-70 years were eligible for the study if they had a history of dyslipidemia for at least 3 months despite of strict diet control and had fasting TC=200-250 mg/dl; LDL 130-170 mg/dl and TG=200-300 mg/dl. Type-2 diabetes mellitus patients with dyslipidemia were also included if they had good glycaemic control (HbA1C < 6.5%) with diet only or diet and oral hypoglycemic agents.

**Exclusion criteria:**
Subjects were excluded from the study if they had Type 1 diabetes; uncontrolled type 2 diabetes or hypertension; hypothyroidism; nephrotic syndrome or renal failure; active hepatic dysfunction; history of coronary insufficiency/ myocardial infarction or CVD; history of estrogen therapy in post-menopausal women; women taking hormonal contraceptives, and body mass index >35 kg/m².

**Informed Consent:**
All patients were included in the study after obtaining written informed consent. Eligible subjects as per the inclusion/exclusion criteria were enrolled in the study and written informed consent was obtained from all the subjects before their enrolment.

At visit 1 lipid profile determinations were conducted and the participants were instructed to follow cholesterol lowering diet for 2 weeks.

After this diet only period (visit-2) lipid profile determinations and laboratory safety tests were performed and the eligible cases as per the inclusion/exclusion criteria were randomly assigned to receive either Lipotab or placebo in the dose of 2 tablets once daily at 4 p.m.

All the patients were instructed to maintain low cholesterol diet as they were advised 2 weeks before their inclusion in the study (visit-1).

Patients underwent an interim checkup after 6 weeks (visit-3) and a final evaluation after 12 weeks (visit-4). Physical examination and laboratory tests were done at each visit. Adverse events were recorded and compliance with study medications was assessed at visit 3 and visit 4.

**Efficacy Analysis:**
Data for efficacy analysis were obtained from all patients who completed 12 weeks study. Lipid profile samples were drawn from 8.30 to 9.00 Am after a 12 hour overnight fast at each visit. The change in LDL- cholesterol levels was considered the primary efficacy variable. Treatment was considered effective only of each of LDL cholesterol, total cholesterol and triglyceride levels were reduced by more than 10% compared with baseline.

**Safety of the Drug:**
Data from the physical examination, laboratory tests and interview for adverse events were
included in the analyses of safety and tolerability. Laboratory safety tests included blood urea, serum creatinine, serum bilirubin, alanine amino transferase (AST), aspartate amino transferase (ALT), haemogram with ESR and fasting & postprandial blood sugar. All data were recorded on case record forms; analysis was restricted to patients who completed the study up to 12 weeks. The changes between pre-treatment and post-treatment values of lipid profile components obtained in drug group (Lipotab) were compared with those obtained in Placebo group by using unpaired “t” test. Statistical calculations were performed with GraphPad InStat version 3.10.

RESULTS
Total 88 subjects were enrolled in the study, 6 subjects did not meet the inclusion criteria because total cholesterol levels were <200mg/dl (4 subjects) and triglyceride levels were > 300 mg/dl (2 subjects), of the 82 cases included in the study, 9 cases (4 receiving Lipotab and 5 receiving Placebo) dropped out from the study for unknown/ personal reasons. Total 73 subjects (38 in Lipotab group and 35 in Placebo group) completed the study according to protocol up to 12 weeks (Figure-1)
There were no significant differences in the characteristics between the two groups at baseline (Table-1 & 2). The incidence of dyslipidemia was highest in upper socio-economic class (65.52%) and there was a moderate frequency of coronary risk factors, mainly obesity (32.18%), diabetes mellitus (29.88%), arterial hypertension (12.06%), and smoking (12.90%). The mean levels of lipid profile at baseline and after treatment and percentage of change in these levels are shown in Table-3.

Twelve week Lipotab treatment, was significantly effective than placebo on the primary efficacy measure, reducing LDL-C by 18.80% compared with 4.36% in the placebo group (p < 0.001). Lipotab also significantly reduced total cholesterol (TC) by 15.09% compared with 3.625 in placebo group (<.001). Triglycerides were too reduced significantly by 18.41% with Lipotab treatment as compared to 4.16% with placebo (p<. 001). A rise in HDL–C was observed in both Lipotab (9.62%) and placebo (4.45%) group. But, this rise was significantly greater in Lipotab group as compared with placebo group (p<. 005)

Safety and tolerability:
Lipotab (also placebo) treatment for 12 week did not impair physical safety indicators such as body weight, pulse rate or blood pressure. Laboratory safety indicators e.g., kidney function test (blood urea, serum creatinine), Liver function test (ALT, AST, serum bilirubin, serum alkaline phosphalase) and haemogram remained within the normal limits in all study patients.
No significant change was observed in mean concentrations of blood glucose levels during the study.
Lipotab was well tolerated, however 6 subjects complained of heartburn. No other adverse events like nausea, anorexia, vomiting muscle cramps and skin rash were reported

DISCUSSION
In the present clinical trial the effects of Lipotab (a polypharmaceutical herbal drug) have been observed on all the components of lipid profile in a double blind, randomized fashion and the safety of the drug has also been established. Lipotab in the daily dose of 2 tablets was discovered significantly effective in reducing mean serum LDL- cholesterol levels, which was defined in the study protocol as the main efficacy variable. As LDL-Cholesterol is the
more accurate predictor of CVD. The LDL cholesterol was reduced by 18.80% with Lipotab, significant reduction in total cholesterol (15.09%), triglycerides (18.41%) was also detected with Lipotab treatment.
The most important result of Lipotab treatment is the increase in HDL-cholesterol (9.62%).
Allium sativum has been reported to be HMG-CoA reductase inhibitor in rats (25), this supports the lipid lowering effect of Lipotab.
Moreover, Lipotab has not been found associated with side effects like muscle cramps, liver dysfunction as associated with other HMG CoA-reductase inhibitors (statins).
Allium sativum has also demonstrated multiple beneficial affects e.g. lowering BP, inhibiting platelet aggregation, enhancing fibrinolysing activity and protecting the elastic properties of the aorta (26). All these support the cardiovascular protective effect of Lipotab.
Recent clinical trials have shown positive results for antioxidants on cholesterol levels (53, 54).
Both Allium sativum (27) and Curcuma longa (23) have been reported potent antioxidants; these findings also support cardiovascular protective effect of Lipotab.
Nepeta hindostana is known to prevent myocardia infarction, which supports its lipid lowering action (20).
The results of the present study suggest that Lipotab is a safe and efficacious drug in treating dyslipidemia. This polypharmaceutical herbal drug can be valuable in prevention of atherosclerosis and cardiovascular disease by antiplatelet, fibrinolytic, antioxidant and cholesterol lowering activities of its various ingredients.

CONCLUSION
The results of this study can be concluded as under:
- Lipotab significantly reduced LDL, total cholesterol and Triglycerides as compared with Placebo
- Improvement in HDL obtained with Lipotab treatment was significantly greater than that of Placebo.
- Lipotab was well tolerated and no adverse/side effects were observed, except mild heart burn, which was reported by 6 cases.

ACKNOWLEDGEMENTS
Authors are indebted to Dr. Asad Mueed (Director) and Prof. M.S.Y. Khan (Co-Director), R & D Extension and Projects Office, CIUI, HNF, Jamia Hamdard, New Delhi, for their esteemed suggestions and kind support throughout the period of this study. We are also thankful to Dr. M.J.U. Khan, Medical Superintendent, Majededia Hospital, for his cooperation and Administrative support during this research work.
Authors acknowledge the immense help received from the scholars whose articles are cited and included in references of this manuscript. The authors are also grateful to authors / editors / publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

REFERENCES
among urban population of Siliguri, West Bengal. Indian J Community Med. 34:19-23
7. Chad R. Worz, Pharm.D., Michael Bottorff, Pharm.D (2003), Treating Dyslipidemic Patients with Lipid-Modifying and Combination Therapies, Pharmacotherapy;23(5):625-637
20. Satyavati GV, Gupta AK, Tondan N (1987), Medicinal Plants of India Vol.2 (Indian Council of Medical Research, New Delhi), 329-32
turmeric extract inhibits LDL oxidation and has hypocholesterolemic effects in rabbits with experimental atherosclerosis. *Atherosclerosis;* 147:371-378


### Table 1: Baseline Characteristics of Study Subjects

<table>
<thead>
<tr>
<th>Sl.No.</th>
<th>Characteristics</th>
<th>Lipotab</th>
<th>Placebo</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total Number of Subjects</td>
<td>38</td>
<td>35</td>
<td>73</td>
</tr>
<tr>
<td>2</td>
<td>Sex (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>25 (65.79)</td>
<td>23 (65.71)</td>
<td>48 (65.75)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>13 (34.21)</td>
<td>12 (34.29)</td>
<td>25 (34.25)</td>
</tr>
<tr>
<td>3</td>
<td>Age (Years) - Mean± SD</td>
<td>45.18±12.21</td>
<td>46.38±10.46</td>
<td>45.78±11.38</td>
</tr>
<tr>
<td>4</td>
<td>BMI (Kg/m²-Mean± SD)</td>
<td>25.40±1.62</td>
<td>24.88±1.28</td>
<td>25.14±1.49</td>
</tr>
<tr>
<td>5</td>
<td>Socio-economic Status-n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Upper Class</td>
<td>25 (65.79)</td>
<td>23 (65.72)</td>
<td>48 (65.75)</td>
</tr>
<tr>
<td></td>
<td>Middle Class</td>
<td>12 (31.58)</td>
<td>11 (31.42)</td>
<td>23 (31.51)</td>
</tr>
<tr>
<td></td>
<td>Lower Class</td>
<td>01 (02.63)</td>
<td>01 (02.86)</td>
<td>02 (2.74)</td>
</tr>
<tr>
<td>6</td>
<td>Personal History n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>06 (15.78)</td>
<td>05 (14.28)</td>
<td>11 (15.06)</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>13 (34.21)</td>
<td>12 (34.29)</td>
<td>25 (34.25)</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td>12 (31.58)</td>
<td>12 (34.29)</td>
<td>24 (32.87)</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>06 (15.78)</td>
<td>05 (14.28)</td>
<td>11 (15.06)</td>
</tr>
<tr>
<td></td>
<td>Vegetarian diet</td>
<td>13 (34.21)</td>
<td>11 (31.42)</td>
<td>24 (32.87)</td>
</tr>
<tr>
<td></td>
<td>Non vegetarian diet</td>
<td>25 (65.79)</td>
<td>24 (68.58)</td>
<td>49 (67.13)</td>
</tr>
</tbody>
</table>

SD= Standard deviation; BMI=Body mass index; n= Number of patients; %= Percentage.

### Table 2: Baseline Lipid profile (mean ± SD) of patients

<table>
<thead>
<tr>
<th>Lipid profile (mg/dl)</th>
<th>Lipotab (Mean ± SD)</th>
<th>Placebo (Mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>232.32±13.24</td>
<td>233.68±14.84</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>158.41±13.62</td>
<td>180.22±16.06</td>
</tr>
<tr>
<td>HDL Cholesterol</td>
<td>39.48±2.03</td>
<td>39.08±1.02</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>236.34±16.77</td>
<td>234.04±19.95</td>
</tr>
</tbody>
</table>

LDL= Low density lipoprotein; HDL= High density lipoprotein;
Mg=Milligram; dl=Deciliter

### Table 3: Effects of Lipotab and Placebo on Lipid profile (Mean ± SD) of patients

<table>
<thead>
<tr>
<th>Lipid profile (mg/dl)</th>
<th>BT (Mean ± SD)</th>
<th>AT (Mean ± SD)</th>
<th>% Change</th>
<th>Mean Difference</th>
<th>SD of Difference</th>
<th>SE of Difference</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>232.32±13.24</td>
<td>197.26±9.72</td>
<td>-15.09</td>
<td>32.90</td>
<td>17.22</td>
<td>2.80</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>158.41±13.62</td>
<td>128.62±9.74</td>
<td>-18.80</td>
<td>15.53</td>
<td>17.90</td>
<td>2.75</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>236.34±20.96</td>
<td>192.82±26.47</td>
<td>-18.41</td>
<td>14.44</td>
<td>38.39</td>
<td>6.32</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HDL-Cholesterol</td>
<td>39.48±2.03</td>
<td>43.28±5.33</td>
<td>9.62</td>
<td>4.04</td>
<td>4.384</td>
<td>4.79</td>
<td>&lt;.05</td>
</tr>
</tbody>
</table>
TC=Total Cholesterol; LDC= Low density lipoprotein
HDL= High Density Lipoprotein

Figure-1: Flow Chart of Participants through the Study

Total subjects assessed for eligibility (N=88)

Excluded (N=06)

Randomized (N=82)

Allocated to Lipotab (N=42)

Allocated to Placebo (N=40)

Drop out (N=04)

Drop out (N=05)

Allocated to Lipotab (N= 38)

Allocated to Placebo (N=35)

Total subjects evaluated (N=73)
Figure-2: Effects of Lipotab and Placebo on Lipid Profile

![Graph showing effects of Lipotab and Placebo on lipid profile.]

Figure-3: Mean Percentage of Improvement in Lipid Profile

![Graph showing mean percentage of improvement in lipid profile.]

Lipotab vs Placebo: Comparison of lipid profile improvement.