

Community Based, Multicentered, Randomized, Double Blinded, Placebo controlled Clinical trial of Trachyspermum Copticum Extract Against Stable Angina

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Abstract:

Introduction: Trachyspermum copticum (Carom seeds) has been reported to have anti-platelet aggregatory, hypolipidemic and anti-oxidant effects. In the present study, this was evaluated for its efficacy in the management of stable angina.

Patients and Methods. A prospective double blind, randomized, placebo controlled, multicentered interventional study was conducted with patients of stable angina randomized in two groups (100 in each) in Lahore urban community for a period of 6 weeks.

In trial group, patients were treated with oral T.copticum extract for 6 weeks in addition to their conventional medical therapy. In placebo group similar preparation was given to the patients along with conventional therapy taking already. Anginal symptoms (chest pain, chest tightness, difficulty in breathing, nausea, light headedness and anxiety) were evaluated after every fortnightly i.e. after 2, 4 and 6 weeks regarding their presence.

Results: In this trial 200 patients of stable angina were randomly placed in two groups i.e. T.copticum (trial) and placebo. There was found no difference in both groups regarding age and sex. All patients were adults. There was significant improvement in the angina signs/symptoms in the T.copticum group as compared with placebo group ($p < 0.0001$) after the completion of trial period. Regarding safety profile, there was no difference found in the routine examination before and after trial in both groups, however lipid profile was improved in the T.copticum group.

Conclusion: T.copticum extract significantly improved patients with stable angina.

Key Words: *trachyspermum copticum, stable angina, randomized, placebo controlled*

Introduction:

Angina is a Latin word that means squeezing of the chest. Generally it is chest pain, tightness or discomfort, due to less blood oxygen flow to some portion of cardiac muscle. It is one major symptom of coronary heart disease (CHD).

Most commonly observed symptoms of angina may be chest pain, tightness in chest, feeling of pressure in the chest, pain in arms, jaw, neck, back or shoulders, difficulty in breathing, nausea, vomiting and anxiety. It may clinically presented in two forms: Stable or Unstable.

Stable angina is angina with all or some of angina symptoms mentioned above that triggers on with reliable and predictable amount of exercise or stress and which might persist for more than four weeks. For example, if a person usually has chest discomfort every time he climbs ten stairs, that would be understood as stable angina. If the pattern

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Received 07-06-2017; Accepted 10-10-2017

of discomfort varies over the course of a short period then this is not stable angina rather labeled as unstable angina. On the other hand unstable angina is the chest discomfort or pain that often occurs when a person is in resting, sleeping phase, or with little physical exertion. There is no effect of taking rest or any medication rather it may aggravate and resulting into a full heart attack. There is no effect of taking rest or using any sort of medicine. Also, if a person experiences a change in his routine pattern of angina occurring with exertion is also in unstable angina state.

Since birth there has been no mechanism to stop or at least minimize the process of plaque formation within the blood vessels which are power channels carrying food and fresh oxygen to all organs of body enabling them to function adequately. This plaque formation if not controlled in time may lead to atherosclerosis which in turn produces threatening cardiovascular problems like angina and infarction of various vital organs resulting into heart attack and stroke. *T.copticum* extract may resolve this problem to some extent if adequate precautionary measures may be adopted along with its use.

Atherosclerosis (or arteriosclerosis) is a pathological condition in which there is narrowing and hardening of arteries because of an excessive deposition and building up of plaque around the inside of artery wall. Plaque is composed of cholesterol, calcium, and other substances found in the blood. With the passage of time, plaque turns the arteries hard and narrows causing reduction in the flow of oxygenated blood to body resulting into fatal cardiovascular issues.^{1,2}

Cardiovascular disease (CVD) is the No. 1 killer in many countries. It is also No.1 Killer in Pakistan as it is prevalent in 223 persons out of 100000 population and in the world ranking it is at No.17.3 In Pakistan cardiovascular diseases account for 19% mortality as reported by WHO.⁴ World Health Organization (WHO) estimated that in the low-income countries the number of deaths due to cardiovascular disease is on rise. There is 80% mortality due to CVD and the global burden of

CVD is 86% in the developing countries including Pakistan. 17.5 million people die each year from CVDs, a number that is expected to grow to more than 23.6 million by 2030, an estimated 31% of all deaths worldwide.⁵ Major symptoms of coronary insufficiency feature chest pain, chest tightness, faintness, coughing, nausea, vomiting, anxiety, general weakness, breathing difficulty, numbness, headache, stroke and paralysis.⁶ In most of the cases atherosclerosis may be leading cause of heart attack, stroke, chronic kidney disease, peripheral arterial disease, or even mortality.⁷

Many psycho-social factors may predispose to angina or CVD. Among them obesity, lack of physical activity, smoking, consuming fatty diets, hypertension, hypercholesterolemia, excessive alcohol intake, diabetes mellitus, heredity, high level of LDL and low level of HDL play a major role.⁸

Most of premature heart attacks and strokes may be prevented through eating a diet rich in soluble fiber, having protein from fish and plant sources^{9,10}, limiting intake of alcohol, saturated fats, sodium salt, using polyunsaturated oils for cooking.^{11,12} and avoiding fatty foods. Regular physical exercise for 30-60 minutes on daily basis, no smoking, avoiding obesity, controlling hypertension and diabetes and managing stress are the fundamental precautions leading to a healthier life pattern.^{13,14,15} *T.copticum* is also known as Bishop weed due to its medicinal effects. Regular intake of tomatoes and water melon and Bishop weed is quite helpful as they contain lycopene and other antioxidant properties.¹⁶

According to World Health Organization (WHO) estimate, 17.5 million people die each year from CVDs, an estimated 31% of all deaths worldwide. About 80 percent of the population of some Asian and African countries presently practicing intake of herbal therapies for some aspect of primary health care.¹⁷ There is common practice in China of using herbal medicine.^{18,19}

Traditional medicines are drawing attention in world health dialogues. They have been the main

source of primary health care in many communities. Plants and herbs have been a rich source of effective and safe medicines from ancient times,. Due to their safe and effective nature, indigenous remedies are getting popularity in China, India and Pakistan. Among these herbs, *Trachyspermum copticum* (*T.copticum*) commonly known as 'Carom seeds' a common kitchen spice, has been found having marvelous anti anginal, antihyperlipidemia and anti stroke properties²⁰

Extract of *T.copticum* showed antiplatelet aggregatory effects (Platelet agregatory effect was induced by arachidonic acid, epinephrine and collagen²¹. *T.copticum* also produced coronary arterial vasodilatation thus preventing the onset of angina attacks²². In one animal study lipid-lowering effect of *T.copticum* seeds was observed.²³ This study was carried on rabbits and *T.copticum* lowered cholesterol, triglycerides and low density lipoproteins along with increased high density lipoproteins.²⁴ Same effect was observed in another study on albino rabbits who were fed on alcoholic extract of *T.copticum*. Anti-inflammatory role of *T.copticum* was also revealed in this study²⁵

Materials & Methods

This study was conducted with the objective of evaluating the efficacy of alcoholic extract of *T.copticum* to prevent and manage stable angina. 100 grams *T.copticum* seeds powder was processed through anaerobic sublimation followed by ethanolic-aqueous extraction. The resultant extract was diluted to prepare 1 ppm solution (0.0625 microgram extract in one drop). Placebo was simple aqueous solution.

This was a community based, multicenter, placebo controlled, double-blind, randomized clinical trial, in which two hundreds patients suffering from stable angina were randomly selected and placed in two equal groups to receive either *T.copticum* extract (trial group) or Placebo (control group) for a period of 6 weeks. All patients were already using the conventional medicines but exhibiting stable angina . Written consent was taken

before the start of trial. A flow chart has been given at the end of this article.

Trial was conducted for a period of 6 weeks. All participants were cases of stable angina and of age group 40 to 70 years. Participants were excluded if they had any of the following: uncontrolled hypertension , heart failure, cardiac arrhythmias; hepatic or renal disease or impairment; pregnant or lactating women or participating in other clinical trial. Frequency and duration of angina attack were counted and measured. Symptoms such as chest pain, chest discomfort, breath shortness, nausea, lightheadedness and anxiety were evaluated in the start of trial and then after every 2weeks i.e.week 2, 4 and 6 weeks during the treatment course. Routine tests of blood(complete blood count, hemoglobin, liver profile, renal profile ,blood sugar and lipid profile) were taken at the start and after completion of trial. *T.copticum* extract and placebo were similar in appearance, color and smell.

T.copticum extract(10 drops containing 10 mcg extract twice a day) and placebo (10 drops of placebo twice a day) were given for a period of six weeks. Evaluation was made at each fortnightly visit (week 2, 4 and 6) .Outcome measures were based on the relief from angina symptoms.

Results

In this trial all participants were suffering from stable angina. All were adults .There was no significant difference in both groups regarding age and sex. See Table 1.

Table 1: General information before treatment for control and trial groups

Item	Trial (n=100)	Control (n=100)	P
Age (years)	42.23±5.12	42.48±4.98	0.765
Male (cases)	48	41	0.319
Female (cases)	52	59	

No significant change was found in routine blood safety indices at pre- and post-treatment in both groups ($P>0.05$). However, the effect of lowering Cholesterol, triglycerides and low density lipoproteins of the *T.copticum* group was signifi-

cantly more ($P < 0.05$) than that of the control group. the trial group. ($p < 0.05$). See Table 2
 High density lipoprotein was significantly high in

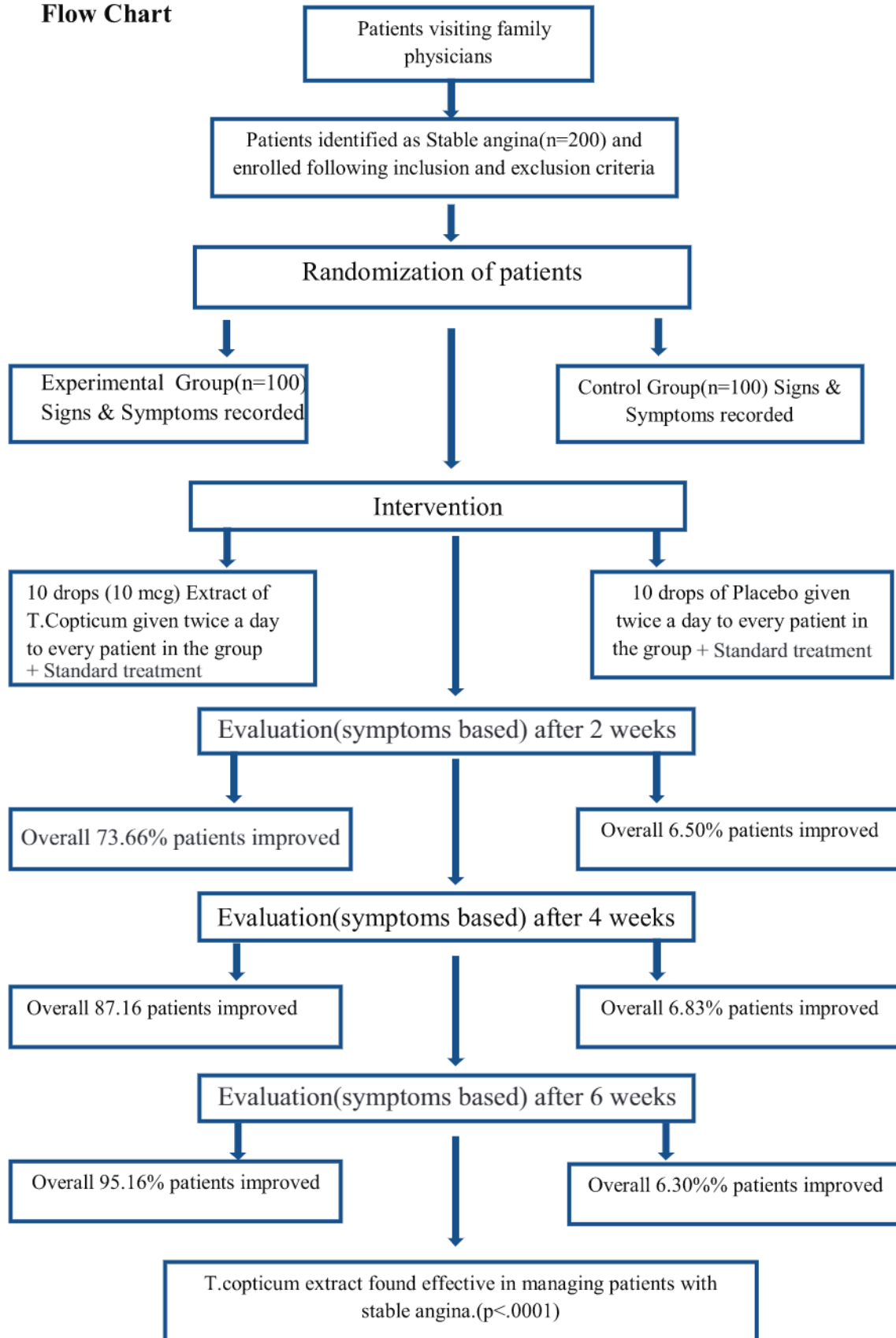
Table 2: Comparison of Blood parameters before and after intervention in both groups

	At Base line	After 6 Weeks	Placebo
	Both Groups	Trial Group	
Parametre	Mean±SD	Mean±SD	Mean±SD
hemoglobin	12.12±1.32	13.21±1.42	12.42±1.44
total leucocyte count	8649±1731	8650±1843	8648±1743
platelets	312567±51987	312566±40132	312564±49501
polymorphs	59.43±1.78	58.02±1.48	60.01±1.51
lymphocytes	32.55±1.59	30.39.46±1.29	32.62±1.32
monocytes	3.26±1.37	3.34±1.63	3.21±1.34
eosinophils	2.77±.64	1.54±.63	2.82±.73
blood sugar random	128.01±19.23	127.43±17.8	128.67±18.4
bilirubin	.62±.17	.60±.21	.61±.19
alanine transaminase	29.25±7.94	27.56±6.98	28.12±7.45
alanine transphosphatase	31.67±6.98	29.11±6.32	30.31±6.87
alkaline phosphstase	128.87±15.29	130.54±14.90	128.62±14.86
blood urea	30.12±14.76	25.17±9.45	29.27±10.23
Serum creatinine	.823±.09	.622±.07	.621±.08
serum cholesterol	196.23±11.67	166.12±10.23	197.98±11.54
serum triglycerides	210.56±19.34	187.11±16.07	209.39±18.37
high density lipoprotein	27.87±5.54	32.56±6.31	26.65±5.12
low density lipoprotein	142.78±12.34	123.45±9.56	140.72±12.12

Significant difference was found between the efficacy of the T.copticum group and that of the control group after 2,4 and 6 weeks ($P < 0.05$). A flow chart has been given at the end. The effect of the T.copticum group on frequency and duration of angina attack was much better ($P < 0.05$). Table 3

Table 3: Therapeutic effects on angina pectoris for control and trial groups after 2,4 and 6 weeks

Symptoms	Relief after 2 weeks			Relief after 4 Weeks			Relief after 6 Weeks		
	T.copticum	Placebo	P-value	T.copticum	Placebo	P-value	T.copticum	Placebo	P-value
Chest pain	70%	5%	.0001	80%	8%	.0001	95%	5%	.0001
Tightness in chest	60%	4%	.0001	85%	5%	.0001	95%	5%	.0001
Difficulty in Breathing	75%	2%	.0001	87%	2%	.0001	93%	2%	.0001
Nausea	80%	10%	.0001	90%	8%	.0001	98%	10%	.0001
lightheadedness	75%	8%	.0001	86%	10%	.0001	94%	7%	.0001
Anxiety	82%	12%	.0001	95%	10%	.0001	96%	9%	.0001

Flow Chart

Discussion

Traditional medicines are drawing attention in world health dialogues. They have been the main source of primary health care in many communities. Plants have been a rich source of effective and safe medicines from ancient times. Due to their safe and effective nature, indigenous remedies are getting popularity in the world.

One of the most studied element so far is one of every day used spice *Trachyspermum copticum* which is a household spice.¹⁶ Many astonishing health effects have been revealed by various researchers²⁰. However no research study was available to highlight its efficacy in coronary artery disease in humans. In most of these researches *T.copticum* has been used in the form of seeds. In few studies its alcoholic extract has also been tried. *T.copticum* has many beneficial effects on human health system and has been shown to possess hypolipidemic, antiplatelet-aggregatory. It would be better to mention few studies here. An in vitro study conducted with blood samples taken from human volunteers revealed that Extract of a spice (*Trachyspermum*) showed anti-aggregatory effects²¹. In a pilot clinical trial conducted by G. V. Anrep et al, the impact of *C. copticum* on syndrome of cardiovascular disease (angina) was studied and it was reported that this plant could produce coronary arteries vasodilatation along with lowering of systemic blood pressure²². Lipid-lowering effect of *C. copticum* seeds has been studied in rabbit. In these studies, methanolic extract of the plant (2 g/kg) significantly decreased total cholesterol, triglycerides, and LDL-cholesterol (71%, 53%, and 63%, resp.) and increased HDL up to 60% which was comparable to the effect of simvastatin (0.6 mg/kg). It was also suggested that possibly due to enhanced removal or catabolism of lipoproteins and inhibition of HMG CoA reductase produced anti-hyperlipidemic effect.²³ This effect has also been obtained in albino rabbits who were given methanolic extract of *T.copticum*. In another study *T.copticum* was found producing remarkable role in lowering heart rate and blood pressure due to its

calcium channel blocking effect. Kumar et al. examined the effect of juice of *C. copticum* leaves on isolated frog heart. It had positive inotropic effect and negative chronotropic effect on cardiac muscle perfused heart. Effects of *T.copticum* extract on hexachlorocyclo hexane (HCH)-induced oxidative stress and toxicity in rats were investigated in one study. It was concluded that HCH administration resulted in hepatic free radical stress, causing toxicity, which could be reduced by the dietary *T.copticum* extract.²⁴ Anti-inflammatory potential of the total alcoholic extract (TAE) and total aqueous extract (TAQ) of the *T.copticum* seeds was determined. TAE and TAQ exhibited significant ($P < 0.001$) anti-inflammatory activity in both the animal models as weights of the adrenal glands were found to be significantly increased in TAE and TAQ treated animals.²⁵

So it is evident that *T.copticum* is a multi-dimensional preventive measure regarding coronary artery disease. In this study main focus was on angina because of its anti-platelet aggregatory, hypolipidemic and anti-oxidant effects.

Conclusions

Coronary artery diseases are leading cause of mortality in many communities. Many herbs, fruits, vegetables and spices have been researched to find out any preventive measure to check the onset of disease or reduce the unwanted effects of disease. In the present study, *T.copticum* extract has been found significantly effective in preventing and managing stable angina. The extract provided significant improvement in anginal symptoms in very little amount as compared with placebo without producing any side effect. The result focused on reduction or absence of anginal symptoms at fortnightly interval. There was found consistent findings of an increasing proportion of angina-free patients at each visit in the *T.copticum* group indicating the beneficial effect of *T.copticum* extract in stable angina patients. Findings also indicated that *T.copticum* extract might be more feasible and effective therapeutic choice for the long term prevention

stable angina. In the study, action of *T.copticum* was found quick without showing any undesirable effect. It may be given in the form of continuous treatment to abolish or reduce the frequency and severity of anginal attacks, or to relieve individual severe attacks of pain.

Particular thing about this study is that *T.copticum* in extremely little amount (0.0625 microgram extract in one drop) effectively prevented and managed angina without any unwanted side effect. This preliminary clinical trial seems sufficiently favourable to justify a further and more extensive therapeutic test of *T.copticum* in angina pectoris and coronary occlusion.

References

1. Atherosclerosis [internet]. [place unknown] :[publisher unknown] ;2017 [Updated: Jul 5,2017; cited 2015 Jun 15]. Available from: AHA.. http://www.heart.org/HEARTORG/Conditions/Cholesterol/WhyCholesterolMatters/Atherosclerosis_UCM_305564_Article.jsp
2. NIH[internet][place unknown] :[publisher unknown]; 2017[updated :May 10, 2017; cited 2017 Aug 10] .available from <http://www.nhlbi.nih.gov/health/health-topics/atherosclerosis>
3. Nordqvist J. Atherosclerosis [Internet]. [place unknown]:[publisher unknown]; [Last updated Mon 3 July 2017 ; cited 2017 Aug 10] Medical. News Today: Causes, Symptoms and Treatments.Available from <http://www.medicalnewstoday.com/articles/247837.php>
4. Epidemiology of Coronary Heart Disease. <http://patient.info/doctor/epidemiology-of-coronary-heart-disease>
5. Heart Disease and Stroke Statistics. At-a-Glance,American Heart Association [Internet]. [Place unknown]: American Heart Association; 2017 [Updated 2017 Jan 24; Cited 2017 Jun 21]. Available from: https://www.heart.org/idc/groups/ahamah-public/@wcm/@sop/@smd/documents/downloadable/ucm_491265.pdf
6. Heart disease,Mayo clinic[http:// www.mayoclinic.org/diseases-conditions/heart-disease/ basics/symptoms/con-20034056](http://www.mayoclinic.org/diseases-conditions/heart-disease/basics/symptoms/con-20034056)
7. Aftab K., & Usmanghani K., "Blood pressure lowering action of active principle from *Trachyspermum ammi* (L.) Sprague," *Phytomedicine*. 1995; vol. 2, no. 1, pp. 35–40,.
8. Cardiovascular disease risk factors. World Heart Federation [internet]. [Place unknown] .world heart federation ; 2010 [Updated 2014 Jan 4; Cited 2015 Jun 21]. Available from: <http://www.world-heart-federation.org/cardiovascular-health/ cardiovascular-%20disease-risk-factors>
9. World Health Organization [Internet]. New initiative launched to tackle cardiovascular disease, the world's number one killer. Geneva: world Health Organization; 2015 [Updated 2017 Apr 23; Cited 2017 Jun 21]. Available from:[www.who.int/ cardiovascular_diseases](http://www.who.int/cardiovascular_diseases)
10. P. Kumar, M. Prabhakara, K. Satyavathi, and A. Kumar, "Evaluation of cardiac activity of some traditionally used backyard Indian medicinal plants," *Research Journal of Pharmaceutical, Biological and Chemical Sciences*. 2010. vol. 1, no. 4, pp. 643–654.
11. Atherosclerosis. Harvard Health Publications [Internet]. [Place unknown]: Harvard Health Publications; 2016 [Updated 2017 May 12; cited 2017 Jul 16]. Available from: [http://www.drugs.com/health-guide/ atherosclerosis.html](http://www.drugs.com/health-guide/atherosclerosis.html)
12. Anilakumar KR, Saritha V, Khanum F, Bawa AS. Ameliorative effect of *T.copticum* extract on hexachlorocyclohexane-induced lipid peroxidation in rat liver. *Food Chem Toxicol*. 2009;47:279–82.
13. Rodriguez-Porcel M, Lerman LO, Herrmann J, Sawamura T, Napoli C, Lerman A.. Hypercholesterolemia and hypertension have synergistic deleterious effects on coronary endothelial function. *Arterioscler Thromb Vasc Biol*. 2003; 23: 885–891.
14. Fruchart JC, Nierman MC, Stroes ES, Kastelein JJ, Duriez P. New risk factors for atherosclerosis and patient risk assessment. *Circulation*. 2004; 109 (suppl): III-15–III-19
15. World Health Organization [Internet]. New initiative launched to tackle cardiovascular disease, the world's number one killer. Geneva: World Health Organization; 2016 [updated 2017 Mar 13; Cited 2017 Jul 08]. Available from: http://www.who.int/cardiovascular_diseases/en/
16. Bishop's Weed [Internet]. [Unknown Place]: Bishop's weed; 2017. Available from: <http://www.aku.edu/aboutaku/news/Pages/mortality-rate.aspx>
17. Wikipedia [Internet]. [Place unknown]: [Publisher

- unknown]; 2017 [updated 2017 Jun 17; Cited 2017 Jul 25]. Available from: <https://en.wikipedia.org/wiki/Herbalism>
18. SARS. clinical trials on treatment using a combination of traditional Chinese medicine and western medicine. Geneva: WHO; 2003. pp. 53-61.
 19. World Health Organization [Internet]. traditional medicine strategy 2002–2005. Geneva: World Health Organization; 2002 [Updated 2017 Feb 09; Cited 2017 Jul 23]. Available from: <http://www.who.int/bulletin/volumes/86/8/07-042820/en/>
 20. Javed IM, Akhtar T, Khaliq MZ, Khan G, Muhammad M. Antihyperlipidaemic effect of *Trachyspermum ammi* (T.copticum) in rabbits. In: Faisalabad: Proc 33rd All Pakistan Science Conference University of Agriculture. 2002:80–1.
 21. Srivastava KC. Extract of a spice-omum (*Trachyspermum ammi*)-shows antiaggregatory effects and alters arachidonic acid metabolism in human platelets. *Prostaglandins Leukot Essent Fatty Acids*. 1988;33:16.
 22. G. V. Anrep, G. S. Barsoum, M. Kenawy, and G. Misrahy, “*Ammi visnaga* in the treatment of the anginal syndrome,” *The British Heart Journal*. 1946. vol. 8, no. 4, pp. 171–177.
 23. H. Gilani, Q. Jabeen, M. Ghayur, K. Janbaz, and M. Akhtar, “Studies on the antihypertensive, antispasmodic, bronchodilator and hepatoprotective activities of the *Carum copticum* seed extract,” *Journal of Ethnopharmacology*. 2005 vol. 98, no. 1-2, pp. 127–135.
 24. Javed, M. Z. Khan, F. Muhammad et al., “Antihyperlipidaemic efficacy of *Trachyspermum ammi* in albino rabbits,” *Acta Veterinaria Brno*. 2009 vol. 78, no. 2, pp. 229–236.
 25. Javed, Z. Iqbal, Z. Rahman et al., “Comparative antihyperlipidaemic efficacy of *Trachyspermum ammi* extracts in albino rabbits,” *Pakistan Veterinary Journal*. , 2006. vol. 26, no. 1, pp. 23–29

Conflict of Interest : None
Funding Source: None