Original Article

Efficacy of *Dioscorea villosa* 6CH in Treatment of Dyslipidemia: A Double-Blind, Randomized, Placebo-Controlled, Clinical Trial

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Abstract

Background: Keeping in view the current scenario of increasing risk of dyslipidemia leading to coronary heart diseases in Indian population and dearth of conclusive evidences in support of homeopathic treatment of dyslipidemia, we intended to evaluate the efficacy of a frequently prescribed medicine *Dioscorea villosa* 6CH in comparison with placebo. **Methods:** In this prospective, double-blind, randomized, parallel arm, placebo-controlled trial, 100 patients diagnosed with dyslipidemia were randomized in 1:1 ratio to one of the two interventions – *D. villosa* 6CH or identical looking placebo in the mutual context of lifestyle modification advices. The outcome measure was the blood lipid profile – triglyceride, total cholesterol (TC), low-density lipoprotein cholesterol (LDLc), very LDLc (VLDLc), and high-density lipoprotein cholesterol (HDLc), assessed at baseline and 2 months after intervention. Comparative analysis was conducted on intention-to-treat basis to detect group differences using SPSS. **Results:** The groups were comparable at baseline. After 2 months of intervention, pre–post comparison showed significant changes in triglyceride, TC, and VLDLc in the verum group and triglyceride, TC, and LDLc in the placebo group; however, the group differences were non-significant: triglyceride ($P = 0.809$), TC ($P = 0.316$), HDLc ($P = 0.430$), LDLc ($P = 0.192$), and VLDLc ($P = 0.251$). Per protocol analysis also revealed similar non-significant trends. **Conclusion:** *D. villosa* 6CH could not produce any differentiable effect from placebo in treatment of dyslipidemia. Trial registration: Clinical Trials Registry – India/2018/04/013511.

Keywords: *Dioscorea villosa*, dyslipidemia, homeopathy, placebo, randomized controlled trial

Introduction

Dyslipidemia refers to the derangements of one or many of the lipoproteins. The role of high serum cholesterol, especially a high level of low-density lipoprotein cholesterol (LDLc), as a risk factor for coronary artery diseases (CAD) is well established.[1] Asian Indians have double risk of CAD than the other ethnic groups.[2] The National Cholesterol Education Program expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) reinforced LDLc as the primary target of cholesterol-lowering therapy with the optimal goal of its level below 100 mg/dL. The panel recommended treatment beyond LDLc lowering for patients with triglyceride levels of 200 mg/dL and above. Lifestyle modifications (LSM) such as maintenance in regular aerobic physical activity, increased intake of omega-3 polyunsaturated fatty acids in diet, and therapeutic interventions such as statins (HMG-CoA reductase inhibitors), fibrates, or a combination of statins with fibrates or niacin have been suggested for their beneficial role in lowering LDLc levels, triglycerides, and increasing high-density lipoprotein cholesterol (HDLc) levels, but with their adverse effects.[3]

Of late, a short review[4] of published homeopathy research evidences on dyslipidemia identified four preclinical, three observational studies, and two case records. There

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were positive leads in managing patients suffering from dyslipidemia. However, more well-designed studies were warranted to generate effectiveness/efficacy of homeopathy. An observational study conducted by Govekar *et al*., 2009[5] on hyperlipoproteinemia on 322 patients showed improvement in 290 patients with a reduction in total cholesterol (TC) and triglyceride levels in 100 and 37 patients, respectively. Although the study was carried out on a large number of patients and threw light on the role of indicated homeopathic medicines on patients with lipoproteinemia, it was methodologically and statistically compromised. Another cohort study[6] with 57 patients of hypercholesterolemia treated with complex homeopathy showed a significant reduction in lipid parameters. There were few promising case series and case reports also.[7-9] A preclinical study on chickens[10] showed reduction in lipid parameters with the homeopathic medicine *Baryta carbonicum* and *Baryta muriaticum*. Another study[11] highlighted the remedial effect of the homeopathic drug *Syzygium jambolanum* on carbohydrate and lipid metabolic disorders in streptozotocin-induced diabetic rats. The lipid-lowering effect of cholesterinum was also found.[12] A multicentric, open-label, randomized, placebo-controlled exploratory trial Clinical Trials Registry – India (CTRI/2014/12/005257) has been undertaken by Central Council for Research in Homoeopathy[13] on 120 patients, randomized to either homeopathy or placebo. In a recent review,[14] diosgenin, the active ingredient of *Dioscorea villosa*, was hypothesized to have promising potential as homeopathic medicine in dyslipidemia on the ground of its definite lipid-lowering properties in material doses. In experimental rat and guinea-pig models, diosgenin was found to exert definite hypolipidemic and antioxidative effects,[15,16] and such potentials were identified long back,[17,18] although clinical evidences remained sparse.

Keeping in view the current scenario of increasing risk of dyslipidemia leading to coronary heart disease in Indian population and dearth of conclusive evidence suggesting a beneficial role of homeopathy, we aimed to evaluate whether ultradiluted *D. villosa* 6CH has any lipid-lowering properties in comparison with placebo in treatment of dyslipidemia. The rationale behind the choice of 6CH potency was its use, although undocumented or unpublished until now, as a specific medicine to treat dyslipidemia in homeopathy practice. We intend to initiate a series of trials with different potencies of *D. villosa*, and to start with 6CH.

Methods

Study design

It was a prospective, double-blind, randomized, placebo-controlled, two parallel arms trial with a 2 months' follow-up duration for each patient and was conducted in the outpatients of National Institute of Homeopathy (NIH) and D N De Homeopathic Medical College and Hospital (DNDHMCH). The study protocol was approved by the respective institutional ethics committees before initiation (NIH: 5–23/NIH/PG/Ethical Comm. 2009/Vol 5/2685 [A/S]; March 28, 2018; and DNDHMCH: DHC/Estt-175/15/403/2017; October 12, 2017). The trial was registered prospectively in the CTRI vide registration number CTRI/2018/04/013511.

Participants

Inclusion criteria were newly diagnosed dyslipidemia patients not undergoing any therapy, age 18–65 years, both sexes, and patients providing written informed consent to participate. Exclusion criteria were self-reported familial hypertriglyceridemia, patients who were too sick for consultation, unable to read patient information sheet, unwilling to take part or not giving consent to join the study, diagnosed cases of systemic diseases, unstable mental or psychiatric illness or other uncontrolled or life-threatening illness affecting quality of life or any organ failure, pregnancy and lactation, substance abuse and/or dependence, self-reported immunocompromised state, and patients availing homeopathic treatment for chronic disease within last 6 months.

Intervention

Verum was planned as administering *D. villosa* 6CH, two doses orally every day for consecutive 2 months. Each dose consisted of 4 medicated globules no. 30 (moistened adequately with *D. villosa* 6CH preserved in 90% v/v ethanol) and was instructed to be taken orally on clean tongue with empty stomach. The homeopathic medicine *D. villosa* 6CH was manufactured by Dr. Reckeweg and Co. GmbH®, v1114, D-64625 Bensheim, Germany, Lot No. 3257IN42411D, Mfg. 05/2017, Exp. 02/2022. The vials were labeled with code, name of medicine, and potency. These were dispended according to the random number list provided to the pharmacist. Dietary advices in terms of low saturated fat diet with increased fiber and brisk physical activity for minimum 30 min a day for at least 5 days a week were advised. Duration of therapy was 2 months. In the comparator arm, placebo, indistinguishable in appearance from verum, was administered orally on clean tongue with empty stomach for 2 months. Each placebo dose consisted of 4 cane sugar globules no. 30 moistened with 90% v/v ethanol. Advices on dietary restrictions and physical activity were given similarly. Duration of therapy was 2 months.

Outcomes

The outcome measure was the blood lipid profile (triglyceride, TC, LDLc, very LDLc [VLDLc], and HDLc), assessed at baseline and after 2 months. As routine procedure, the patients were advised to avoid fatty foods 24 h before blood testing and fasting (12 h, water only); blood samples were collected for the purpose. All tests were performed at the hospital laboratories of the two institutions.

Sample size

Formal effect size calculation was not possible on account of the absence of any earlier study of similar design. In a recent multicenter randomized controlled trials[19] conducted in India on dyslipidemic patients, the baseline mean (±standard

deviation [SD]) of LDLc level (mg/dL) in the verum group was reported to be 148.5 ± 24.0, and it was reduced by 29.4% over 3 months of treatment with one capsule of a proprietary bioactive phytonutrient formulation containing red yeast rice, grape-seed, niacinamide, and folic acid. Homeopathy was never been experimented under controlled situation in dyslipidemia. (LSM; dietary restrictions and physical exercise) would be implemented in both the arms. Hence, we expected mean reduction of LDLc by 20% (i.e., 118.8 ± 24.0) and 10% (133.65 ± 24.0) in the verum and control arm, respectively, over 2 months of therapy. Effect size (Cohen's *d*) was estimated to be 0.619. With this assumed effect size, accounting for an expected attrition rate of up to 20%, and to detect a significant difference between two independent means (two groups) of LDLc over 2 months of intervention through unpaired *t*-test, a study with 2 × 50 patients would give 80% power based on a two-sided significance level of 5% (*D. villosa* 6C + LSM: 50, Placebo + LSM: 50).

Randomization

Computer-generated permuted block randomization method was adopted to generate 10 blocks of 10 random numbers (10 × 10 = 100) to maintain 1:1 distribution. Random sequence (1 and 2 for either of medicine or placebo) was generated by a third party, not allowed to influence the study in any way. This chart was made available to the pharmacist in strict confidentiality and was not disclosed to the patients or doctors under any circumstances. The pharmacists were instructed to dispense from either of the coded vials in accordance with the random number chart. The allocated code was maintained till the end of the trial until the dataset was frozen.

Blinding

Double-blinding method was adopted – the participants, investigators, the outcome assessors, and the pharmacists were blinded to the identity of the two treatment groups until the end of the study. Concealment was maintained by identically coded alike vials, filled with cane sugar globules no. 30, moistened with either the medicine *D. villosa* 6CH or non-medicinal 90% v/v ethanol.

Statistical methods

A specially designed Microsoft Office Excel spreadsheet was used for data extraction and statistical analysis. It followed both intention-to-treat (ITT) and per protocol (PP) approaches. In ITT analysis, we used the multiple imputation technique with 50 simulation runs and constraints between 0 and 100 to impute missing values for the 2nd and the 3rd visits. Each group-specific imputation model comprised 11 socio-demographic features [Table 1] as well as available measurements of the respective outcomes [Table 2]. In PP analysis, the protocol compliant sample was subjected to statistical analysis. Descriptive data (categorical and continuous) were presented in terms of absolute values, percentages, means, and SD. Before comparison, the groups were checked for comparability of socio-demographic features and outcome measures at baseline.

Table 1: Comparison of baseline sociodemographic features between two groups (*n*=100)

Items	Verum (*n*=50)	Placebo (*n*=50)	*P**
Age (years)[a]	43.7 (10.7)	44.6 (9.6)	0.651
Sex[b]			
Male	22	24	0.841
Female	28	26	
Residence[b]			
Urban	20	23	0.686
Rural	30	27	
SBP (mm Hg)[a]	127.2 (20.7)	131.9 (10.3)	0.151
DBP (mm Hg)[a]	81.9 (7.1)	82.6 (7.4)	0.632
BMI[a]	24.6 (4.7)	25.9 (4.3)	0.159
WHR[a]	0.9 (0.1)	0.9 (0.1)	0.589
WHtR[a]	0.6 (0.1)	0.6 (0.1)	0.553
Educational status[b]			
8th standard or less	35	38	0.155
9th - 12th standard	9	3	
Higher than 12th standard	6	9	
Employment status[b]			
Self-employed	13	14	0.824
Service	7	5	
Dependent	30	31	
Income status[b]			
Poor	25	24	0.572
Middle	22	20	
Affluent	3	6	

[a]Continuous data presented as mean±SD and compared using unpaired *t*-tests, [b]Categorical data presented as absolute values and compared using Chi-squared tests with Yates correction; *P*<0.05 considered as statistically significant. SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure, BMI: Body mass index, WHR: Waist-hip ratio, WHtR: Waist-height ratio

Table 2: Comparison of baseline values between two groups (*n*=100)

Items	Mean±SD		Mean difference (95% CI)	*P**
	Verum (*n*=50)	Placebo (*n*=50)		
Triglyceride (mg/dl)	198.5±71.8	198.7±76.9	−0.2 (−29.8-29.3)	0.987
TC (mg/dl)	207.0±42.4	219.0±41.8	−12.0 (−28.7-4.7)	0.157
HDL-c (mg/dl)	47.9±9.0	49.8±10.1	−1.9 (−5.7-1.9)	0.318
LDL-c (mg/dl)	122.8±37.6	125.2±38.5	−2.4 (−17.5-12.7)	0.754
VLDL-c (mg/dl)	39.5±19.0	38.3±15.2	1.2 (−5.6-8.0)	0.733

*Unpaired *t*-test, *P*<0.05 considered as statistically significant.
SD: Standard deviation, CI: Confidence interval, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, VLDL-c: Very low-density lipoprotein cholesterol, TC: Total cholesterol

Intragroup changes over 2 months in both the groups were estimated by paired *t*-tests. Parametric unpaired *t*-tests were used to detect group differences. *P* values were set at less than 0.05 two-tailed as statistically significant. Statistical Package for the Social Sciences (SPSS®), version 20.0 (IBM Corp., IBM SPSS Statistics for Windows, Armonk, NY: USA) was used for statistical analysis. Reporting of the study adhered

to the CONSORT[20] and RedHot (homeopathy specific CONSORT)[21] statements.

Results

In this study, 100 patients were enrolled and randomized. After 2 months of intervention, 4 and 6 patients dropped out in the verum and placebo groups, respectively, 90 completed the trial [Figure 1]. Starting from April 2018 to April 2019, total 100 patients were enrolled and followed up for 2 months in this study.

Baseline data

The two groups were comparable as per baseline characteristics; no significant baseline differences existed between groups, both in terms of socio-demographic characteristics (age $P = 0.651$, sex $P = 0.841$, residence $P = 0.686$, systolic blood pressure $P = 0.151$, diastolic blood pressure $P = 0.632$, body mass index $P = 0.159$, waist–hip ratio $P = 0.589$, waist–height ratio $P = 0.553$, educational status $P = 0.155$, employment status $P = 0.824$, and income status $P = 0.572$) and distribution of outcome measures (triglyceride $P = 0.987$, TC $P = 0.157$, HDLc $P = 0.318$, LDLc $P = 0.754$, and VLDLc $P = 0.733$) [Tables 1 and 2].

Outcomes and estimation

Pre–post comparison revealed significant intragroup changes in triglyceride ($t_{49} = 4.261$, $P = 0.001$), TC ($t_{49} = 4.130$, $P = 0.001$), and VLDLc ($t_{49} = 3.050$, $P = 0.004$) in the *D. villosa* group over 2 months of intervention [Table 3]. In the placebo group also, over 2 months of intervention, pre–post comparison revealed significant changes in triglyceride ($t_{49} = 3.348$, $P = 0.002$), TC ($t_{49} = 4.844$, $P = 0.001$), and LDLc ($t_{49} = 2.512$, $P = 0.015$) [Table 4]. ITT analysis revealed that there were no significant group differences over 2 months (triglyceride: $t_{98} = 0.243$, $P = 0.809$;

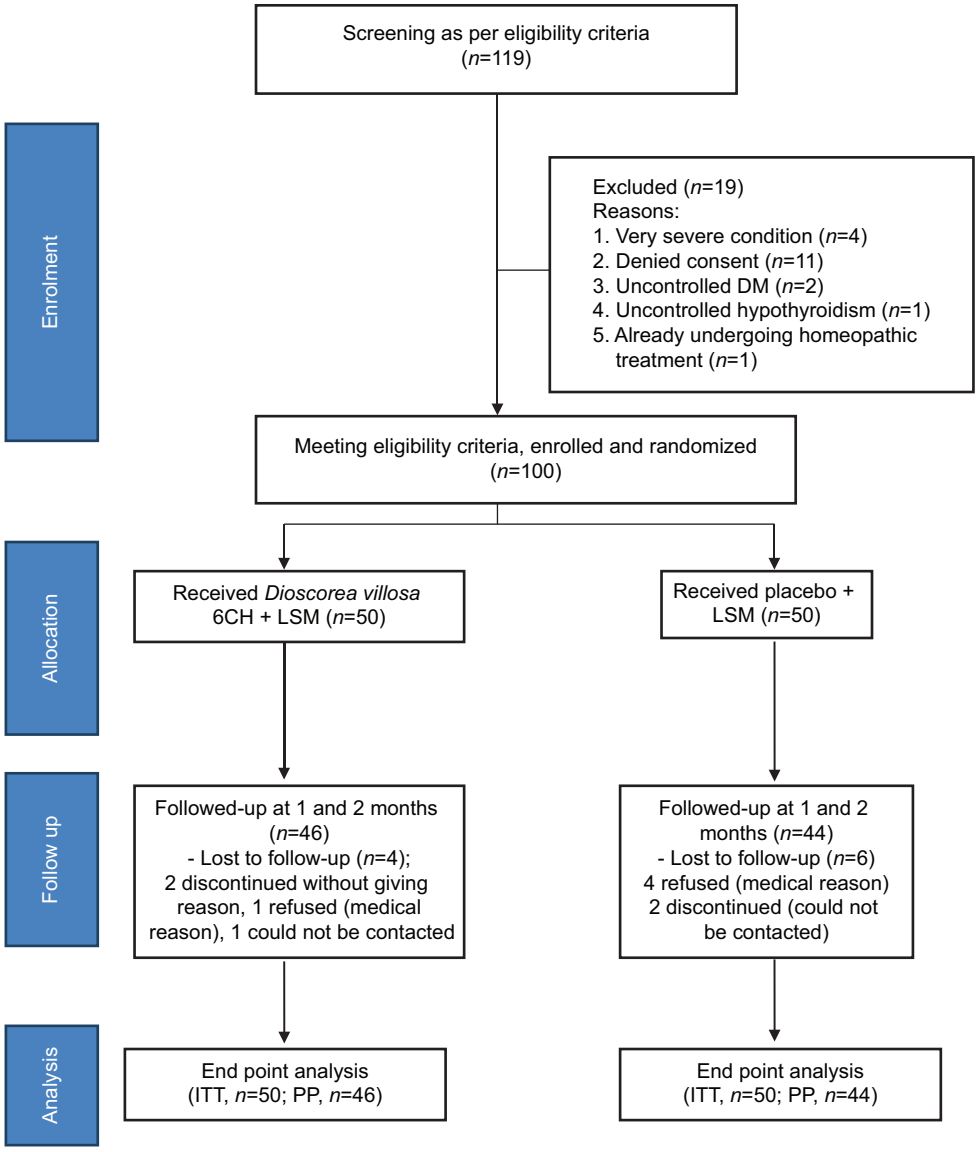

Figure 1: Study flow diagram

Table 3: Intragroup changes in the verum group over 2 months (*n*=50; intention-to-treat analysis)

Items	Mean±SD		Mean difference (95% CI)	*P**
	Baseline	After 2 months		
Triglyceride (mg/dl)	198.5±71.8	169.0±66.4	29.5 (15.6-43.4)	<0.001*
TC (mg/dl)	207.0±42.4	189.5±43.5	17.5 (9.0-26.0)	<0.001*
HDL-c (mg/dl)	47.9±9.0	48.1±12.5	−0.1 (−2.7-2.4)	0.918
LDL-c (mg/dl)	122.8±37.6	119.5±40.8	3.3 (−5.7-12.3)	0.467
VLDL-c (mg/dl)	39.5±19.0	31.0±11.4	8.4 (2.9-14.0)	0.004*

*Paired *t*-test, *P*<0.05 considered as statistically significant. SD: Standard deviation, CI: Confidence interval, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, VLDL-c: Very low-density lipoprotein cholesterol, TC: Total cholesterol

Table 4: Intragroup changes in the placebo group over 2 months (*n*=50; intention-to-treat analysis)

Items	Mean±SD		Mean difference (95% CI)	*P**
	Baseline	After 2 months		
Triglyceride (mg/dl)	198.7±76.9	171.8±65.9	26.9 (10.8-43.0)	0.002*
TC (mg/dl)	219.0±41.8	194.9±42.5	24.1 (14.1-34.1)	<0.001*
HDL-c (mg/dl)	49.8±10.1	51.5±10.6	−1.6 (−4.5-1.2)	0.249
LDL-c (mg/dl)	125.2±38.5	113.4±39.7	11.8 (2.4-21.3)	0.015*
VLDL-c (mg/dl)	38.3±15.2	34.8±22.9	3.5 (−3.0-10.0)	0.286

*Paired *t*-test, *P*<0.05 considered as statistically significant. SD: Standard deviation, CI: Confidence interval, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, VLDL-c: Very low-density lipoprotein cholesterol, TC: Total cholesterol

Table 5: Group differences over 2 months (*n*=100; intention-to-treat analysis)

Items	Mean±SD		Mean difference (95% CI)	*P**
	Changes in verum (*n*=50)	Changes in placebo (*n*=50)		
Triglyceride (mg/dl)	29.5±48.9	26.9±56.8	2.6 (−18.5-23.6)	0.809
TC (mg/dl)	17.5±30.0	24.1±35.2	−6.6 (−19.6-6.4)	0.316
HDL-c (mg/dl)	−0.1±9.0	−1.6±9.9	1.5 (−2.3-5.3)	0.430
LDL-c (mg/dl)	3.3±31.6	11.8±33.2	−8.5 (−21.4-4.3)	0.192
VLDL-c (mg/dl)	8.4±19.5	3.5±22.9	4.9 (−3.5-13.4)	0.251

*Unpaired *t*-test, *P*<0.05 considered as statistically significant. SD: Standard deviation, CI: Confidence interval, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, VLDL-c: Very low-density lipoprotein cholesterol, TC: Total cholesterol

TC t_{98}= [−1.008], P = 0.316; HDLc t_{98} = 0.792, P = 0.430; LDLc t_{98}= [−1.314], P = 0.192, and VLDLc t_{98} = 1.155, P = 0.251) [Table 5]. Similar trend of non-significance was observed in PP analysis also (triglyceride t_{88}= [−0.282], P = 0.778, TC t_{88}= [−0.880], P = 0.381, HDLc t_{88} = 0.586, P = 0.560; LDLc t_{88}= [−1.008], P = 0.280, and VLDLc t_{88} = 0.946, P = 0.347) [Table 6].

Discussion

Although the homoeopathic medicine *D. villosa* was selected on the basis of lipid-lowering properties of its active ingredient Diosgenin as well as possible background pathophysiological effects on altered lipid metabolism, our study found that *D. villosa*, in its 6CH dilution, could not show its lipid-lowering effect beyond placebo in blood in 2 months' duration.

This study examined the efficacy of *D. villosa* 6CH in dyslipidemia in blinded and randomized design for the first time toward generating quality evidence. Although the use of homeopathic medicines in dyslipidemia is quite popular and the use of *D. villosa* in dyslipidemia is one of the usually accepted conjectures (unpublished) prevailing in many homeopathy practices in 6CH dilutions, findings of our study do not support the claims.

Two of the authors (SS and MK) rated the study independently using Mathie's criteria of model validity of homeopathic treatment (MVHT).[22] The six domains were scored likewise: U-U-Y-Y-Y-Y (Y = Yes; U = Uncertain), overall quality B2; thus indicating MVHT was inadequate.

There may broadly the following explanations for the negative results derived from the study:

- Other homeopathic dilutions other than 6CH may have significant lipid-lowering property beyond placebo
- Individualistic approach of selecting the medicine *D. villosa* may produce significant effect beyond placebo
- Other individualized homeopathic medicines may be suitable for the condition.

Conclusion

D. villosa 6CH could not produce differentiable effect beyond placebo in treatment of dyslipidemia. Future trials

Table 6: Group differences over 2 months (per protocol analysis; *n*=90)

Items	Mean±SD		Mean difference (95% CI)	*P**
	Changes in verum (*n*=46)	Changes in placebo (*n*=44)		
Triglyceride (mg/dl)	31.2±46.9	34.0±49.0	−2.9 (−22.9-17.2)	0.778
TC (mg/dl)	15.6±29.8	21.2±30.6	−5.6 (−18.3-7.1)	0.381
HDL-c (mg/dl)	−0.2±6.9	−1.2±9.4	1.0 (−2.4-4.5)	0.560
LDL-c (mg/dl)	2.2±27.3	8.8±30.3	−6.6 (−18.7-5.5)	0.280
VLDL-c (mg/dl)	8.8±19.9	4.6±22.6	4.2 (−4.7-13.2)	0.347

*Unpaired *t*-test, *P*<0.05 considered as statistically significant. SD: Standard deviation, CI: Confidence interval, HDL-c: High-density lipoprotein cholesterol, LDL-c: Low-density lipoprotein cholesterol, VLDL-c: Very low-density lipoprotein cholesterol, TC: Total cholesterol

with different strategies like Dioscorea in other potencies (for example, 3X, 30CH or 50 millesimal potencies) or in individualistic approach may be up taken in near future.

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Conflicts of interest

There are no conflicts of interest.

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