The Effect of Combined Administration of Fish Oil with Garlic to Lower Cholesterol in Hypercholesterolemic Subjects (Comparative Study)

Abdil Razzak, A.*
Hnoosh, L. J.

* University of Kufa, College of Pharmacy

Abstract

Background: Garlic and its preparations have been widely recognized as agents for prevention and treatment of cardiovascular and other metabolic diseases, atherosclerosis, hyperlipidemia, thrombosis, hypertension and diabetes.

Elevated total cholesterol, especially low-density lipoprotein has been documented as the leading risk factor for the coronary artery disease. Studies with fish oil supplementation alone have shown an increase in low-density lipoprotein, thereby enhancing the risk associated with incidence of coronary artery disease in hypercholesterolemic subjects. In view of this, the effect of a combined supplementation of fish oil with garlic pearls on the serum lipid profile of hypercholesterolemic subjects was studied.

Methods and Results: We administered 600 mg of fish oil with 500 mg of garlic pearls (garlic oil) per day to 16 hypercholesterolemic subjects with a total cholesterol above 220 mg/dl for 60 days. The effect of this combined supplementation was compared with group that administered 500mg garlic only per day to 16 hypercholesterolemic subjects with a total cholesterol above 220 mg/dl for 60 days also while the comparison done with garlic group(16 hypercholesterolemic subjects) that take only garlic and with a control group (16 hypercholesterolemic subjects) without any supplementation. Significant reductions were seen in all the lipid parameters (except high-density lipoprotein which was increased) in the test groups after 60 days compared to that of the control group. The total cholesterol, low-density lipoprotein, serum triglyceride, very low-density lipoprotein, and the total cholesterol: high-density lipoprotein ratio reduced significantly.

Key Words: Garlic**,** Coronary artery disease, Hypercholesterolemia, Fish oil

الخلاصة

استخدم الثوم في الآونة الأخيرة على نطاق واسع كواحد من العوامل للوقاية والعلاج من أمراض القلب والأوعية الدموية وغيرها من الأمراض الايضية ، وتصلب الشرايين ، تخثر الدم ، وارتفاع ضغط الدم والسكري وتبعا لذلك أجريت هذه الدراسة لبيان تأثير الثوم منفردا ومجتمعا مع زيت السمك في تقليل الكولسترول عند المرضى الذين يعانون من ازدياد مستوى الكولسترول لديهم وقد تم إجراء الفحص على 48 مريضا تم تقسيمهم إلى 3 مجاميع بواقع 16 مريض لكل مجموعة واحدة وكانت المجموعة الأولى هي الضابطة والثانية كانت مجموعة الثوم (500 ملغرام) لوحده والثالثة كانت مجموعة الثوم(500 ملغرام) مع زيت السمك(600 مليغرام) واجري الفحص على هذه العينات مرتان قبل التجربة أو في اليوم الأول وهو الفحص الابتدائي والفحص الثاني كان في نهاية التجربة أو بعد مرور 60 يوما وهو الفحص النهائي.وقد أظهرت النتائج أن الثوم استطاع أن يقلل (بدلالة معنوية) من الارتفاع الحاصل مستوى الكولسترول والأنواع المرادفة له في فحص صورة الدهون الكاملة وان زيت السمك مع الثوم كان تأثيره أقوى من الثوم لوحده (بدلالة معنوية)

Introduction

Coronary artery disease (CAD) is the leading cause of death in developed countries and is emerging as a major cause of death even in developing countries. [1]

Many developing countries face a major challenge of adult morbidity and mortality due to non-communicable diseases especially cardiovascular diseases like CAD and hypertension. [2]

Since a number of studies have revealed the central role of elevated blood cholesterol [especially increased low density lipoprotein (LDL) cholesterol] in the pathogenesis of CAD, it is clear that one of the biggest challenges facing public health authorities and medical practitioners is the control of blood cholesterol in individual patients and at the population level. [3, 4]

Studies with fish oil supplementation [n-3 fatty acid containing eicosapentenoic acid (EPA) and docosahexenoic acid (DHA)] in hypercholesterolemic subjects have shown significant reductions in the serum triglyceride and very low-density lipoprotein (VLDL) concentrations, whereas there was a significant increase in the serum LDL concentration which plays a major role in the development of atherosclerotic CAD. [5, 6]

Griffin [7] has reported that n-3 fatty acids shift LDL away from harmful small dense particles to larger, lighter less pathogenic ones. The Framingham Heart Study and the 4S study have reported that triglyceride levels >100 mg/dl and high-density lipoprotein cholesterol (HDLc) levels < 40 mg/dl are indicators of the presence of harmful small dense LDL-c particles.[8]

Fish oils have been used in the trial involving survivors of myocardial infarction. After 3.5 years of follow-up, the group that received fish oil had a 20% reduction in total mortality, a 30% reduction in cardiovascular death and 45 % decrease in sudden death. [9]

Garlic (or allium sativum) has been used as both food and medicine in many parts of the world [10]. Garlic contains an active substance called 'allicin' and sulphur compounds like diallyl disulphide and allyl propyl disulphide which are responsible for the therapeutic properties of garlic. [11, 12].

In order to provide a more complete management of dyslipidemia with fish oil, it may be beneficial to use an additional nutritional supplement to simultaneously lower LDL concentrations. Supplementation with garlic alone has been found to significantly lower LDL and total cholesterol (TC) concentrations. [10, 11]

The purpose of this study was to determine whether fish oil, when given in combination with garlic pearls could provide an effective and well tolerated nutritional regimen for controlling dyslipidemia which is a well established major risk factor for CAD. [17]

Methods

The subjects in this study were selected based on a simple random sampling technique. The hypercholesterolemic male subjects in the age group of 40-60 years with a serum TC level above 220 mg/dl registered as outpatients in the *Alhakeem hospital*, were included in the study. The sample size was 48 hypercholesterolemic subjects and they were equally divided into three groups (control, garlic alone and garlic +fish) of 16 subjects in each group. [18]

Control group: receive empty capsule orally twice daily.
Garlic group: receive garlic 500mg only orally twice daily [17].
Garlic + fish group: receive combined supplementation of fish oil capsule (Omega-3) containing n-3 fatty acids (eicosapentenoic and docosahexaenoic acid in the ratio 180:120 mg, respectively) with garlic pearls containing 0.25% of pure garlic oil orally twice daily [17].
The measurements of lipid profile were recorded at the beginning of the experiment, so the measurements called ***(initial)*** while the measurements that taken at the end of experiment called ***(final)*** and all measurements have done in

the morning of day of measurements. The study was carried out for a period of 60 days. An interview schedule was used to elicit personal and dietary information / habits of the subjects. The serum lipid profile comprising of serum TC, LDL-c, HDL-c, VLDL-c, triglyceride and TC-HDL ratio was analyzed on the day 1and after 60 days of the study period.

The subjects were asked to consume two garlic pearls and two fish oil capsules daily i.e. one of each after lunch and dinner, respectively. Each gelatin capsule of garlic pearl was of 250 mg and each fish oil capsule was 300 mg. At the end of the study period, diet counseling was given to all the subjects.

Statistical analysis: All data represented as a mean ± S.E.M. statistical significance (P value was 0.05 or less). Paired *t* test used to prove significance between tow means while One-way ANOVA to show comparison between three means of three groups and LSD of post hoc test to show the difference in significance between three groups.

Results

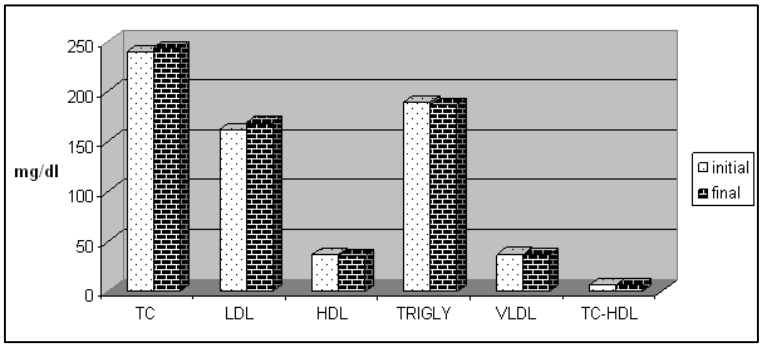
Serum lipid profile of the control group (Table -1-):

The percentage reduction / increment in all the parameters after 60 days of the study period in the control group were as follows: serum TC was increased by 0.6%, LDL by 1.1% and TC-HDL ratio by 3.5%, whereas HDL was decreased by 1.9%, triglyceride by 0.7% and VLDL by 2.1% after 60 days of the study period but all these changes have no significant value

(FIG1)

Table-1- The mean serum lipid parameters of hypercholesterolemic subjects in the control group before and after the study period

Parameters	No	Initial Mean ±SE	final Mean ±SE	p-value
Total cholesterol (mg/dl)	16	239.75±0.288	241.656± 0.217	NS
LDL (mg/dl)	16	162.156± 0.197	163.968± 0.293	NS
HDL (mg/dl)	16	36.312± 0.305	35.625± 0.268	NS
Triglyceride (mg/dl)	16	188.75± 0.534	187.33± 0.266	NS
VLDL (mg/dl)	16	37.156± 0.414	36.375± 0.139	NS
TC-HDL ratio	16	6.562± 0.250	6.783± 0.437	NS



Fig(1) Control group

Serum lipid profile of the garlic group (Table -2-): The percentage reduction / increment in all the lipid parameters after 60 days in the garlic group were as follows: serum TC was reduced significantly by 12.9% (P : **<0.001),** LDL by 20%(P : **<0.001),** triglyceride by 19.4% (P : **0.001),** VLDL by 23.7%(P : **0.001),** TC-HDL ratio by 15.9%(P : **0.001)** and HDL was increased not significantly by 2.7% after 60 days of garlic administration Fig (2).

Table -2-. The mean serum lipid parameters of hypercholesterolemic subjects in the garlic group before and after the study period

Parameters	No	Initial Mean ±SE	final Mean ±SE	p-value
Total cholesterol (mg/dl)	16	247.625±0.597	215.562±0.456	<0.001
LDL (mg/dl)	16	167.562± 0.836	133.562± 0.682	<0.001
HDL (mg/dl)	16	36.187± 0.476	37.1± 0.516	NS
Triglyceride (mg/dl)	16	210.875± 0.499	169.75± 0.461	0.001
VLDL (mg/dl)	16	40.687± 0.480	32.875± 0.286	0.001
TC-HDL ratio	16	6.7938±0.354	5.712± 0.3324	0.001

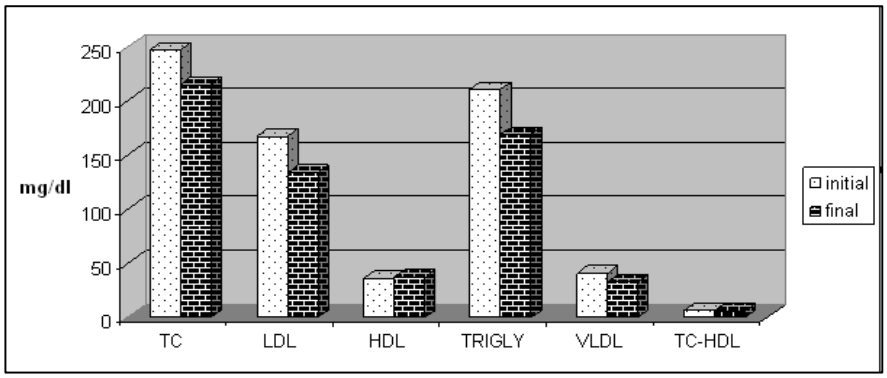


Fig (2) Garlic group

Serum lipid profile of the garlic +fish group (Table -3-): The percentage reduction/increment in all the lipid parameters after 60 days of supplementation in the garlic plus fish group were as follows: serum TC was reduced significantly by 18.5%(P : **0.001),** LDL by 37.9%(P : **0.001),** triglyceride by 36.2%(P : **0.001),** VLDL by 44.7%(P : **0.001),** TC-HDL ratio by 26.3%(P : **0.001)** and HDL was increased significantly by 8.8%(P : **0.001)** after 60 days of garlic plus fish administration Fig (3).

Table -3- The mean serum lipid parameters of hypercholesterolemic subjects in the garlic +fish group before and after the study period

Parameters	**No**	**Initial Mean ±SE**	**final Mean ±SE**	**p-value**
Total cholesterol (mg/dl)	16	247.562±0.547	201.75±0.635	0.001
LDL (mg/dl)	16	166.625± 0.855	103.442± 0.682	0.001
HDL (mg/dl)	16	36.062± 0.347	39.5± 0.408	0.001
Triglyceride (mg/dl)	16	207.665± 0.4	132.325±0.378	0.001
VLDL (mg/dl)	16	41.607± 0.280	23.062± 0.535	0.001
TC-HDL ratio	16	6.837±0.268	5.075±0.226	0.001

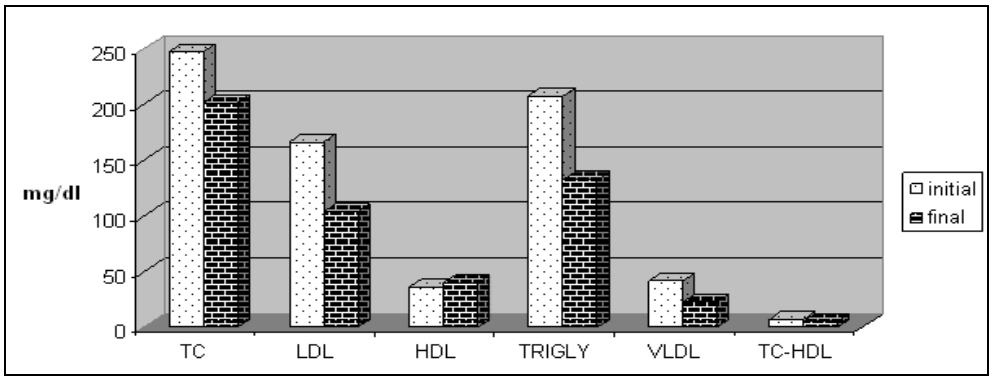


Fig (3) Garlic + Fish group

One-way ANOVA test has done to show the significance between three groups [control, garlic and garlic +fish]. For each parameter in the table the test matches the mean of control with garlic and garlic +fish, also the test matches the mean of garlic with control and garlic +fish and the test matches the mean of garlic +fish with control and garlic .All recordings show the significant values between the means of groups for any parameter in lipid profile. While LSD in post hoc test of SPSS was demonstrated to show the significance differences between the control, garlic, and garlic+fish groups in the table (5).

Table -4- Comparison of changes in the mean lipid parameters of final measurements between the control group, garlic group and garlic+fish group.

Parameters	Group	N	final Mean ±SE	p-value*
Total cholesterol (mg/dl)	control	16	241.656± 0.217	0.000
	garlic	16	215.562± 0.456	
	garlic +fish	16	201.75 ± 0.635	
LDL (mg/dl)	control	16	163.968± 0.293	0.000
	garlic	16	133.562± 0.682	
	garlic +fish	16	103.442± 0.682	
HDL (mg/dl)	control	16	35.625± 0.268	0.000
	garlic	16	37.1± 0.516	
	garlic +fish	16	39.5± 0.4082	
Triglyceride (mg/dl)	control	16	187.33± 0.266	0.000
	garlic	16	169.75± 0.461	
	garlic +fish	16	132.325±0.378	
VLDL (mg/dl)	control	16	36.375± 0.139	0.000
	garlic	16	32.875± 0.286	
	garlic +fish	16	23.062± 0.535	
TC-HDL ratio	control	16	6.783± 0.437	0.000
	garlic	16	5.712± 0.3324	
	garlic +fish	16	5.075±0.226	

Table -5 - Multiple Comparisons of changes in the mean lipid parameters of final measurements between the control group, garlic group and garlic+fish group.

Parameters	(i) group	(j)group	Mean difference (i-j)	Std. Error	Sig	95%Confidence Lower	upper
Total cholesterol (mg/dl)	control	garlic	28.0938	.6636	.000	26.7563	29.4312
		garlic+fish	41.7896	.6746	.000	40.4300	43.1492
	garlic	control	-28.0938	.6636	.000	-29.4312	-26.7563
		garlic+fish	13.6958	.6746	.000	12.3362	15.0554
	garlic+fish	control	-41.7896	.6746	.000	-43.1492	-40.4300
		garlic	-13.6958	.6746	.000	-15.0554	-12.3362
LDL (mg/dl)	control	garlic	35.4063	.8102	.000	33.7734	37.0391
		garlic+fish	35.1687	.8236	.000	33.5089	36.8286
	garlic	control	-35.4063	.8102	.000	-37.0391	-33.7734
		garlic+fish	-.2375	.8236	.004	-1.8974	1.4224
	garlic+fish	control	-35.1687	.8236	.000	-36.8286	-33.5089
		garlic	.2375	.8236	.004	-1.4224	1.8974
HDL (mg/dl)	control	garlic	-1.8750	.5863	.003	-3.0565	-.6935
		garlic+fish	-3.8417	.5960	.000	-5.0427	-2.6406
	garlic	control	1.8750	.5863	.003	.6935	3.0565
		garlic+fish	-1.9667	.5960	.002	-3.1677	-.7656
	garlic+fish	control	3.8417	.5960	.000	2.6406	5.0427
		garlic	1.9667	.5960	.002	.7656	3.1677
Triglyceride (mg/dl)	control	garlic	17.0000	.6099	.000	15.7708	18.2292
		garlic+fish	53.8167	.6200	.000	52.5672	55.0661
	garlic	control	-17.0000	.6099	.000	-18.2292	-15.7708
		garlic+fish	36.8167	.6200	.000	35.5672	38.0661
	garlic+fish	control	-53.8167	.6200	.000	-55.0661	-52.5672
		garlic	-36.8167	.6200	.000	-38.0661	-35.5672
VLDL (mg/dl)	control	garlic	3.5000	.4951	.000	2.5023	4.4977
		garlic+fish	13.4417	.5033	.000	12.4274	14.4559
	garlic	control	-3.5000	.4951	.000	-4.4977	-2.5023
		garlic+fish	9.9417	.5033	.000	8.9274	10.9559
	garlic+fish	control	-13.4417	.5033	.000	-14.4559	-12.4274
		garlic	-9.9417	.5033	.000	-10.9559	-8.9274
TC-HDL ratio	control	garlic	1.0813	9.431E-02	.000	.8912	1.2713
		garlic+fish	1.7138	9.587E-02	.000	1.5205	1.9070
	garlic	control	-1.0813	9.431E-02	.000	-1.2713	-.8912
		garlic+fish	.6325	9.587E-02	.000	.4393	.8257
	garlic+fish	control	-1.7138	9.587E-02	.000	-1.9070	-1.5205
		garlic	-.6325	9.587E-02	.000	-.8257	-.4393

Discussion

The recording measurements were high for all the lipid parameters in the control group except for serum triglyceride and VLDL which were within the normal range. A value of < 200 mg/dl for triglyceride and <40 mg/dl for VLDL is considered normal. A strong positive association between elevated serum cholesterol and CAD has been reported in observational, interventional and epidemiologic studies [2]. The Framingham Heart Study has indicated a three-fold increase in the risk of CAD mortality with TC levels above 240 mg/dl [4]. The Helsinki Heart Study has reported a 2% rise in CAD risk with 1% increase in LDL levels [13, 14]. A slight reduction was seen in the triglyceride and VLDL levels of the subjects after the study period. The TC-HDL ratio (coronary risk ratio) which is an important determinant of CHD risk was significantly increased by 3.5%, thereby indicating the need for effective treatment of the coronary risk factors which will reduce the incidence of CAD. A slight reduction was seen in the HDL level after the study period. The Multiple Risk Factor Intervention Trial (MRFIT) and the Framingham Heart Study have reported an increase in CAD risk by 3% in men and 34% in women with every milligram decrease in HDL level [8, 15].

In our study, there was a statistically significant reduction in all the serum lipid parameters (except increase in HDL-c) after 60 days of the supplementation period (Fig.3) in the garlic+fish group. The serum TC reduced significantly from 241.656± 0.217mg/dl (high risk level) to 201.75±0.635mg/dl which is the cut-off for the normal cholesterol level according to NCEP classification [2]. A statistically significant reduction was found in the serum LDL level from 166.625± 0.855mg/dl to 103.442± 0.682 mg/dl after the supplementation period. The fish oil alone induced rise in LDL as reported by Adler and Holub [5] and Connor and Connor, [6] that was not seen in this study. The serum HDL had significantly increased by 8.8 %. Elevated triglycerides, which were associated with multiple metabolic abnormalities including low HDL, small dense LDL, insulin resistance and a subsequent risk for CAD, had significantly decreased to normal levels after the supplementation period [4].

Hypertriglyceridemia has been reported as a more powerful risk factor for CAD than TC alone, especially in females [14]. The hypotriglyceridemic effect of fish oil was brought about by an inhibition of hepatic fatty acid synthesis by EPA and DHA and by impaired triglyceride synthesis [6, 16] The TC-HDL ratio had significantly reduced by 26.3 % after the supplementation period, thereby reducing the risk of CAD.

When comparing the changes in the mean serum lipid profile between initial measurements and final measurements in the control and test groups (garlic alone and garlic+fish), it was shown that there was a significant reduction in the serum TC, LDL, triglycerides, VLDL and TC-HDL ratio and a significant increase in the HDL-c in the garlic group and garlic+fish group as compared to that of the control group, but this comparison with control shown be larger in garlic+fish than garlic alone as shown by table-5- . In the control group, the major risk factors for CAD, i.e. the serum TC, LDL and TC-HDL ratio increased and HDL was found to decrease after 60 days of the study period. A slight reduction was seen in triglycerides and VLDL levels. Due to financial constraints, the effect of this combined supplementation of fish oil with garlic pearls could not be compared with fish oil supplementation alone.

Conclusions

Garlic shows significant decreases in lipid profile in hypercholesterolemic but this effects greatly potentiated by fish oil. A co-administration of garlic oil with fish oil seems to be beneficial. This finding needs to be confirmed by larger trials comparing this combination with fish oil alone.

Acknowledgements

We are especially thankful to Dr ABDIL KAIREEM ALMYAAH for his expert guidance to perform statistical analysis.

References

1. Marmot M, Elliot P. *Coronary Heart Disease Epidemiology*, 1st ed, Oxford University Press, London, 1992; pp 299-305
2. Braunwald E. *Heart Disease: A textbook of Cardiovascular Medicine*,5th ed. WB Saunders Company, USA, 1997; pp 1176-1180
3. Kannel WB, Wilson PW. An update on coronary risk factors. *MedChin North Am* 1995; 79: 951–971
4. Sethi KL. Coronary artery disease in Indians. *Cardiology Today* 1997;2: 21–26
5. Adler AJ, Holub BJ. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. *Am J Clin Nutr* 1997; 65: 445–450
6. Connor SL, Connor WE. Are fish oils beneficial in the prevention and treatment of coronary artery disease? *Am J Clin Nutr* 1997; 66 (Suppl 4): 1020–1031
7. Griffin BA. The effect of n-3 fatty acids on low density lipoprotein subfractions. *Lipids* 2001; 36 (Suppl 5) : S97
8. Enas A, Mehta J. Malignant coronary artery disease in young Asian Indians: thoughts on pathogenesis, prevention and therapy.*Cardiothorac J* 3; 26–30
9. GISSI-Prevenzione investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1991; 354:447–455
10. Krishnamoorthy S. *Onions and Garlic*, 2nd ed, DK Publishers, NewDelhi, 1995; pp32-54
11. Bordia A, Verma SK, Srivastava KC. Effect of garlic (Allium sativum) on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease. *Prostaglandins Leukot EssentFatty Acids* 1998; 58: 257–263
12. Lau HS. Anticoagulant and lipid regulating effects of garlic. *Lancet*1988; 4: 150–156
13. Biyani MK, Sheorey DS. Carotenes: a ray of hope in prevention of cardiovascular disorders, cancers and cataract. *J Assoc Physicians India* 1994; 42: 899–903
14. Morell JM, Betteridge DJ. *Lipids and Coronary Heart Disease*, 1st ed.

Panther Publishers Limited, Bangalore, 2001; pp 332-338

15. Schlant RC, Wayne R. *Hurst's The Heart- Arteries and Veins*,8th ed. Mc.Graw-Hill Inc, New York, 1994;pp 978-986
16. Connor WE. Omega-3 fatty acids and heart disease. *Atherosclerosis* 1994; 109: 201–203
17. Sheba Jeyaraj, Gomathy Shivaji, SD Jeyaraj, A Vengatesan .Effect of Combined Supplementation of Fish Oil with Garlic Pearls on the Serum Lipid Profile in Hypercholesterolemic Subjects (Indian Heart J 2005; 57: 327–331)
18. Mathew BC 1, Prasad NV 2, Prabodh R3. Cholesterol-Lowering effect of organosulphur compounds from garlic: a possible mechanism of action. Kathmandu University Medical Journal (2003) Vol. 2, No. 2, Issue 6, 100-102