Research Article

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EFFICACY OF TUKHM-E-SUDDAB (*RUTA GRAVEOLENS*) IN THE MANAGEMENT OF SALABAT-E-NABZ (ATHEROSCLEROSIS): A RANDOMIZED, SINGLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL

Iram Naaz [1], Mohd Shahid *[2], Tanzeel Ahmad [3]

[1]Assistant Professor, Department of Amraze Jild wa Taziniyaat, Hakim Rais Unani Medical College & Hospital, Sambhal, India

[2]Assistant Professor, Department of Moalajat, Hakim Rais Unani Medical College & Hospital, Sambhal, India

[3]Professor, Department of Moalajat, Ajmal Khan Tibbiya College, AMU, Aligarh, India

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***Corresponding author**
E-mail: drshahidkhan2005@gmail.com

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ABSTRACT

Aim: Presently, atherosclerosis is one of the prime threats worldwide as only in India CVD causes 37 million deaths annually raised by 59% from 23.2 million in last two decades which is higher than the global average. The standard treatment available for it had appalling side effects in long terms. This condition can be correlated to Salabat-e-Nabz in Unani system of medicine, treated since centuries through numerous compounds and single drugs. Tukhm Suddab (*Ruta graveolens*) is one of the single drugs which is indicated for the same, but has not been evaluated on the scientific parameters. Thus, a randomised, single blind placebo controlled clinical study was designed with an objective to determine the efficacy and safety of Tukhm Suddab (*Ruta graveolens*) in the management of Salabat-e-Nabz (atherosclerosis). Methods: The present clinical trial was a single blinded, randomized, placebo control study conducted at NIUM hospital, Bangalore, on sample size of 40 patients. Test group was treated with three capsules twice a day (each capsule contain 1 gm powder of test drug) and control group was treated with same dose filled with wheat flour for consecutive 90 days. Objective parameters and BP were assessed at every 15th day from baseline to 90th day of treatment in each group respectively. Result: Significant results were observed in right ABI ($p < 0.002$), left ABI ($p < 0.01$) and LDL level ($p < 0.05$), at 90th day from baseline. While no significant result were observed in ASI and other objective parameters. Conclusion: This trial validates the effectiveness and safety of Tukhm Suddab *(Ruta graveolens*) in the treatment of Salabat-e-Nabz (atherosclerosis).

Keywords: Salabat-e-Nabz, Atherosclerosis, Ankle Brachial Index. Arterial Stiffness Index, LDL, Tukhm-e-Suddab, Unani, CTRI

INTRODUCTION

Atherosclerosis is a disease that has plagued mankind since antiquity[1]. Epidemiologically it is one of the prime threats worldwide as only in India CVD causes 37 million deaths annually raise by 59% from 23.2 million in last two decades which is higher than the global average.[2,3] It is "a chronic, progressive, inflammatory disease of the arterial wall that is characterised by focal lipid- rich deposits of atheroma and remains asymptomatic until they become large enough to impair arterial perfusion or until ulceration or disruption of lesion results in thrombotic occlusion or embolization of the affected vessel.[4]

Atherosclerosis has not been mentioned in Unani system of medicine, but Salabat-e-Nabz (atherosclerosis) has widely discussed which simulates it. Unani physicians maintain risk factors, etiopathogenesis of Salabat-e-Nabz and Tangi Urooq (stenosis of vessels) with its complications. Morbific Balgham (phlegm) and Sauda (black bile) with its Imtila (abnormal collection of morbific humour) in human body are attributed to genesis of Salabat-e-Nabz (atherosclerosis) and Tangi Urooq.[5] Pathogenesis is based on Barid (cold) and Yabis (dry) temperament of the vessel wall, Suddae Urooq (stenosis) and disproportionately Ghaleez Akhlat (abnormal viscous humour) in the circulation.[6] The major causes of hardening of blood vessels are; Yabusat (dryness) and over stimulation of Quwwat Masika (retentive faculty) of the vessels, which causes retention of Ghaleez Laisdar Khilt (viscous morbific matter) within the vessel. The Hararat (body heat) resolves excess Rutubat (water) from Ghaleez Laisdar Khilt which makes it more viscous and it firmly adheres within the vessel wall.[7,8,9] Fundamental principle of management in Unani medicine is to eliminate the causatives Akhlat from the body and restore the Mizaj (temperament). In Salabat-e-Nabz (atherosclerosis), it can be facilitated by drugs having Talteef (demulcent), Tahleel (dissolution), Taqtee (disintegration), and Mufattahe Suddad pharmacological properties.[7, 10] Currently, standard conventional medicines available for atherosclerosis are lovastatin, atorvastatin, simvastatin, clofibrate, bezafibrate and niacin etc. Although, it gives a good results in short run but has been reported catastrophic side effects in long term uses such as hepatotoxicity, myopathy, dyspepsia, renal failure and cholelithiasis.[11,12]

Hence, a single blinded, randomized, placebo controlled clinical trial has been proposed to evaluate the efficacy and safety of single drug Tukhm Suddab (*Ruta graveolens*) as it posses all the above mentioned pharmacological properties.

METHODOLOGY

This study was a single blinded, randomized, placebo controlled clinical trial approved by the Institutional ethical committee of N.I.U.M, Bengaluru vide ref no: NIUM/IEC/2012-13/002/Moal/02 dated 18.04.13 and was conducted from November 2015 to February 2017 in the O.P.D and I.P.D of N.I.U.M. hospital. This study has been registered in Central Trial Registry of India (CTRI/2018/03/012714). The patients were selected on the basis of objective parameters {periscope report i.e., ABI (Ankle Brachial Index) and ASI (Arterial Stiffness Index)} and simultaneously fulfilling inclusion criteria. The following were the inclusion criteria: (a) Patient of either sex (b) Patients of age 25-60 years (c) Peripheral arterial diseases (PAD) (d) ABI $\leq$ 0.9 or (e) ASI > 80. Exclusion criteria included: (a) Patients < 25 or > 60 years of age (b) Uncontrolled diabetes

(HbA1c > 9) and hypertension (160 \ 110 mm of Hg) (c) Severe systemic diseases like chronic kidney disease or congestive heart failure etc. (d) Pregnant and lactating women (e) Patient who fails to follow up or give consent.

MODE OF INTERVENTION

The test drug was procured from registered herbalist in K. R. market, Bengaluru. It was properly cleaned and identified to ascertain its originality by the chief pharmacist of N.I.U.M. pharmacy before preparing powder. Test group patients were given 6 grams powder of Tukhm Suddab (*Ruta graveolens*) in two divided doses i.e. three capsules twice a day before meal, for the period of 90 days. In placebo group, patients received identical capsules filled with wheat flour in same dose and duration.

EFFICACY ASSESSMENT

Total duration of protocol was divided into 6 follow up i.e., at every 15th day up to 90th day. The assessments of efficacy in the test and control groups were based on objective parameters. Objective parameters were total ABI, ASI, cholesterol, triglycerides, Blood pressure, HDL and LDL cholesterol. BP was assessed at every 15th day while lipid profile and periscope were done at every 30th day. Subjects were instructed to report any kind of side effects experienced during the whole clinical trial to the chief investigator.

STATISTICAL METHOD

The data were analysed using Student t test for inter (unpaired) and intra (paired) group comparison with $p < 0.05$ is the level of significance. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in number (%). The following assumptions while collecting the data was considered. (i) Dependent variables should be normally distributed. (ii) Samples drawn from the population should be random. (iii) Subjects were selected independently.

RESULT

A total of 97 patients screened for the study out of 25 patients were denied to participate in trial. Among them, only 40 patients were fulfilled inclusion criteria and randomly allocated by using computer generated table into two groups comprising **A** (test) and **B** (placebo) respectively. During the course of the trial 3 patients lost to follow up [2 from test and 1 from placebo group (due to non compliance)]. Statistical analysis was evaluated only on those subjects who accomplished the study. The demographic data of the study has been demonstrated in (Table-1). The maximum number of subjects 16 (43.24%) were observed within 51-60 years of age group which corroborate the observations made by the Sung-sheng tsai et al. which conclude that arterial stiffness increases with aging process.[13] The highest incidence were observed in male patients 26 (70.3%) confirmed by Monika Garg et al.[14] and A. S. Keche et al. in prevalent studies.[15] Subjects with mixed dietary habit 36 (97.3%) were predominant which substantiate the finding of Razi [6] and Ibn Sina [7] in their books that Sudda (obstruction) and Imtila (abnormal collection of morbific humour) are major risk factors for development of Salabat-e-Nabz (atherosclerosis) which are produced by excessive diet, physical inactivity, alcohol intake, and Mizaj-e-Barid (cold temperament). This study reveals that atherosclerosis is more prevalent among the low socioeconomic class 19 (51.4%) coincide with Olivier Grimaud et al. (2013)[16] and Rajeev Gupta et al.[17] which maintains conjointly that there is inverse relationship between subclinical atherosclerosis and socio-economic status may be due to exposure to higher risk factors such as hypertension, smoking, heavy alcohol intake etc. Patients with Balghami Mizaj (phlegmatic) 21 (56.8%) were prepotent in the trial which corroborate the observation of Ibn Sina[7] and Razi [6] who maintains that excessive Buroodat is one of the main cause of Salabate Sharayin (atherosclerosis), found in excess quantity in Balghami Mizaj (phlegmatic) subjects.

The most prevalent risk factors in this study was hypertension present in 28 (75.7%) patients, followed by DM in 18 (48.6%), smoking in 16 (43.2%), and alcoholism in 8 (21.6%) patients. Hypertension alone or in combination with DM, smoking and alcohol, represents the major risk factors for the development of atherosclerosis and coincides with the findings of Yadon Arad MD et al. (2005)[18] and Amit H.A gravat et al. (2013).[19] This study strongly suggested inherited nature of disease as 30 (81.1%) subjects had positive family history which is in accordance with the finding of Arvind K Panday et al. [20] (Table-1).

Table 1: Demographic Data

S. No	Demographic data	Unit	Test group n=18	Placebo group n=19	Total
1	Age	<30	2 (11.1%)	0 (0%)	2 (5.4%)
		30-40	5 (27.8%)	1 (5.3%)	6 (16.2%)
		41-50	5 (27.8%)	8 (42.1%)	13 (35.1%)
		51-60	6 (33.3%)	10 (52.6%)	16 (43.2%)
		Mean ± SD	45.61±10.11	51.00±6.77	48.38±8.87
2	Gender	Female	4 (22.2%)	7 (36.8%)	11 (29.7%)
		Male	14 (77.8%)	12 (63.2%)	26 (70.3%)
3	Diet	Mixed	17 (94.4%)	19 (100%)	36 (97.3%)
		Veg	1 (5.6%)	0 (0%)	1 (2.7%)
4	Socio-economic status	Upper **(I)**	0 (0%)	0 (0%)	0 (0%)
		Upper Middle **(II)**	3 (16.7%)	8 (42.1%)	11 (29.7%)
		Lower Middle **(III)**	3 (16.7%)	0 (0%)	3 (8.1%)
		Upper Lower **(IV)**	4 (22.2%)	0 (0%)	4 (10.8%)
		Lower **(V)**	8 (44.4%)	11 (57.9%)	19 (51.4%)
5	Mizaj	Balghami(phlegmatic)	11(61.1%)	10(52.6%)	21 (56.8%)
		Damvi (sanguine)	7(38.9%)	4(21.1%)	11 (29.7%)
		Saudavi(melancholic)	0(0%)	5(26.3%)	5 (13.5%)
		Safravi (choleric)	0(0%)	0(0%)	0 (0%)
6	Risk Factors	Family History	14 (77.8%)	16 (84.2%)	30 (81.1%)
		Hypertension	13 (72.2%)	15 (78.9%)	28 (75.7%)
		Diabetes Mellitus (DM)	5 (27.8%)	13 (68.4%)	18 (48.6%)
		Smoking	9 (50%)	7 (36.8%)	16 (43.2%)
		Alcohol	5 (27.8%)	3 (15.8%)	8 (21.6%)

Table 2: Changes in objective parameters

Lipid Profile		Test Group	Placebo Group	P value
Serum Cholesterol	0th day	217.67±41.69	201.53±35.39	0.212
	30th	215.56±33.16	207.63±27.18	0.431
	60th	205.61±32.47	206.95±20.87	0.882
	90th	212.72±36.41	206.16±22.85	0.513
	Diff (0-90th)	4.944	-4.632	-
	P value	0.720	0.642	-
Serum Triglyceride	0th day	234.89±113.07	217.47±80.85	0.592
	30th	190.94±66.47	204.42±90.81	0.611
	60th	209.33±92.30	195.42±74.85	0.617
	90th	229.33±108.21	199.05±72.23	0.321
	Diff (0-90th)	5.556	18.421	-
	P value	0.813	0.185	-
Serum HDL	0th day	40.72±5.58	41.21±10.62	0.863
	30th	40.33±5.24	41.26±7.01	0.652
	60th	38.39±4.26	41.47±6.41	0.095+
	90th	40.50±7.29	42.79±5.98	0.302
	Diff (0-90th)	-11.222	-1.579	-
	P value	0.511	0.485	-
Serum LDL	0th day	136.94±24.63	129.47±35.59	0.465
	30th	151.28±41.83	138.63±44.12	0.378
	60th	149.39±45.22	142.68±39.43	0.633
	90th	148.17±65.20	144.32±40.20	0.829
	Diff (0-90th)	-0.218	-14.842	-
	P value	**0.045***	0.123	-

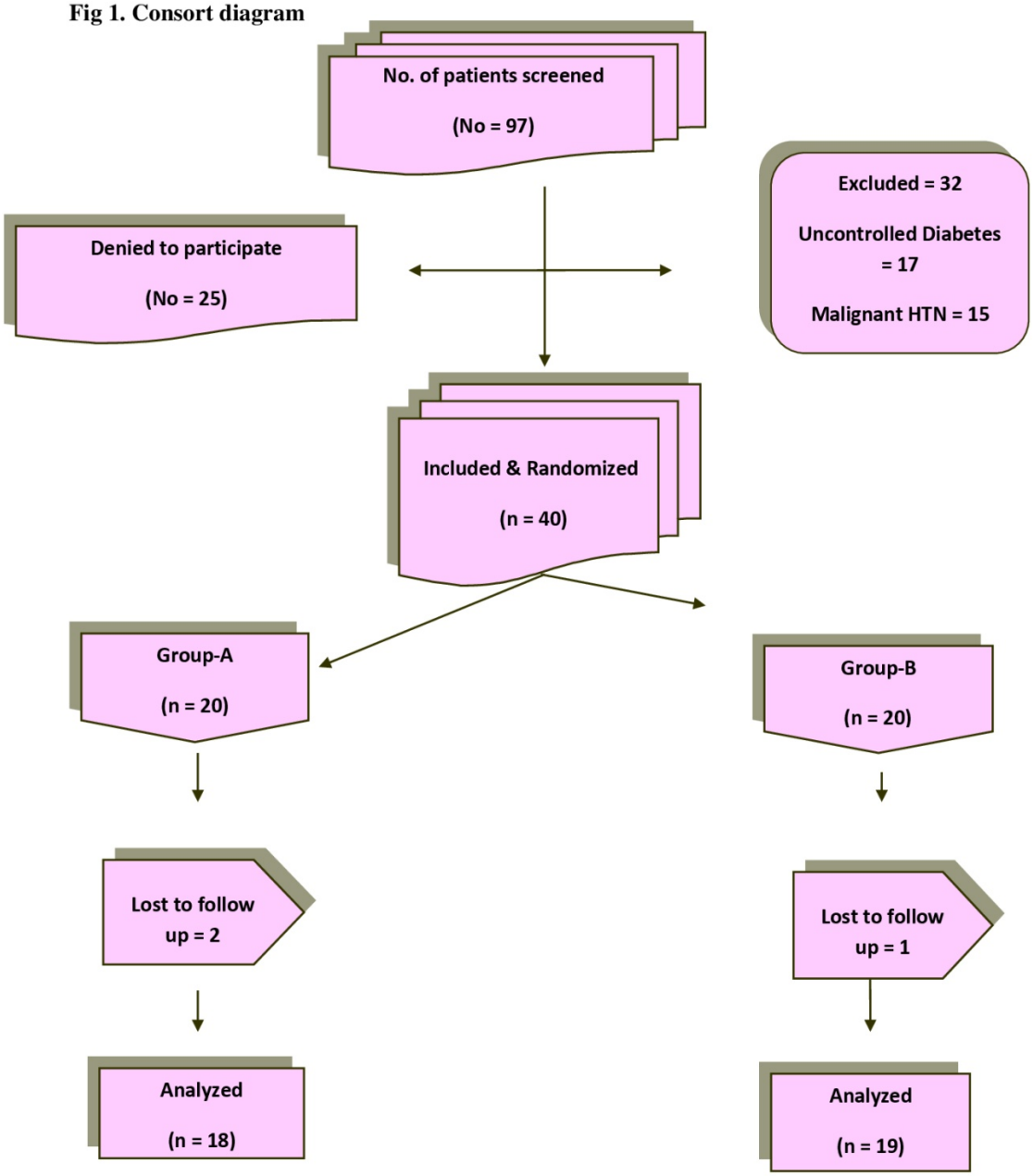
Table 3: Changes in ABI and ASI parameters

		Right			Left		
Arterial Brachial Index		**Test Group**	**Placebo Group**	**P value**	**Test Group**	**Placebo Group**	**P value**
	0th day	0.74±0.48	0.70±0.50	0.800	1.05±0.12	1.04±0.15	0.902
	30th	0.97±0.36	0.81±0.44	0.228	1.07±0.10	1.02±0.12	0.179
	60th	0.96±0.36	0.75±0.47	0.146	1.05±0.05	1.03±0.10	0.493
	90th	0.96±0.36	0.69±0.49	0.063+	1.12±0.07	1.01±0.11	0.037
	Diff (0-90th)	-0.016	0.012	-	0.088	0.014	-
	P value	**0.002***	0.940	-	**0.017***	0.737	-
Brachial ASI	0th day	34.03±12.02	31.93±13.61	0.622	31.66±20.40	31.06±13.80	0.918
	30th	31.11±11.06	31.45±11.90	0.930	26.08±12.36	30.17±8.66	0.249
	60th	31.36±10.27	30.83±10.22	0.877	28.72±7.90	28.17±10.46	0.859
	90th	28.76±13.51	32.68±9.63	0.313	28.68±9.43	30.24±11.81	0.660
	Diff (0-90th)	2.978	-0.758	-	2.311	0.821	-
	P value	0.514	0.811	-	0.778	0.735	-
Ankle ASI	0th day	42.06±33.46	33.98±27.33	0.426	42.53±17.49	51.77±26.99	0.228
	30th	46.11±24.39	50.48±32.20	0.646	37.72±12.91	44.03±17.47	0.222
	60th	39.64±18.28	47.82±34.30	0.376	40.85±10.67	46.63±19.31	0.271
	90th	39.74±17.67	44.17±34.69	0.631	39.40±10.93	46.01±18.37	0.195
	Diff (0-90th)	0.514	-10.184	-	3.133	5.758	-
	P value	0.778	0.161	-	0.424	0.253	-

Table 4: Safety parameters in two groups studied

Variables	Test Group		Control Group	
	BT	**AT**	**BT**	**AT**
Hb%	13.67±1.73	13.60±1.63	13.02±1.72	13.12±1.78
TLC	9066.67±1765.02	13300.00±19219.54	8557.89±1448.11	7978.95±1658.51
Po	57.61±6.14	56.17±7.29	59.53±5.65	57.26±7.26
L	33.17±5.23	35.22±7.43	33.00±5.98	34.37±7.53
E	4.78±1.11	4.39±1.46	4.37±1.16	4.53±1.17
B	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
Mo	4.56±1.38	4.39±1.46	3.63±1.16	3.95±1.31
ESR	19.17±11.25	20.06±14.07	27.21±20.46	27.74±21.73
HbA1c	6.51±1.43	6.98±1.72	6.71±1.12	6.59±1.00
RBS	142.72±58.13	164.11±62.16	168.26±74.48	171.00±64.48
B. Urea	25.89±5.51	26.89±5.59	26.26±4.62	26.47±4.45
S. creatinine	0.81±0.16	0.86±0.16	0.85±0.13	0.87±0.11
AST	32.34±22.79	25.56±13.75	27.21±9.45	27.84±11.90
ALT	32.78±15.43	29.28±15.73	25.37±9.46	24.89±9.74
Alk. Phosphate	177.83±40.77	190.11±45.01	193.42±49.80	184.21±48.03

Fig 1. Consort diagram



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DISCUSSION

The study reveals that the Test drug is effective in LDL and ABI parameter, which indicates anti-hyperlipidemic and anti-atherosclerotic effect of Test drug. This improvement may be due to Muhallil (resolvent), Mulattif (desiccative), Mufattehe Sudad (vasodialators), and Musakhkhin (depressant) properties of Tukhme Suddab. *Ruta graveolens*. L (Family Rutaceae) is a medicinal plant, used since time immemorial. Traditionally Rue is considered to be emmenagogue, ecbolic, anthelminthic, abortefacient, diuretic, antiepileptic, vermifuge, anaphrodisiac and antispasmodic.[21-29] It has been approved by Food and Drug Administration (FDA) as a flavouring agent. It possess anti-inflammatory, anti-oxidant[30] (Ratheesh M, et al, 2009) anti-fungal, anti-bacterial[31] (H. Pushpa, et al., 2015), anti-arrytyhmic[32] (Vabid khori et al. 2008), anti-tumour[33] (K.C Preethi, Girija Kuttan, Ramadasan Kuttan, 2006) and cytotoxic activities[34] (Rethy B, et al.,2015) proven scientifically. Another recent preclinical study revealed that Tukhme Suddab possess anti-hyperlipidemic, anti-atherosclerotic and antioxidant properties.[35] According to the findings of Soo-Jin Kang et al. (2015) [36] patients having a higher BMI had more hyperlipidemia, DM, HTN and more frequent plaque ruptures as compared with low BMI group. Present study coincide with same pattern as 17 (45.9%) patients were found with BMI ranges from 25-30, followed by 14 (37.8%) with >30 and 6(16.2%) with 18.5-25, while no patient was found with BMI <18.5. (Table No 7) Jurjani [37] stated that any exertion in the state of Imtila Bi Hasbil Aui'ya (congestion in the vessels / cavities) may lead to rupture of vessels; these rupture, occurs because of hardening (Salabate Nabz) of vessels and Imtila. Based on these elucidations of ancient Unani scholars, concept of Imtila may be correlated with hypertension, though these two terms cannot be used interchangeably. As seen in Table. 04 that the parameters relating to toxicity of drugs like Hb%, TLC, DLC, ESR, RBS, HbA1c, AST, ALT, blood urea and serum creatinine, remained within the normal limits in the Test group before and after the treatment. This shows the safety of test drug for therapeutic use in atherosclerosis.

CONCLUSION

The study demonstrates the efficacy of Tukhm Suddab in the management of atherosclerosis. Efficacy was evaluated with statistically significant improvement with $p<0.05$ in the objective parameter like Ankle Brachial Index (ABI) and Low density lipoprotein (LDL) during the treatment period while there was no effect of Test drug on other objective parameters like S. Cholesterol, S. triglyceride and ASI. It may be inferred that Tukhm Suddab is safe and effective treatment for Salabate Sharayin. The benefit of Suddab appears to be due to the multiple pharmacological activities, notably the Muhallil, Mullatif and Mufateh Suddad properties.

Limitations of the study were small sample size and short duration of protocol therapy. Hence, controlled clinical trials with large sample size are required to further prove the efficacy and safety of this treatment. Noncompliance of the participants like improper adherence to dietary intervention physical activity and other lifestyle covariates was a related problem.

Ideally for blinding the study, test and control both should be identical in shape, size, texture, taste and other physical attributes. In our study, both were almost identical. Notwithstanding these limitations, we can conclude that the test drug is an acceptable alternative in management of atherosclerosis.

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