



# INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND DEVELOPMENT (IJPRD)

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## SINGLE BLIND PLACEBO CONTROLLED COMPARATIVE STUDY OF HYPOLIPIDEMIC EFFECTS OF KALONJI AND ATORVASTATIN

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### ABSTRACT

*Hyperlipidemia can cause coronary vascular disease, partial or complete heart block leading to mortality if untreated for long time. Conventional hypolipidemic drugs some time have low compliance for chronic hyperlipidemic patients and concerned cardiologist. To get good compliance of therapeutic goal of hypolipidemic agents by physician and patient, some herbal drugs have had been used by some expert cardiologists. Among those herbal medicines Kalonji is most important drug used as hypolipidemic agent. In this research work hypolipidemic effects of kalonji are compared with standard allopathic hypolipidemic agent ATORVASTATIN. It was single blind placebo-controlled comparative study, conducted at LIPID RESEARCH CLINIC, Jinnah Hospital, Lahore, Pakistan from January to March 2011. Ninety hyperlipidemic patients were enrolled after written and well explained consent approved by Research Approval Committee, Jinnah Hospital, Lahore. All patients were divided in three groups, one group as placebo and other two groups for atorvastatin and kalonji. After six weeks research proved 39.47 mg/dl decrease in LDL-cholesterol and 6.14 mg/dl increase in HDL-cholesterol by using 20 mg of atorvastatin in 30 hyperlipidemic patients. Kalonji increased 3.49 mg/dl HDL-cholesterol and 11.37 mg/dl decrease in LDL-cholesterol in six weeks therapy. Change in both lipid parameters is statistically significant. We concluded from this research work that kalonji seeds or its oil may be used to lower serum lipids effectively in mild to moderate Hyperlipidemia.*

**Key words:** Atorvastatin. Kalonji. Low Density Lipoprotein cholesterol. High Density Lipoprotein cholesterol.

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## INTRODUCTION

There has been renewed interest in the protective role of high-density lipoprotein (HDL) against atherosclerosis and Coronary Vascular Disease. Patients with central obesity, insulin resistance, hypertension, and type 2 diabetes mellitus, conditions associated with the metabolic syndrome, have a unique dyslipoproteinaemia characterised by hypertriglyceridaemia, elevated levels of apolipoprotein B, small dense low-density lipoprotein (LDL) cholesterol, and low levels of HDL-cholesterol. These lipoproteins represent major cardiovascular risk factors in these conditions. Although the focus in treating lipid disorders is on reducing LDL-cholesterol concentrations, additional lipid-related independent risk factors, such as triglyceride, HDL-cholesterol, and lipoprotein (a) levels should be used clinically to assess cardiovascular risk. Among other factors, lipoprotein lipase, hepatic lipase, lecithin: cholesterol acyltransferase, and cholesteryl ester transfer protein play an important role in abnormal HDL metabolism in insulin resistance and type 2 diabetes mellitus. Insights gained from study of the postprandial state on atherosclerosis and Cardiovascular Disease may also aid in risk assessment.<sup>1</sup> Conventional hypolipidemic therapy by statins, Nicotinic acid, resins and Fibrates is well established, but they have side effects and low compliance. To combat these problems scientist are going to determine lipid lowering effects of some plants, like Kalonji, nuts, bitter melon (*Momordica charantia*), Chlorophytum borivilianum root, *Sempervivum tectorum* extract, garlic, *Milletia pinnata*, stone apple (aegle marmelos) etc. Among lipid lowering drugs, HMG-CoA reductase inhibitors are widely used drugs for lowering so called “bad” cholesterol and increasing “good” cholesterol.<sup>2,4,9</sup> Statins (or HMG-CoA reductase inhibitors) are a class of drugs used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase, which plays a central role in the production of cholesterol in the liver. Increased cholesterol levels have been associated with cardiovascular diseases, and statins are therefore used in the prevention of these diseases.

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Evidence has found that they are most effective in those with cardiovascular disease (secondary prevention), with questionable benefit in those without previous Cardiovascular Disease but with elevated cholesterol levels. Statins have rare but severe adverse effects, particularly muscle damage, and some doctors believe they are overprescribed.<sup>3-9</sup> In South Asia *Nigella sativa* is known as Kalonji, its Arabic name is Habat-ul-Sauda and its English name is Black cumin. The plant is widely grown in different parts of the world and is an annual herb cultivated in India. As an oriental spice, *Nigella sativa* has long been used as a natural remedy for the treatment of many acute as well as chronic diseases. This plant has been a great focus of research and has several traditional uses and consequently has been extensively studied for its chemical constituents and biological activities.<sup>10</sup>  $\beta$ -Sitosterol inhibits cholesterol absorption in the intestine.<sup>11</sup> When the sterol is absorbed in the intestine, it is transported by lipoproteins and incorporated into the cellular membrane.<sup>12</sup> Phytosterols and phytostanols both inhibit the uptake of dietary and biliary cholesterol, decreasing the levels of LDL and serum total cholesterol. Because the structure of  $\beta$ -sitosterol is very similar to that of cholesterol,  $\beta$ -sitosterol takes the place of dietary and biliary cholesterol in micelles produced in the intestinal lumen. This causes less cholesterol absorption in the body.<sup>12</sup>

## MATERIAL & METHOD

The designed research was comparative single blind study, which was conducted at Jinnah Hospital, Lahore from January 2011 to March 2011. Ninety hyperlipidemic patients were enrolled, excluding individuals having alcohol intake history, patients of diabetes mellitus, renal disease, hepatic disease, hypothyroidism, peptic ulcer. Written and explained consent was taken from all participants. Important data like name, age, gender, occupation, residential address, phone/contact number, previous medical history, disease in family history, drug history was recorded in specific Performa. Three groups I, II, and III were made (30 patients in each group). Group-I was allocated for placebo, to take placebo capsule once daily, after breakfast for

six weeks. Group-II was advised to take atorvastatin 20 mg, once daily after breakfast for the period of six weeks. Group-III was advised to take 2 tea spoons of kalonji after breakfast for the period of six weeks. Their base line LDL-cholesterol and HDL-cholesterol level was measured and kept in record. They were advised to come fortnightly at LIPID CLINIC at Jinnah Hospital, Lahore for follow up. Their serum was taken at follow up visits for lipid profile. Serum LDL-cholesterol was calculated by formula (LDL-Cholesterol = Total Cholesterol - (Triglycerides/5 + HDL-Cholesterol). Serum HDL-cholesterol was determined by using kit Cat. # 303210040 by Eli Tech Diagnostic, France. Data were expressed as the mean  $\pm$  SD and "t" test was applied to determine statistical difference in results. A p-value  $>$  0.05 was considered as non-significance and P-value  $<$  0.001 was considered as highly significant change in the results.

## RESULTS

After six weeks of treatment with kalonji and atorvastatin, results were summed up in mean values of LDL-cholesterol and HDL-cholesterol in three groups. Results were analyzed biostatistically using Statistical Product and Service Solutions (SPSS) version 19. In placebo group (group-I), LDL-cholesterol decreased from 160.41 $\pm$ 2.22 mg/dl to 159.90 $\pm$ 3.61 mg/dl. This change is 0.51 mg/dl, which is statistically non-significant (p-value  $>$ 0.05). High density lipoprotein cholesterol in this group

increased from 34.79 $\pm$ 2.11 to 35.06 mg/dl, which is statistically non significant change (p-value  $>$ 0.05). In group II, out of 30 hyperlipidemic patients, 27 patients completed over all study period. Two patients withdrew taking drug due to their personal problems and one due to side effects of atorvastatin. LDL-cholesterol in this group decreased from 180.11 $\pm$ 1.71 to 140.64 $\pm$ 2.74 mg/dl in six weeks. In mean values it is 39.47 mg/dl decrease and in percentage it is 98.70 % change in results, when placebo and drug group were compared. This change is highly significant statistically (p=  $<$ 0.001). HDL-cholesterol in this group increased from 33.99 $\pm$ 3.01 to 40.13 $\pm$ 3.07 mg/dl. Over all it is 6.14 mg/dl increase, but in percentage it is 95.60 % increase, which is highly significant change with probability value  $<$  0.001. In group III, two patients discontinued to take kalonji due to its bizarre taste and 28 patients out of 30 completed study period. LDL-cholesterol in this group decreased from 163.66 $\pm$ 2.21 to 152.29 $\pm$ 1.92 mg/dl, which in percentage 95.51 % decrease. It is highly significant change (p-value  $<$  0.001). HDL-cholesterol in this group as mean value at baseline was 34.17 $\pm$ 3.71 mg/dl, which increased to 37.66 $\pm$ 2.90 mg/dl in six weeks, which is statistically significant (p-value  $<$  0.01). Values of both parameters at baseline and after treatment with all aspects of differences and p-values are shown in following table.

**Table:** Showing sample size of groups, baseline and after treatment values, difference in mean values of LDL-C, HDL-C, difference in mean values of drug groups as compared to Placebo group and Difference in percentage

Groups	Baseline values	After treatment	Diff bw day-0 & day-45 in mg/dl (Diff bw placebo and drug group) Difference in percentage	p-value
I (n=30)	LDL-c=160.41 $\pm$ 2.22 HDL-c=34.79 $\pm$ 2.11	LDL=159.90 $\pm$ 3.61 HDL=35.06 $\pm$ 2.91	0.51 0.27	$>$ 0.05 $>$ 0.05
II (n=27)	LDL-c=180.11 $\pm$ 1.71 HDL-c=33.99 $\pm$ 3.01	LDL=140.64 $\pm$ 2.74 HDL=40.13 $\pm$ 3.07	39.47 (38.96) 98.70% 6.14 (5.87) 95.60%	$<$ 0.001 $<$ 0.001
III (n=28)	LDL-c=163.66 $\pm$ 2.21 HDL-c=34.17 $\pm$ 3.71	LDL=152.29 $\pm$ 1.92 HDL=37.66 $\pm$ 2.90	11.37 (10.86) 95.51% 3.49 (3.22) 92.26%	$<$ 0.001 $<$ 0.01

KEY: All parameters are measured in mg/dl, n stands for sample size, LDL-c stands for low density lipoprotein cholesterol, HDL-c stands for high density lipoprotein cholesterol, p-value  $>$ 0.05 indicate non-significant,  $<$ 0.01 indicate significant and  $<$ 0.001 indicate highly significant change in results.

## DISCUSSION

Lipoproteins in serum are carriers of lipids and proteins all over the circulatory system. In excess amount low density lipoprotein cholesterol in blood cause oxidation and production of free radicals, leading to increased oxidative stress, eventually development of atherosclerosis. In this study hypolipidemic drug atorvastatin decreased LDL-cholesterol 98.70 % by six weeks treatment. HDL-cholesterol increased 95.60 % by taking this drug for six weeks. In mean values LDL decreased 39.47 mg/dl and HDL-C increased 6.14 mg/dl in six weeks treatment. These results match with El-Dakhkhny M<sup>13</sup> who proved that 20 mg of atorvastatin decreased 35.12 mg/dl serum LDL-cholesterol, and HDL increased 7.11 %. His sample size was 45 hyperlipidemic patients. Results of our study also match with results of research work conducted by Bustos C et al<sup>14</sup> who observed 30.90 mg/dl decrease in serum LDL-cholesterol and 5 % increase in HDL-cholesterol in animal models. They used atorvastatin in albino rats. These results also match with results of research conducted by Nawrocki BJW et al<sup>15</sup> who observed almost same changes in LDL and HDL-cholesterol in 200 hyperlipidemic patients, suggesting very effective role of HMG CoA reductase inhibitors to raise “good” cholesterol (HDL-C) and to lower “bad” cholesterol (LDL-C). These results are in contrast with results of study conducted by Hussein O et al<sup>16</sup> who proved lesser effect of HMG-CoA reductase inhibitors on LDL-cholesterol and HDL-cholesterol in 13 hyperlipidemic patients. They observed only 14 % decrease LDL-cholesterol and 7.16 % increase in HDL-cholesterol after administration of 20 mg fluvastatin for the period of one month. Remarkable difference in results of two research studies may be due to small sample size and lesser exposure of drug in their research work. These results match with results of research study conducted by O’ Driscoll et al<sup>17</sup> who observed 12.88 mg/dl decrease in LDL-cholesterol and 4.09 % increase in HDL-cholesterol when atorvastatin 20 mg OD dose for the period of one month was used in hyperlipidemic patients. Kalonji used for centuries for medicinal and culinary purposes and Available online on [www.ijprd.com](http://www.ijprd.com)

reported to possess a number of pharmacological properties, including antioxidant, anti-inflammatory, hypoglycemic, antihypertensive and antihyperlipidemic properties. In our research kalonji decreased LDL-cholesterol 11.37 mg/dl and increased HDL-cholesterol 3.49 mg/dl in six weeks therapy. These results match with results of study conducted by Chaudhary et al<sup>18</sup> who observed 13.99 mg/dl decrease in low density lipoprotein cholesterol and 4.96 mg/dl increase in high density lipoprotein cholesterol in 24 albino rats by administration of one teaspoon of kalonji oil for the period of 4 months. Our results do not agree with results of study conducted by Abdul Sattar et al<sup>19</sup> who observed/proved 19.03 mg/dl decrease in LDL-cholesterol and 14.57 mg/dl increase in HDL-cholesterol, when they used one spoon of kalonji in 50 albino rats for the period of 3 months. Difference in results of our and their study may be due to some another mechanism in animal models that can cause LDL-cholesterol reduction and remarkable increase in HDL-cholesterol. But they have not mentioned the different mechanism of action. Abdellatif Settaf et al<sup>20</sup> have proved lesser effects of Kalonji when they used it in 100 hyperlipidemic-induced albino rats. They proved that Kalonji decreased LDL-cholesterol about 3.77 mg/dl in six weeks treatment in hyperlipidemic-induced rats. They did not mentioned about change in high density cholesterol. Results of our research are in contrast with results of Bamos AO et al<sup>21</sup> who observed 19.00 mg/dl decrease in low density lipoprotein cholesterol and 11.77 mg/dl increase in high density lipoprotein cholesterol in 15 hyperlipidemic patients also suffering from diabetes mellitus when two tea spoons of kalonji oil were used for the period of one and half month in these patients. The suggestive mechanism of action of kalonji in this case or either may be due to  $\beta$ -Sitosterol content of kalonji which inhibits cholesterol absorption in the intestine.<sup>11</sup> When the sterol is absorbed in the intestine, it is transported by lipoproteins and incorporated into the cellular membrane. Phytosterols and phytostanols both inhibit the uptake of dietary and biliary cholesterol, decreasing the levels of LDL and serum total

cholesterol. Because the structure of  $\beta$ -sitosterol is very similar to that of cholesterol,  $\beta$ -sitosterol takes the place of dietary and biliary cholesterol in micelles produced in the intestinal lumen. This causes less cholesterol absorption in the body.<sup>12</sup>

## CONCLUSION

It was concluded from this research study that to get good patient and doctor/physician compliance regarding treatment or prevention of chronic illness like Hyperlipidemia, herbal medicines work, though not equal to but at least near to as good effects as allopathic drugs. It is hereby recommended reference to this research results that kalonji seeds or its oil is very effective as hypolipidemic agent used for prevention of cardiovascular diseases eventually leading to morbidity or mortality due to Myocardial Infarction or Heart Block.

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