Clinical Evaluation of a Unani Formulation for the Treatment of *Fart-e-Tadassum-Fid-Dam* (Hyperlipidaemia): A randomized, Double Blind, Placebo Controlled Clinical Study

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Abstract

Hyperlipidemia is a major public health problem throughout the world. Consequent atherogenic disorders occupied the first place in five major killer diseases due to high mortality and high morbidity in the world.

Adouble blind, placebo controlled, randomized clinical trial was conducted to test the safety and efficacy of a unani formulation in subjects with hyperlipidaemia. Unani formulation significantly improved lipid profile as compared to placebo. During 60 days therapy, no noticable adverse/side effectes were detected in both treatment groups.

Keywords: Hyperlipidaemia; Badranjboy; *Bombyx mori;* Abresham; Cardioprotective

Introduction

Hyperlipidemia is considered as lifestyle disorder in present age and it is a major public health problem throughout the world. It is characterized by increased lipids in blood due to either increase in rate of synthesis or decrease in rate of breakdown of lipoproteins (Clayton *et al.*, 1999). Hyperlipidemia is a common condition which may either results from primary abnormality in lipid metabolism or is a secondary manifestation of some other conditions (Christofer *et al.*, 2004). Worldwide, the prevalence of hyperlipidaemia is about 39,000 per 100,000 patients. In developed countries, the prevalence of hyperlipidaemia is about 57,000 per 100,000 patients. In developing countries, the prevalence of hyperlipidaemia is about 26,000 per 100,000 patients (Michael Gibson, 2013). Epidemiological evidence suggests 1% increase in Coronary Heart Disease (CHD) risk for each 1% increase in Low Density Lipoprotein (LDL), 2-3% reduction in CHD risk for each 1% increase in High Density Lipoprotein (HDL) (Annonymous, 2001). According to the available data, the atherogenic disorders occupied the first place in the five major killer diseases due to high mortality and high morbidity in the world. The diseases are usually considered as disease of atherogenic pathology and affect the various parts of the body viz. ischemic heart disease, cerebrovascular accidents and peripheral vascular disorders etc. Various epidemiological studies suggest that the development of atherosclerosis and ischemic heart disease is strongly associated with hyperlipidemia.

To overcome the problem of hyperlipidaemia, day by day several synthetic drugs of better efficacy are being introduced in the modern system of medicine.

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In this series nicotinic acid was the first drug to be introduced by the Altschul et al in 1955 (Rudolf *et al.*, 1960). Use of hypolipidaemic agents and low fatty diet is the corner stone of the management of hypercholesetrolaemia. Several hypolipidaemic drugs have been already introduced in main stream medicine such as Hydroxy methyl glutaryl CO-A (HMG CO-A) reductase inhibitors (levostatin, atorvastatin), bile acid sequestrents (colestipol) and fibric acid derivetives (gemfibrozil, and fenofibrates) etc. But the long term use of these drugs causes various side effects like myalgia, arthragia, dyspepsia and cholelithiasis loss of libido, impotence etc (Tripathi, 1994). Such side effects limit the use and the efficacy of these drugs. Hence, there is a need to develop a drug from herbal source which should be safe, cost effective, easily available and efficacious. Keeping in view all the above mentioned drawbacks of modern medicine in the management of hyperlipidaemia, need was felt to conduct a clinical trial with dried aqueous extract of Abresham (*Bombyx mori*), Badranjboya (*Nepeta hindostana*) and Arjun Bark (*Terminalia arjuna*) in the ratio of 1:2:1. Preclinical study of this unani formulation has already been conducted on isoproterenol treated rats, which showed remarkable hypolipidemic and cardioprotective effects of test drug comparable to control (Tajuddin *et al.*, 2006 & 2007).

Materials and Methods

This study was double blind, randomized, placebo controlled clincal trial , carried out in the department of Moalejat , A &U Tibbia College, Karol Bagh, New Delhi, from September 2012 to March 2013. The aim of the study was to evaluate the efficacy and safety of unani formulation in the treatment of *Fart-e-Tadassum Fiddum* (Hyperlipidaemia) on scientific parameters.

Study Drug

The study drug was a combination of three Unani drugs supplied by Dehlvi Naturals, India, in the form of capsule. Placebo capsules were also supplied by Dehlvi Naturals, India, the composition of test drug is given in Table-1.

Table 1: Composition of Unani Formulation

Each 500 mg capsule contains dried aqueous extract of:			
Unani Name	Scientific Name	Part Used	Quantity
Abresham	*Bombyx mori*	Raw Silk Cocoon	125 mg
Badranjboya	*Nepeta hindostana*	Whole Plant	250 mg
Arjun	*Terminalia arjuna*	Bark	125 mg

Partcipants

Eligible subjects as per the inclusion/exclusion criteria were enrolled in the study after obtaining written informed consent according to Helsinki declaration.

Inclusion Criteria

Subjects (men and women) aged 18-65 years were eligible for the study if they had a history of dyslipidemia regardless of strict diet control and had fasting LDL-Cholesterol= 130-159 mg/dl, Total Cholesterol= 200-239 mg/dl, Triglycerides= 150-190 mg/dl and HDL-Cholesterol: <40 mg/dl (Anonymous, 2001).

Exclusion Criteria

The exclusion Criteria were pregnancy, lactation, intake of oral contraceptives or any other medication that might affect serum lipids (thyroid or steroid hormones, beta blockers, diuretics etc), H/O cardiovascular disease, impaired hepatic, renal function, malignancy, secondary hyperlipidaemia and body mass index >30 kg/m^2.

Treatment

At baseline, 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 drug or placebo capsule in the dose of 1 capsule twice daily for a period of 60 days. All the patients were instructed to maintain low cholesterol diet. Clinical examination and laboratory tests were done at each visit. Adverse events were recorded and compliance with study medications was assessed at each follow up visit.

Primary Outcome Measures

The primary efficacy end point was percentage reduction from baseline in LDL-Cholesterol, Triglycerides and Total-Cholesterol.

Secondary Outcome Measures

Percentage of change from baseline in HDL, LDL/HDL ratio and TC/HDL ratio. were the secondary outcome measures.

Safety Assaessment

For the assesment of safety, Liver function test, Kidney function test, Haemogram and ECG were carried out at baseline, on first follow up visit i.e., on on 15^{th} day of treatment and at the end of therapy i.e., on 60^{th} day. Data from the

physical/clinical examination, laboratory tests and interview for adverse events as recorded in CRF were included in the analyses of safety and tolerability.

Statistical Analysis

The changes between pre-treatment and post treatment values of primary and secondary outcome obtained in test group were compared with those obtained in placebo group by using unpaired 't' test. Statistical calculations were performed with GraphPad InStat statistical softwere version 3.10 . Statistical analysis was done only for those patients who completed the course of treatment for 60 days.

Results

Total 70 patients were registered out of them 10 cases (4 receiving test drug and 6 receiving placebo) were dropped out from the study, only 30 patients in test group and 30 in the placebo group completed the treatment..

Pretreatment and post treatment (after 60 days) maean values of lipid profile components are their percent changes areshown in Table-2 & Figure-1.

Sixty days treatment with test drug was significantly effective than placebo on the primary efficacy measures in reducing LDL-C by 15.98% as compared with 4.21% in the placebo group ($p < 0.001$). Test drug also significantly reduced total cholesterol (TC) and triglycerides by 10.30% (compared with 0.94% in placebo group) and 12.05% (compared with 1.77% in placebo group) respectively (p value was <.0001 in both cases). The mean reduction in total lipids was 10.24%, in drug group, compared with placebo group (0.64%).

The test drug was also found significantly effective than placebo on the secondary efficacy measures in reducing LDL/HDL ratio by 26.87% compared with 2.47% in the placebo group and TC/HDL ratio by 24.22% (compared with 6.27% in placebo group). A significant rise in HDL was observed in test group (10.57%) compared to placebo group (3.00%), ($p<0.001$) respectively (p value was <.0001 in both cases).

Safety and Tolerability

Unani formulation (also placebo) treatment for 60 days 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.

Table 1: Effects of Test Drug (Unani Formulation) and Control (Placebo) on Lipid Profile

Lipid Profile	Mean±SEM 0 Day	Mean±SEM 60th Day	% Change	t value	p value
LDLCholesterol (mg/dl)					
Test Drug	145.23±1.61	122.02±2.2	15.98%	2.69	0.001
Control	140.30± 2.3	134.38±4.04	4.21%		
Total Cholesterol (mg/dl)					
Test Drug	217.80±1.63	195.37±1.77	10.30%	7.28	0.0001
Control	216.97±1.82	214.93±1.64	0.94%		
Triglycerides (mg/dl)					
Test Drug	171.01±1.50	150.40±1.63	12.05%	5.138	0.0001
Control	163.97±1.75	161.07±1.84	1.77%		
Total Lipids					
Test Drug	607.3±4.07	545.13±3.82	10.24%	7.77	0.0001
Control	598.23±3.77	594.40±5.06	0.64%		
HDLCholesterol (mg/dl)					
Test Drug	38.23±0.84	42.27±0.87	10.57%	2.206	0.001
Control	40.87±1.54	42.10±1.39	3.00%		
LDL/HDL ratio (mg/dl)					
Test Drug	3.87±0.14	2.83±0.10	26.87%	2.056	0.04
Control	3.24±0.13	3.16±0.13	2.47%		
TC/HDL ratio					
Test Drug	5.78±1.94	4.38±2.03	24.22%	3.832	0.02
Control	5.1±1.18	4.78±1.17	6.27%		

N=30 in each group; LDL=Low Density Lipoprotiens; HDL= High Density Lipoprotiens; TC=Total Cholesterol, SEM=Standard error of Mean

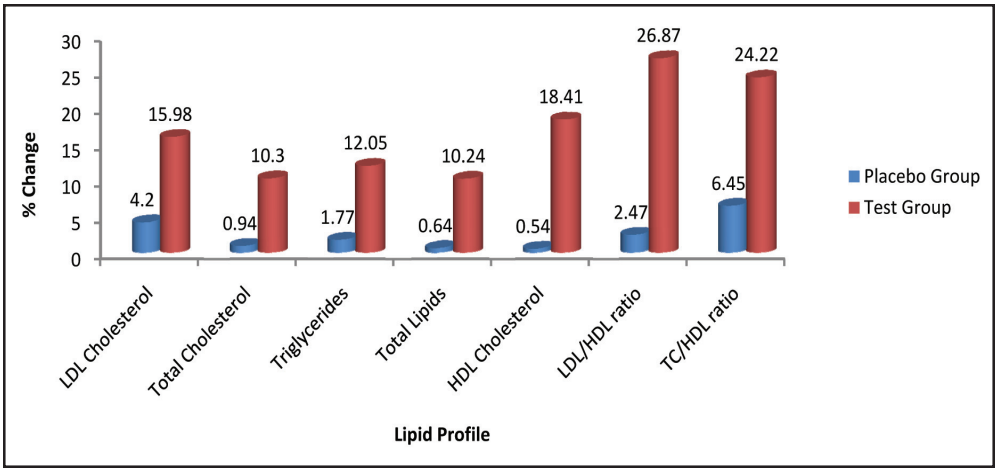

Figure 1: Mean Percent Change in Various Components of Lipid Profile After Treatment

Discussion

In the present clinical trial the effects of test drug have been tested on all the components of lipid profile in a double blind, randomized fashion and the safety of the drug has also been established. Unani formulation (test drug) significantly reduced LDL,TC, triglycerides, LDL/HDL and TC/HDL comparable with control(placebo). Unani formulation also significantly improved HDL level than that observed in control group. Individual ingredients of unani formulation have been reported to possess important pharmacological actions that directly or indirectly support our contention regarding efficacy of test drug on human being. Abresham, Arjun chhaal and Badranjboya possess diverse pharmacological activities like cardio tonic, anti inflammatory, anti-oxidant, anxiolytic, fibrinolytic, and anti-platelet activities as evident by previous pharmacological studies (Collabawalla, 1951; Ghani, ynm; Mahdi *et al*., 2011; Singh *et al.*, 2001; Maulik *et al*., 1997).

The effect of unani test formulation on various components of lipid profile could be due to hypolipidaemic, cardiotonic and cardiac stimulant activities of Arjun (*Terminalia arjuna)* and cardiotonic, anti hypercholesterolemic and antiatherogenic effects of Abresham (*Bombyx mori*) & Badranjboya (*Nepeta hindostan*) (Monahan, 2007; Halleys Khan *et al*., 2011; Ghani, ynm).

All these support the cardiovascular protective effects of test drug. Both Abresham (*Bombyx mori*) and Arjuna (*Terminalia arjuna*) have been reported to have potent antioxidant activity; these findings also support cardioprotective effects of test drug. Badranjboya (*Nepeta hindostana*) is known to prevent myocardial infarction which supports its lipid lowering action.

The results of present study suggest that the unani test formulation is safe and efficacious in treating hyperlipidaemia.This formulation can be valuable in prevention of atherosclerosis and cardiovascular disease by anti-platelet, fibrinolytic, anti-oxidant and cholesterol lowering activities of its ingredients.

Conclusion

The results of this study can be concluded as:

- The unani formulation significantly reduced LDL Cholesterol, Total Cholesterol, Triglycerides, LDL/HDL ratio, and TC/HDL ratio as compared with placebo.
- Improvement in HDL Cholesterol obtained with unani fornulation treatment was significantly greater than that of placebo.
- The unani test formulation was well tolerated and no adverse/side effect were observed during the entire period of protocol therapy.

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