TANG [HUMANITAS MEDICINE]

Original article

A Randomized single blind controlled clinical trial on safety and efficacy of a Unani formulation (*Itrifal-e-Sagheer*) in dyslipidemia

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ABSTRACT

Aim: '*Itrifal-e-Sagheer'*, a compound Unani formulation has been indicated in disease conditions simulating dyslipidemia. The present study was done to substantiate the efficacy of '*Itrifal-e-Sagheer'* in dyslipidemia on scientific parameters.

Materials and methods: A randomized, single blind, controlled, clinical trial was carried out on 30 patients of dyslipidemia who were randomly allocated into test (n = 15) or control (n = 15) groups. The test drug, *Itrifal-e*-Sagheer and control drug, Abana® were given to respective group for 45 days along with lifestyle modification.

Results: The test drug significantly alleviated the symptoms of subjective parameters (palpitation, breathlessness and weight gain) ($p<0.05$). There was statistically significant reduction in lipid profile of the patients in test group ($p<0.05$) than control drug treatment.

Conclusion: The study evidenced that *Itrifal-e-Sagheer* is potentially effective and safe in the treatment of dyslipidemia. However, a multicentric study with robust study design is required to generalize the results.

Keywords: Dyslipidemia, Itrifale sagheer, Unani medicine, Clinical trial, Obesity, Abana

INTRODUCTION

Dyslipidemia is a disorder of lipoprotein metabolism, which includes overproduction or deficiency of lipoproteins or both. It can manifest as an elevation of plasma cholesterol, triglycerides, or both, or a low high density lipoprotein level or all three together that contributes to the development of atherosclerosis (Shah SN, 2012).

Dyslipidemia is a major contributor to cardiovascular morbidity and mortality. Although awareness toward the risk of dyslipidemia has increased in the mass. However, its treatment strategies have not improved accordingly. Even though the actual number of individuals receiving treatment has increased, the proportion of those who are treated but did not reach the recommended treatment goal is still disturbing (Bolli P, 2014).

Gupta *et al.* (2017), reported that dyslipidemia is the most important atherosclerotic risk factor. Recent studies have reported that high cholesterol is present in 25–30% of urban and 15–20% rural subjects. This prevalence is lower than high-income countries. The most common laboratory presentation of dyslipidemia in India are borderline high LDL cholesterol, low HDL cholesterol and high triglycerides. Studies have reported that over a 20-year period, total cholesterol, LDL cholesterol and triglyceride levels have increased among urban populations (Ajay RS *et al*., 2016).

Dyslipidemia is an outcome of shifting from rural to urban that leads to sedentary lifestyle so the prevalence of dyslipidemia is higher in urban than rural areas (Ajay RS *et al*., 2016). There are several risk factor associated with dyslipidemia viz; diabetes, obesity, hypertension, hypothyroidism, sedentary life style, fatty/oily diets, excess alcohol intake, smoking etc (Park K, 2017).

Currently, various synthetic lipid lowering agents are being used in the treatment of dyslipidemia such as statins (atorvastatin, lovastatin, pravastatin and simvastatin), bile-acid sequestrants (cholestyramine and colestipol), resins, niacin, fibric acid analogs (bezafibrate, fenofibrate and ciprofibrate) and ezetimibe (Tripathi KD, 2013). However, long term use of these medicine may leads to various adverse effects like: hepatotoxicity, dyspepsia, myopathy, bloating, constipation, renal dysfunction, flushing, pruritus of the face and upper trunk, skin rashes, acanthosis nigricans, urticaria, myalgias, fatigue, headache, impotence, anemia and hair loss (Brunton LL, 2006). Hence, there is a need to provide a safe and effective novel therapeutic agents for better management of dyslipidemia and prevention of its consequences.

Unani medicine is an age old traditional system of medicine which utilizes preventive and therapeutic regimes and drugs to treat lifestyle disorder such as dyslipidemia. Regimes of *ilaj bit tadbeer* which helps in changing lifestyle such as dietary control *(ilaj bil ghiza),* exercises *(riyazat), turkish bath (hammam)* are

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used along with therapeutic control with drugs of herbal origin. The term dyslipidemia, as such is not mentioned in classical Unani literature; however disease terminology such as "Dasumat-e-Dam" and "Siman-e-Mufrit" simulate the presentation of dyslipidemia. Hence, the treatment of the above mentioned Unani diseases can be used in the treatment of dyslipidemia to achieve benefit goals (Ahmad SI, 1980; Majoosi AIA, 2010; Varady KA and Jones PJ, 2005).

Itrifal-e-Sagheer is one of the famous compound formulation in Unani medicine. It is a sugar based semisolid formulation which contains for herbal ingredient viz. *Post Halela Zard (Terminalia chebula,* Retz.), *Post Halela Kabuli (Terminalia chebula,* Retz.), *Post Halela Siyah (Terminalia chebula* Retz.), *Post Balela (Terminalia bellerica* Retz.) and *Amla Muqashshar (Phyllanthous officinali). Itrifal-e-Sagheer* has been indicated in the treatment of obesity, hyperlipidemia, *amraze barida wa balghamiya* (disorders with dominance of coldness or phlegmatic humour) (Kabeeruddin HM, YNM; Anonymous, 2007). Thus, made *Itrifal-e-Sagheer* worthwhile to be investigated in treatment of patients with dyslipidemia in the present single blind controlled clinical trial.

MATERIALS AND METHODS

Ethical consideration and informed consent:
Institutional Ethical Committee (IEC No: BJP/LUMC/ PG/IEC/2015-16/01/Moal/04) had approved the clinical trial. Informed consent was taken from the patient in their known language. Patient was given enough time to understand the patient information sheet and encouraged to ask question regarding the trial. The trial was performed as per Declaration of Helsinki and ICMR GCP guidelines. Trial is registered in clinical trial registry of India with no. CTRI/2017/09/009783.

Inclusion and exclusion criteria's:
Inclusion criteria's were diagnosed patients of dyslipidemia and patients of either gender in age group of 20-60 years. The exclusion criteria's were systemic disorders like DM, liver failure, kidney failure, etc. and pregnant and lactating women. Withdrawal criteria's were failure to follow protocol therapy and cases in which adverse reaction was noticed. The patients were selected on the basis of subjective parameter i.e. palpitation breathlessness, weight gain and xanthelasma. During selection procedure complete history including interrogation, general, physical and systemic examinations, past history, family history, personal history and socio economic history was taken. For socioeconomic strata, Kuppuswami Socioeconomic Scale (2016) was used. It has been attached with the case report form in annexure whereas objective parameters are serum cholesterol, serum triglyceride, LDL and HDL.

Study design and intervention:
A randomize single blind clinical trial was conducted at Luqman Unani Medical College Hospital and Research Center, Bijapur Karnataka (LUMCHRC). After ethical approval, 30 patients of dyslipidemia which were randomly allocated equally into two group with 15 patients in each test and control group. 198 patients were screened from OPD and IPD of LUMCHRC. Test group was given semi-solid Unani compound drug *Itrifal-e-Sagheer,* 10g twice daily and control group was given Tablet Abana®2 tablets in twice daily dosage orally for 45 days. Both arms had received lifestyle modification therapy (decreasing the intake of saturated fatty acids and cholesterol, selecting foods which could reduce LDL-C, losing weight, increasing regular physical exercise, quitting smoking, limiting salt intake, etc.). The participant flowchart is shown in Figure 1. Study duration was 45 days which was divided into 4 visits (0th, 15th, 30th and 45th day) of follow up which were made at an interval of 15 days. At every visit, patients were asked about the progression or regression in their symptoms and subjected to examination assess clinical findings.

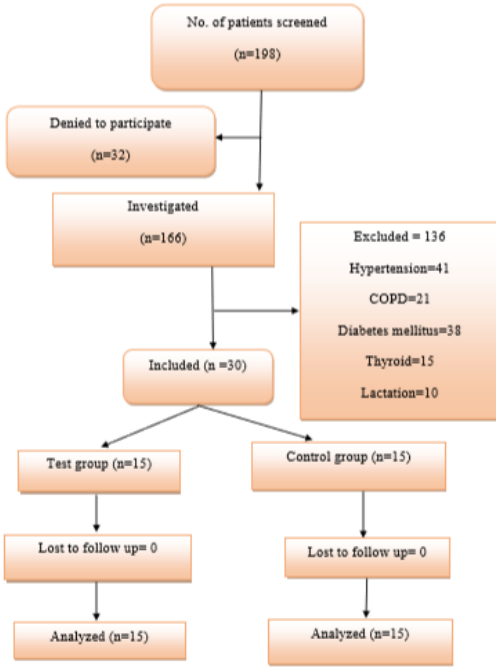

Fig.1 Participants flow chart

Test drug constituents and preparation:
All the ingredients from no.1 to 5 given below were ground to fine powder using pulverizer, separately and the roasted with *Raughan-e-zard (Ghee).* Then all the powders were mixed with already prepared Qiwam (basic solution of particular consistency) of *Shakar-e-safaid* (white sugar) until it became semisolid (Kabeeruddin HM, YNM; Anonymous, 2007).

1. Post Halela *Zard(Terminalia chebula* Retz.): 100.0 g
2. Post Halela *Kabuli(Terminalia chebula* Retz.): 100.0 g
3. Post Halela *Siyah(Terminalia chebula* Retz.): 100.0 g
4. Post *Balela(Terminalia bellerica* Retz Roxb.): 100.0 g
5. Amla *Muqashshar(Phyllanthous officinalis* Gaertn): 100.0 g
6. Shakar *Safaid(Saccharum officinarum*): 1500 g

Outcome measure:
Effects of drugs were evaluated on subjective parameters such as palpitations, breathlessness, weight gain and xanthelasma at 0 day [baseline/ BT (before treatment)], 15 days (F1), 30 days (F2) and 45 days (After treatment). An arbitrary grading scale was adopted for the assessment of subjective parameters in both test and control group. This is as follows: 0 (no symptoms), 1 (mild symptom), 2 (moderate symptom) and 3 (severe symptom).
Serum cholesterol, serum triglycerides, serum HDL-Cholesterol and serum LDL were taken as objective parameters for evaluation of efficacy at 0 day (baseline) and 45 day (After treatment). End points for efficacy were statistical significant improvement in serum levels of cholesterol, triglycerides, HDL-Cholesterol and LDL after 45 days of treatment. For safety

assessment of test drug, blood urea, serum creatinine, SGPT and SGOT were performed at baseline and 45 day (after treatment).

Statistical analysis:

The statistical calculations were performed using the SPSS version 24 and Graphpad prism version 7.03 for the analysis of the data and Graph pad Prism, Microsoft word and excel have been used to generate graphs, tables etc. Statistical significance is defined as a two-sided P value of <0.05. For measurement data, the mean, standard deviation (SD), maximum, minimum and median were reported. For paired measurement data, the mean difference, SD, and confidence interval (CI) were also reported.

RESULTS

Demographic distribution

There was no statistically significant difference in baseline characteristics of patients in test versus control group. Thus both groups were comparable. Mean age in test group and control group were 38.4±2.67 years and 37±2.09 years respectively, showed that majority of the patients 11 (36.67%) were observed in the age group 31-40 years, and 10 (33.33%) in the age group of 41-50 years. It is cumulatively 70% in the age group of 31-50. Among the 30 subjects studied, females outnumbered the males 20 (66.67%). Most patients (96.67%) were reported to have mixed dietary pattern; while 3.33% were vegetarians.

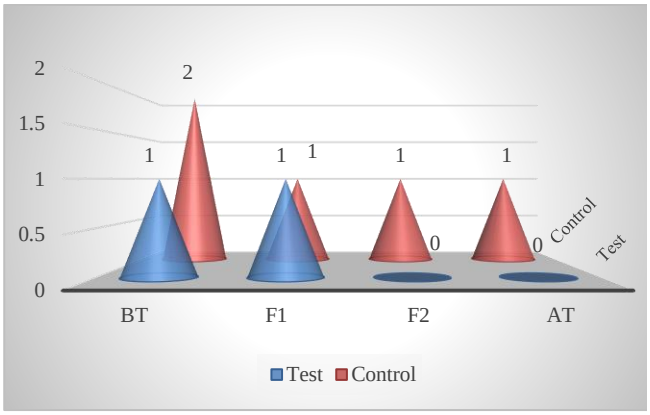

Fig. 2 Effect of drugs on palpitation in dyslipidaemia

Fig. 3 Effect of drugs on breathlessness in dyslipidaemia

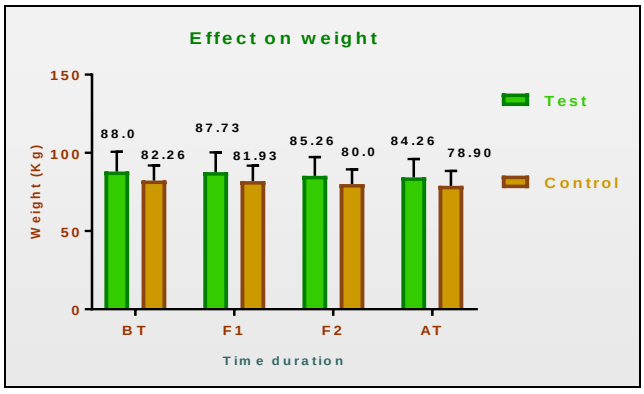

Fig.4 Effect of drugs on weight gain in dyslipidaemia

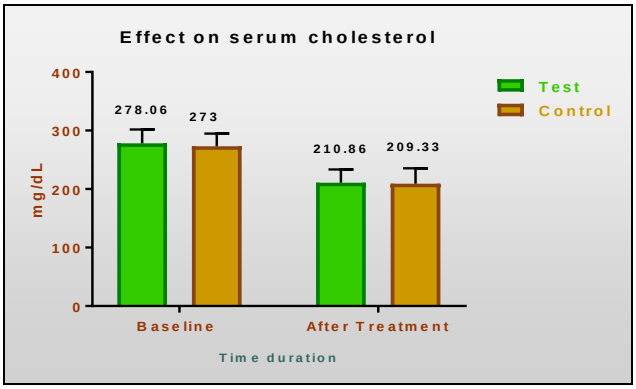

Fig. 5 Effect of drugs on cholesterol in dyslipidaemia

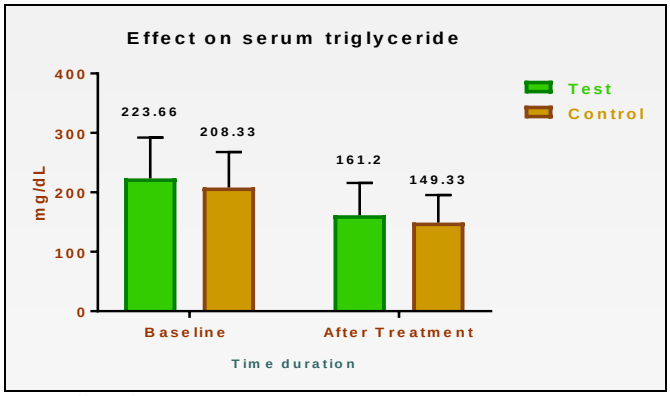

Fig. 6 Effect of drugs on triglyceride in dyslipidaemia

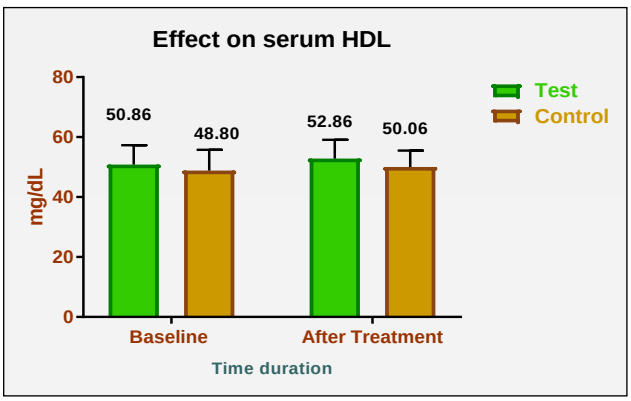

Fig.7 Effect of drugs on HDL-C in dyslipidaemia

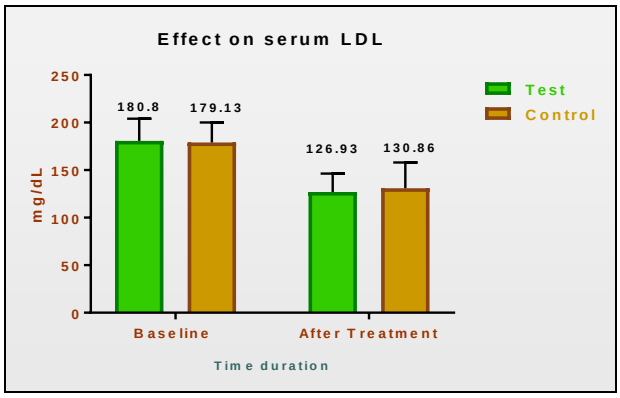

Fig. 8 Effect of drugs on LDL-C in dyslipidaemia

Effect of drugs on subjective parameter

1. Effect of drugs on palpitation [Table 1; Figure 2]
2. Effect of drugs on breathlessness [Table 2; Figure 3]
3. Effect of drugs on weight gain [Table 3; Figure 4]
4. No patients had xanthelasma in both group test and control at Baseline.

Effect of drugs on objective parameters

1. Effect of drugs on cholesterol [Table 4; Figure 5]
2. Effect of drugs on triglyceride [Table 5; Figure 6]
3. Effect of drugs on HDL-C [Table 6; Figure 7]
4. Effect of drugs on LDL-C [Table 7; Figure 8]

Table 1. Effect of drugs on palpitation (median scores with ranges) (n=30)

Groups	Assessment day				P (Friedman test)	P (Kruskal-Wallis test with Dunn's multiple comparison tests)
	BT	F1	F2	AT		
Test N=15	1{1, 2}	1{1, 1}	0{0, 1}	0{0, 0}	* <0.01 # <0.001 $ <0.001	* >0.05 # >0.05 $ >0.05
Control N=15	1{1, 2}	1{0, 1}	0{0, 1}	0{0, 1}	* <0.05 # <0.01 $ <0.01	

*BT versus F1, # BT versus F2, $ BT versus AT

Table 2. Effect of drugs on breathlessness (median scores with ranges) (n=30)

Groups	Assessment day				P (Friedman test)	P (Kruskal-Wallis test with Dunn's multiple comparison tests)
	BT	F1	F2	AT		
Test N=15	2{1, 2}	1{1, 2}	1{1, 1}	1{0, 1}	* >0.05 # <0.01 $ <0.01	* >0.05 # >0.05 $ >0.05
Control N=15	2{1, 2}	2{1, 2}	1{1, 1}	1{1, 1}	* >0.05 # <0.01 $ <0.01	

*BT versus F1, # BT versus F2, $BT versus AT

Table 3. Effect of drugs on weight gain (Mean ± SEM) (n=30)

Groups	Assessment day				P (Friedman test)	P (Kruskal-Wallis test with Dunn's multiple comparison tests)
	BT	F1	F2	AT		
Test N=15	88 ± 3.28	87.73 ± 3.24	85.26 ± 3.10	84.26 ± 3.05	* >0.05 # <0.01 $ <0.01	* >0.05 # >0.05 $ >0.05
Control N=15	2{1, 2}	2{1, 2}	1{1, 1}	1{1, 1}	* >0.05 # <0.01 $ <0.01	

*BT versus F1, # BT versus F2, $BT versus AT

Table 4. Effect of drugs on serum cholesterol (Mean± SEM) (n=30)

Groups	Assessment day		P (Paired t-Test)	P (Unpaired t- Test)
	Before Treatment	After Treatment		
Test N=15	278.06 ± 6.16	210.86 ± 5.83	<0.001	>0.05
Control N=15	273.0 ± 5.64	209.33 ± 6.75	<0.001	

Table 5. Effect of drugs on serum triglyceride (Mean ± SEM) (n=30)

Groups	Assessment day		P (Paired t-Test)	P (Unpaired t- Test)
	Before Treatment	After Treatment		
Test N=15	223.66 ± 17.70	161.20 ± 14.01	<0.001	>0.05
Control N=15	208.33 ± 15.36	149.33 ± 11.90	<0.001	

Table 6. Effect of drugs on serum HDL-C (Mean ± SEM) (n=30)

Groups	Assessment day		P (Paired t-Test)	P (Unpaired t- Test)
	Before Treatment	After Treatment		
Test N=15	50.80 ± 1.68	52.86 ± 1.36	>0.05	>0.05
Control N=15	48.80 ± 1.80	50.06 ± 1.40	>0.05	

Table 7. Effect of drugs on serum LDL-C (Mean ± SEM) (n=30)

Groups	Assessment day		P (Paired t-Test)	P (Unpaired t- Test)
	Before Treatment	After Treatment		
Test N=15	180.80 ± 5.98	126.93 ± 5.0	>0.05	>0.05
Control N=15	179.13 ± 5.40	130.86 ± 7.01	>0.05	

Effect of drug on safety parameters

Blood sugar: At baseline mean random blood sugar in test group and control group were 121.9 ± 4.44 and 113.1 ± 3.09 mg/ dL ($p>0.05$ unpaired 't' test) which remain insignificant after treatment in both group. ($p>0.05$)

KFT (Kidney function test): Blood urea at baseline was 23.40 ± 1.73 and 24.14 ± 1.36mg/dl in test and control drug respectively which significantly reduced to ($p<0.01$) 19.00 ± 1.16 and 21.06 ± 1.4mg/dl after treatment. This reduction of blood urea significant, although it was within the normal limit in both the group ($p>0.05$).

Baseline serum creatinine in test and control group was 1.05 ± 0.03 and 1.02 ± 0.04mg/dl which reduced slightly to 0.94 ± 0.02mg/dl ($p<0.05$) in test group while in control group, mean remained similar 1.02 ± 0.02mg/dl ($p>0.05$). However, mean value of serum creatinine was within normal limit in test group.

LFT (Liver function test): Baseline mean SGOT of test and control group were 29.93 ± 1.22 and 30.73 ± 1.11 U/L which slightly reduced to 27.33 ± 1.04 and 28.06 ± 1.02 U/L at the significance level $p<0.01$. Although, this reduction was equally significant ($p>0.05$) in both the groups (intra-group comparison) but mean values remained within the normal limit.

The mean SGPT in test and control group were 32.53 ± 1.17 and 31.86 ± 1.12 U/L respectively at baseline which reduced to 29.20 ± 1.13 U/L in test group with a significance of $p<0.01$.

While in control group, it slightly reduced to 30.06± 0.94 U/L ($p>0.05$). In intra-group comparison, statics showed that there was no significant difference in reduction of mean values

of SGPT from baseline versus after treatment in test versus control group.

DISCUSSION

Itrifal-e-Sagheer is a polyherbal preparation of Unani medicine that has been marketed in India for several decades. It composed of the three medicinal fruits (5 ingredients) *Phyllanthus emblica* L. or *Emblica officinalis* Gaertn. (Euphorbiaceae), 3 varieties of *Terminalia chebula* Retz. (Combretaceae), and *Terminalia bellerica* Retz. (Combretaceae) and formulated for the treatment and management of obesity viz a viz dyslipidemia and atherosclerosis (Kabeeruddin HM, YNM; Anonymous, 2007). The present study evaluated effect of *Itrifal-e-Sagheer* in reducing symptoms of dyslipidemia, normalizing serum levels of elements of lipid profile and a safety check on biochemical profiles in patients of dyslipidemia in single blind design clinical trial and comparing it with control herbal drug "Abana".

While evaluating effect of test drug on subjective parameters, palpitation was one of the symptoms, reported by majority of the patients of dyslipidaemia. The difference between the median scores of test group at AT, F1 and F2 with respect to baseline was highly significant ($p<0.001$) in intragroup comparison. Intergroup comparison at AT, F1 and F2 was not significant ($p>0.05$) in test group with respect to control group.

Rajak S *et al*. (2004) have reported that fresh *aamla* fruit homogenate (*Emblica officinalis*) caused myocardial adaptation by reduction in basal myocardial lipid peroxidation and by inhibitory effect in depletion of cardiac antioxidants such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) in the treated rat heart (Rajak S *et al*., 2004). Similarly, *Terminalia chebula (halela)* and *Terminalia balerica (balela)* have also shown cardio protective effect against myocardial injury in various animal studies (Suchalatha S and Shyamala Devi CS, 2004; Tariq M *et al*., 1977). Moreover, *aamla, halela* and *balela* possess *mufarrih* (exhilarant) and *muqawwiye qalb* (cardiotonic) properties and are being used for the treatment of palpitation since ages (Ghani N, 2008).

When the median scores of breathlessness in both Groups, A and B, were compared statistically, it was found that the difference between the median scores of test group at AT, and F2 with respect to baseline was highly significant ($p<0.01$) in intragroup comparison. Intergroup comparison at AT, F1 and F2 was not significant ($p>0.05$) in test group with respect to control group. The effect may be due to the triphala (*aamla, halela* and *balela*) present in the formulation, which are being used in *balghami* disorders like usre *tanafus* (breathlessness) (Ghani N, 2008; Baitar I, 2000). They are also used in Ayurveda for the treatment of various respiratory disorders (Bag A, 2013). In addition, balela has also exhibited anticholinergic effect and bronchodilator activity in carbachol induced bronchoconstriction in rodents, conducted by Gilani *et al*. in 2008 (Gilani HA *et al*., 2008).

In our study, the difference between the mean score of weight in test group at AT and F2 with respect to baseline was highly significant ($p<0.001$) in intragroup comparison. Intergroup comparison (test and control group) at AT, F1 and F2 was not significant ($p>0.05$). Our observation was in conformity with the observation of Kamali *et al*. (2012), who in a double blind placebo control clinical study found a significant effect of *Itrifal-e-Sagheer* on obsese individuals in comparison to placebo (Kamali SH *et al*., 2012). The components of *Itrifal-e-Sagheer* e.g. *aamla, halela* and *balela* have exhibited antioxidant activities in various animal models (Baliga MS, 2010). Moreover, they have been proposed to stimulate metabolism, suppress appetite, affect serotonin, or impede digestion of fat and decrease fasting and postprandial blood glucose (Kamali SH *et al*., 2012). In addition, *Itrifal-e-Sagheer* has been used extensively as an anti-obesity medicine in Unani medicine since centuries (Baliga MS, 2010).

Serum lipid profile were evaluated at baseline (0th day) and after treatment (45th day). The mean±SEM values of serum cholesterol in test and control groups at baseline (0th day) were 278.06 ± 6.16 and 273.0 ± 5.64 mg/dl respectively which reduced to 210.86 ± 5.83 and 209.33 ± 6.75 mg/dl with a mean difference of 67.2 and 63.67 respectively after treatment (45th day) which was extremely significant at $p<0.001$ in both test and control group. In inter-group comparison between test and control, the difference was not found significant with $p>0.05$. The mean±SEM score of serum triglycerides in test and control group at baseline (0th day) were 223.66 ± 17.70 and 208.33 ± 15.36 mg/dl respectively which were reduced to 161.20 ± 14.01 and 149.33 ± 11.90 mg/dl with a mean difference of 62.46 and 59 respectively after treatment (45th day) which was extremely significant at $p<0.001$ in both test and control group. In inter-group comparison between test and control, the difference was not found significant with $p>0.05$. The mean ± SEM score of serum HDL-Cholesterol at baseline in test and control groups were 50.80 ± 1.68 and 48.80 ± 1.80 mg/dl which were increased to 52.86 ± 1.36 and 50.06 ± 1.40 mg/dl with a mean difference of 2.06 and 1.26 in test and control group respectively, which was statistically insignificant. The mean ± SEM score of serum LDL-Cholesterol in test and control group at baseline (0th day) were 180.80 ± 5.98 and 179.13 ± 5.40mg/dl respectively which were reduced to 126.93 ± 5.0 and 130.86 ± 7.01mg/dl with a mean difference of 53.87 and 48.27 respectively after treatment (45th day) which was extremely significant at $p<0.001$ in both test and control group. In inter-group comparison between test and control group, the difference was found insignificant with $p>0.05$.

The effect of test drug on objective parameters could be due to properties of various ingredients present in the test formulation such as liver tonic, digestive tonic (*muqwiye jigar, meda wa ama*), blood purifier (*musaffiye khoon*) (Kabiruddin A, 2006). The results are also supported by a randomized, double blind placebo controlled trial conducted by Singh *et al*., in which significant decrease in the LDL/HDL cholesterol ratio; fasting and postprandial blood glucose as well as lipid peroxides and diene conjugates (indicators of oxidative stress) were observed after *triphala* treatment (Singh RB *et al*., 1998). Similarly in another, double-blind, randomized placebo-controlled trial, conducted by kamali *et al*. in which human subjects treated with Itrifal-e-Sagheer have lost ~5 kg weight compared with the placebo controlled group (Kamali SH *et al*., 2012).

Dyslipidaemia is associated with metabolic syndrome in individuals where insulin resistance and oxidants of different varieties produce disturbance in metabolism of lipids and their utilizations. The probable mechanism of hypolipidemic effect of *Itrifal-e-Sagheer* could be due to anti-oxidant activities of *aamla, halela* and *balela* as exhibited in various animal models (Baliga MS, 2010). The other possible mechanism could be due to the presence of active chemical constituents of the ingredients of *Itrifal-e-Sagheer,* including ellagitannins and gallotannins which enhance both PPAR-alpha and gamma signalling, which ultimately leads to increase in insulin responsiveness and glucose uptake without inducing adipogenesis. These polyphenols may also promote decreased blood glucose and

insulin levels in diabetic patients. Thus, *Itrifal-e-Sagheer* may overcome insulin resistance by harmonizing the disturbed metabolism of fat and lipids in the body and can be used in dyslipidaemia viz a metabolic syndrome (Yang MH *et al*., 2013).

CONCLUSION

These observations provide the evidence that *Itrifal-e-Sagheer* is effective in managing patients of dyslipidaemia including relief in associated symptoms without any significant side effects. Further double blind multicentric studies should be performed to ascertain its efficacy in larger population of dyslipidaemia and metabolic syndrome.

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SOURCE OF SUPPORT

Nil

CONFLICT OF INTEREST

None declared.

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