Clinical Evaluation of Anti–Hyperlipidaemic activity of a Unani formulation containing Ritha (*Sapindus trifoliatus* Linn), Methi (*Trigonella foenum-graecum* Linn) and Bartang (*Plantago major* Linn)

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Abstract

Hyperlipidaemia is a metabolic disorder. It produces diseases like atherosclerosis, coronary heart disease (C.H.D) etc, which has an irreversible & fatal systemic effect. Majority of conventional allopathic drugs such as Statins and Fibrates etc have various adverse effects. An effective, safer, cheaper and readily available solution is needed to deal with Hyperlipidaemia. A compound formulation was prepared for this clinical study containing Methi (*Trigonella foenum–graecum* Linn) seeds, Tukhme Bartang (*Plantago major* Linn) seeds and rind of Ritha (*Sapindus trifoliatus* Linn) fruit. Muqil (*Commiphora mukul* Hook ex Stocks) a gum resin was taken as standard drug. Patients were selected from OPD of Mohammadia Tibbia College and Assayer hospital, Malegaon (MS) and randomly divided into two groups 'A'and 'B'of 30 patients in each of either sex. In group 'A' test drug was given in a dose of 6.1 g. and in group 'B' standard drug Muqil (*Commiphora mukul* Hook ex Stocks) in the dose of 1 gm was given before meals, three times a day for the period of 60 days. Assessment of efficacy was done on the basis of lipid profile. Both the groups exhibited highly significant anti hyperlipidaemic activity ($p<0.001$) except HDL (High density lipoproteins) level in standard control group. Test drug reduced the total Cholesterol (14.69%), TG (Triglyceride) (26.81%), and LDL (Low density lipoproteins) level (18.98%) and increased the HDL level (10.05%). Possible lipid lowering action of the test drug may be attributed to different constituents, such as saponin, mucilage, fiber, etc. Test drug exhibited highly significant antihyperlipidaemic activity and is as effective as standard drug.

Key words: Anti-hyperlipidaemic activity, Primary hyperlipidaemia, Methi, Bartang, Ritha

Introduction

Hyperlipidaemia is a metabolic disorder characterized by an excess of plasma lipids including the glycolipids, lipoprotien & phospholipids. Obesity is not a prequisite for hyperlipidaemia, but majority of obese population are found to be hyperlipidaemic. Though it is an easily diagnosable disorder but its effect on various structures is multifactorial, irreversible & fatal. Its abnormalities lead to incurable diseases like coronary heart disease, atherosclerosis, ischaemic heart disease, myocardial infarction, chronic renal failure, pancreatitis, liver diseases etc (Christopher *et al.,* 1999; Panda, 2000; Alagappan, 2001; Shah, 2003). According to classical Unani concept all the white or colourless

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fluids of the body are categorised as *Balgham* (Phlegm) (Istiyaq, 1980), and fat falls in the category of *Balgham,* therefore hyperlipidaemia can be a phlegmatic disorder. The term hyperlipidaemia in Unani literature was found to be attributed to the accumulation of *Akhlat-e-Ghaliza* especially the *Balgham-e-gair mehmooda* obstructing (Tasaddud) the affected vessels (*Urooq*) in favourable conditions & thus pronounced atheromatous plaque. The derangement in the metabolism of *Khilt-e-balgham* affects not only the vascular system, but also cardiac, cerebral & renal system. (Mobin, 2004). The concept of *dusumate akhlat* exits in classical literature, which is responsible for the development of *Salabate Sharaeen* (Atherosclerosis) (Majusi, 2010) "Dosoomat" means "fatty", "oily" and "akhlat" means "Humour", beside this *Samane mufrat* (obesity) has been described by Unani physicians and etiological factors, clinical features, complications of *Saman mufrat* has been discussed in detail. It is also mentioned that the obese persons are more prone to cardiac diseases and cerebrovascular accidents, there are various causative factors and complications of *Samane mufrat* (obesity) which are similar to hyperlipidemia. *Yaboosat, barooadat mizaj* and *Ghalbe sauda wa balgham* is considerd a contributing factor for development of *salabate sharain* (Majusi, 2010; Ibn Sina, 980-1037 A.D.).

The conventional, allopathic treatments for hyperlipidaemia include 1) Statins 2) Fibrates 3) Bile acid sequestrant resins 4) Nicotinic acid & its derivatives 5) Fish oil 6) Probucol (Christopher *et al.***,** 1999; Alagappan, 2001; Satoskar and Bhandarkar, 2001; Shah, 2003). But majority of these drugs have various adverse effects like headache, fatigue, insomnia, nausea, gastrointestinal disturbances, constipation, etc. (Satoskar and Bhandarkar, 2001). Methi (*Trigonella foenum–graecum* Linn), Tukhme Bartang (*Plantago major* Linn) & Ritha (*Sapindus trifoliatus* Linn) are well known drugs to the ancient Unani physicians, and Ritha is mention as Mushil-e-Akhlate-Salasa (Ghani, 1926; Khan, 1353; Ibn-al-Baytar, 1197-1248).

Keeping in view the reported pharmacological activities of these three drugs i.e. *Plantago major* Linn (Bartang) for its plasma lipids, cholesterol, triglycerides lowering activity in rabbits with experimental atherosclerosis (Maksyutina *et al.***,** 1978; Newall Carol *et al.***,** 1996), *Trigonella foenum graecum* (Methi) for its hypocholesterolaemic activity (Sharma, 1986 ; Ribes, 1987), hypoglycaemic activity (Mishkinsky *et al.***,** 1967; Sharma, 1986.; Shani *et al.***,** 1974), and references of Unani classical text for its beneficial effect in Balghami diseases (Ibn-al-Baytar, 1197-1248), and *Sapindus trifoliatus* Linn (Ritha) for its hypocholesterolaemic activity (Prajpati *et al.***,** 2003) and it is mentioned that "it expels Safra, Sauda and Balgham through faeces" (Ibn-al-Baytar, 1197-1248),

used to cure tridosha (Kirtikar and Basu, 1991), it was considered interesting to combine these three drugs and evaluate this formulation clinically to present a safer, cheaper, readily available and highly effective Unani formulation. Muqil (*Commiphora mukul*) (gum resin) was taken as standard drug because of its proven hypolipidaemic activity in human beings (Kuppuranjan *et al.*, 1978; Malhotra and Ahuja, 1971; Malhotra *et al.*, 1977; Nityanand and Kapoor, 1971, 1973; Satyavati *et al.*, 1969).

Materials and Methods

Total sixty cases of primary hyperlipidaemia of age ranging between 20-80years of either sex were selected for the clinical study. They were divided into two groups 'A' & 'B' of 30 patients in each. The study was carried out at the Mohammadia Tibbia College & Assair Hospital, Mansoora Malegaon on O.P.D basis. Voluntary written consent was obtained from all participants.

Inclusion Criteria

- Diagnosed cases of primary hyperlipidaemia were selected for this clinical trial who were not on any hypolipidaemic drugs.
- Patient with serum triglycerides (TG) >160 mg/dl (male), >140 mg/dl (female) and LDL Cholesterol >150 mg/dl, Total Cholesterol >230 mg/dl was included in this study

Exclusion Criteria

- Secondary hyperlipidaemia
- Diabetes
- Severe active Coronary heart disease and ischaemic heart disease
- Alcoholism
- Pregnant women
- Patients with severe systemic disease, & organ failure were excluded.

A clear proforma was prepared. Clinical assessment was done for selection based on the following parameter. history, diet, symptoms: (Subjective Assessment: - Chest pain, palpitation, dyspnoea, giddiness, joints pain, increasing weight), Sign: - (Objective Assessment:-Increasing weight, premature arcus senilis, Xanthomas) (Christopher *et al.*, 1999; Panda, 2000;

Shah, 2003). Efficacy assessment was done primarily on the basis of lipid profile.

Investigations: All the patients were investigated for lipid profile,{Serum cholesterol, triglyceride HDL (High Density Lipoprotein), LDL (Low Density Lipoprotein) & VLDL (Very Low Density Lipoprotein), TC/HDL ratio (Total serum cholesterol & High density lipoprotein ratio) & LDL/HDL ratio (Low Density Lipoprotein & High Density Lipoprotein Ratio)}. Lipid profile was done by using enzymatic method (Fischabach, 2000). Patients were asked not to eat any food accepts water for 12-14 hrs before taking the blood sample. Blood pressure was also recorded.

The study was open, controlled, randomized case control study for the period of 60 days.

Test drug formulation is a non pharmacopoeal compound drug designed for this study containing Tukhme Bartang (*Plantago major* Linn) (seeds), Methi (*Trigonella foenum–graecum* Linn) (seeds), and Ritha (*Sapindus trifoliatus* Linn) (fruit rind), it was given in group A in the dose of 6.1gm (thrice a day) orally and dosage of drugs was fixed according to Unani text for *Plantago major* Linn (Bartang) 3g. (Hakeem, 1894; Khan, 1874) , *Trigonella foenum-graecum* Linn (Methi) 3g. (Anonymous, 1987; Hakeem, 1894; Kabeeruddin, 2000; Rafiquddin, 1985; Lubhaya, 1977) and *Sapindus trifoliatus* Linn (Ritha) 100mg (Lubhaya, 1977). Standard drug Muqil (*Commiphora mukul* Hook.ex Stocks) an Oleo-gum-resin was given to Group B in the dose 1 g. three times a day orally (Hakeem, 1894; Kabeeruddin, 2000).

Muqil was powdered & filled in capsules; 1g. Muqil powder was filled in 2 capsules & given to patients of Group B (Standard control). Tukhme Bartang, Tukhme Methi, & post Ritha were powdered, and 6.1 gm powdered drug (dose) was given in different forms i.e. 3g. powder & 3.100 gm pills (9 pills) in single dose 3 times a day. Ritha was mixed in pills, to avoid its bad taste & nausificient properties. Pills were prepared manually using water as a binder.

Drugs to both groups were given three times a day before meal for a period of 60 days. The patients were advised to have fat free diet & mild walking during the trial, and were assessed on every 15 days of medication. All the patients were treated in the Out Patient Department. Investigations as mentioned earlier were done before, during and after the treatment. Drug compliance was monitored by checking the empty polythene sachet of drugs.

Each patient was recorded on a Performa, especially designed for the study. All base line assessments were taken on the day of inclusion (Day-0) in the study and a similar assessment was taken on Day-60 of treatment. (No separate base line observation was made beside observation for recruitment). The data of both the test and control groups were tabulated and statistically analyzed by calculating the mean and standard deviation (means ± SD) followed by applying 't' test (paired) to the observations recorded at the end of the study (60 days) to determine statistical significance of the test drug (Mahajan, 2003). Findings were compared in each group.

Observations and Results

Sex wise distribution shows that out of 60 cases there were 36 male and 24 female (Table 1). in the age group of 20-40 no of cases were 25, In age group of 41-60 no of cases were 32, and in age group 61-80 no of cases were 03 (Table 2). Maximum no of cases 40 out of 60 had sedentary working style (Table 3). As many as 58 (96%) cases were taking mixed (vegetarian and non vegetarian) diet (Table 4). 20% had hypercholesterolaemia, 53.33% have hypertriglyceridaemia and 26.66% cases were with mixed type of hyperlipidaemia (Table 5).

Patients of both the group A and B have been investigated for parameters like lipid profile, before, during & after treatment during 60 days and statistical significance for test drug was determine for before and after treatment data. After 60 days of medication response of both the group i.e. group 'A' & group 'B' in decreasing the serum total cholesterol was (14.69% & 15.7%), TG (26.81% & 23.3%), LDL (18.98% & 19.54%) & VLDL (25.34%& 23.6%) respectively this reduction was significant (P< 0.001) in comparison to before treatment range (Base line). There was also an increase in the HDL in group A and B (10.05% & 3.92%) respectively but increase in HDL was not significant in group 'B' (control) (Table 6).

Table 1: Distribution of patients according to their sex:

Sr. No.	Sex	No. of Patient	Percentage
1	Male	36	60%
2	Female	24	40%
	Total	60	100%

Table 2: Distribution of patients according to their age:

Sr. No.	Age group	No. of Patients	Percentage
1	20-40	25	41.6%
2	41-60	32	53.3%
3	61-80	03	5.0%
4	Total	60	100%

Table 3: Distribution of patients according to their profession

Sr. No.	Profession	No. of Patients	Percentage
1	Official	12	20%
2	Sedentary	40	66.6%
3	Hard workers	08	13.3%
	Total	60	100%

Table 4: Distribution of patients according to their dietary habits

Sr. No.	Dietary Habit	No. of Patients	Percentage
1	Veg.	02	3.3%
2	Mixed	58	96.6%
	Total	60	100%

Table 5: Distribution of Patients According to increase in type of plasma lipids i.e. Cholesterol, Triglyceride or mixed:

Plasma lipids elevated	No. of patients			Percentage
	Group A	Group B	Total	
* Hypercholesterolaemia	06	06	12	20.00%
* Hypertriglyceridaemia	13	19	32	53.33%
* Mixed type	11	15	16	26.66%
Total	30	30	60	100%

Table 6: Effect of Drugs on serum lipids

Parameters	Test Drug (Group A)			Control Drug (Group B)		
	Before treatment At day-0	After treatment At day-60	% Change ↑ / ↓	Before treatment At day-0	After treatment At day-60	% Change ↑ / ↓
Total cholesterol mg/dl	229.4 ± 29.9	195.7 ± 21.6*	14.69% Reduction	228.8 ± 46.8	192.7 ± 22.1*	15.7% Reduction
Triglycerides mg/dl	181.6 ± 32.1	132.9 ± 30.2*	26.81% Reduction	198.9 ± 49.4	152.5 ± 34.3*	23.3% Reduction
HDL mg/dl	40.1 ± 5.9	44.2 ± 6.4*	10.05% Increase	39.79 ± 9.11	41.35 ± 8.3	3.92% Increase
LDL mg/dl	153.3 ± 26.5	124.2 ± 16.4*	18.98% Reduction	150.9 ± 44.32	121.4 ± 20.75*	19.54% Reduction
VLDL mg/dl	36.6 ± 6.4	27.1 ±4.6*	25.34% Reduction	39.8 ± 10.3	30.4 ± 7.06*	23.6% Reduction
TC/HDL ratio	5.7	4.4	22.8% Reduction	5.8	4.73	18.4% Reduction
LDL/HDL ratio	3.7	2.79	24.59% Reduction	3.8	2.93	22.89% Reduction

Statistical method used, mean ± standard deviation and paired "t" test
P*< 0.001 as compare to before treatment value, (n=30)

Discussion

Majority of cases of hyperlipidaemia were from in the age group of 41-60 and had sedentary life style. Most of the cases were of hypertriglyceridaemia and decrease in TG level was also significant in this study. Possible lipid lowering action of test drugs might be attributed to several constituents of these drugs such as; 1) high concentration of saponin in fruit rind of Ritha. (Kirtikar and Basu, 1991; Rastogi and Mehrotra, 1990, 1995) (Saponin are bile acid sequestrant they combine with bile acids (bile acids are formed in the liver from cholesterol) & retard their re-absorption there by evacuating out lipid through the feces & reduce the plasma lipid levels) (Malinow, 1977; Oakenfull, 1979); 2) mucilaginous fiber & saponin fraction in Methi (Rastogi and Mehrotra, 1993,1995) retard the absorption of fat whereas fiber are not absorbed and form a bulk in intestine, its steroidal saponins also reduces cholesterol (Petit *et al.*, 1995), beside this, it also contains alkaloids (Mainly trigonelline) & protein high in lysine, L-tryptophan, methionine, Vit B (Nicotinic acid) which has lipolytic activity (Anonymous, 2005; Evans, 2002; Kolousek and Coulson,

1955; Lakshmiah and Ramshastri, 1969); 3) Mucilage content in Bartang (Chopra, 2002; Evans, 2002; Khare, 2004; Anonymous, 2005) reduces serum Cholesterol (Maksyumtina, *et al.*, 1978; Newall, 1996) and can also act as corrective (Musleh) for the saponin (GIT irritation if any in given dose).

Both the drugs of group A & B were well tolerated, one of the drugs in formulation-Ritha (Rind Powder) has been used in formulation named Habbe Ritha mention in Qarabadeene sarkari Unani Andhra pradesh for piles since long time (Anonymus, 1988). According to Dymock (1890) *"we have no record of the use of this fruit (Ritha) as a poison for human being, doses of 70 grain (4.53g.) and more appear to have no injurious effect upon the system when taken as purgative''* quantity used in our study is very less.

Test drug formulation had great potential in reducing TG, VLDL and LDL & increasing good cholesterol HDL. One important finding was that HDL level was significantly increased in test group i.e. group A (10.05%) while in group B i.e. standard group HDL level did not increase significantly (only 3.92%) when compared with baseline plasma lipid levels. Lipid imbalance is highly associated with insulin resistance, obesity and diabetes, and studies suggest that many subjects with low HDL level and those with high triglyceride level can also be insulin resistant. (Ginsberg, 2000; Markku, 2004) This means that they are unable to effectively used insulin, which is essential for regulating the storage & use of glucose (Sugar) & amino acids (proteins) in the body. It is now believed to be a major risk factor for the heart disease. Test formulation may be having some role in insulin stimulating activity & research had shown hypoglycemic activity in the drugs present in formulation. In Methi the fraction producing the hypoglycaemic effect is also responsible for its hypocholestrolaemic effect (Puri *et al.*, 1994). Further test formulation reduces TC / HDL ratio upto 22.8% which is a major coronary risk factor, decrease in TG & increase in HDL was highly significant in group A (test group). These effects may be due to the combination of Ritha with Methi which would have potentiated its action. Reetha used in this formulation can be of great potential as an anti - Hyperlipidaemic for which it has not been used so far. And this work might also help to validate classical Unani claims about the action of Ritha that it excretes *Khilt-e-Balgham* through faeces (Ghani, 1926). Results of improvement in test drug are similar to control (standard) drug Muqil. Above mentioned findings of this formulation need further evaluation, also comparative study with Fibrates & Bile acid binding resins is needed.

Conclusion

It may be concluded that the effect of the test formulation in lowering the level of serum total cholesterol, serum triglycerides, serum LDL, serum VLDL and increasing the level of serum HDL is significant in patients of primary hyperlipidaemia, Highly significant reduction in TG & HDL level in group A (test group) was noted.

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