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ALTERNATIVE THERAPIES FOR OXIDATIVE STRESS

Abdul Qudoos, Ajaz Fatima., Asia Firdous., M. Iqbal., Mohsin Ali Hassni & Shah Murad

Professor of Pharmacology, HBSMDC, Islamabad Pakistan
HOD/Prof of Pharmacology at LMDC, Lahore Pakistan
Associate Professor of Pharmacology at LMDC, Lahore Pakistan.
Assoc Prof of Microbiology at QIMS/CMH, Quetta Pakistan.
Research Scholar at CASVAB, UOB, Quetta Pakistan.
Professor of Pharmacology at QIMS/CMH, Quetta Pakistan

ABSTRACT

Free radicals such as reactive oxygen species (ROS) induce oxidative stress and cause cellular damage due to lipid peroxidation. There are three important steps in lipid peroxidation, namely initiation, propagation and termination. Formation of reactive aldehydes such as MDA and 4-HNE takes place when there is a catabolism of lipid hydroperoxides. Hyperlipidemia especially LDL-cholesterol may lead to development of coronary artery disease causing morbidity or mortality due to cardiac arrhythmias. Conventional hypolipidemic drugs have unwanted effects. Herbal therapy for Hyperlipidemia is getting attention due to their less frequent side effects. In this study we have compared hypolipidemic effects of Gemfibrozil with Nigella sativa. Seventy five hyperlipidemic patients from Jinnah Hospital Lahore were enrolled for study. After getting consent all patients were divided in three groups comprising 25 patients in each group. Group 1 was on Nigella sativa, group 2 was on Gemfibrozil and third group was on placebo therapy. They were advised to take drugs for two months. After completion of study pretreatment and post treatment values of LDL cholesterol were analyzed statistically. In Nigella sativa group LDL cholesterol decreased from 191.14 ± 3.45 to 159.40 ± 2.98 mg/dl, means 31.7 mg/dl LDL reduction was observed when compared with placebo group. In Gemfibrozil group of patients LDL cholesterol decreased from 197.77 ± 3.91 mg/dl to 159.62 ± 2.20 mg/dl, means LDL reduction in mean values was 38.2 mg/dl, when compared with placebo group. These changes are highly significant with p-values of <0.001 . We concluded from this study that alternative therapy by herbal medication is as effective as by allopathic medication. Key words: serum lipids, oxidative stress, lethality, toxicity.

INTRODUCTION

Vascular dysfunction mediated by homocysteine is known to be linked to oxidative stress and impaired NO system. Plasma level of MDA was elevated with a decreased NO level in rat treated with homocysteine. In addition, there was a deterioration of vasodilatation in rats. Mitogen-activated protein (MAP) kinases include extracellular signal-regulated kinase (ERK), c-Jun NH₂-terminal kinase (JNK) and p38 MAP kinase. They are important in stress-induced cellular responses including vascular remodeling. An antioxidant defense system consisting of enzymes and non-enzymatic compounds prevents oxidative damage of lipoproteins in the plasma. When the activity of this system decreases or the reactive oxygen species (ROS) production increases, an oxidative stress may occur. Since fatty acids and triglyceride-rich emulsions can stimulate leukocytes to produce ROS, it is conceivable that raised plasma triglyceride-rich lipoproteins such as very low density lipoprotein (VLDL) may overload the antioxidant system. Use of saturated fats cause LDL oxidation in systemic circulation and formation of atherosclerosis and may develop coronary artery disease.^{1,3-9} In some cases, a blood clot may totally block the blood supply to the heart muscle, causing heart attack. If a blood vessel to the brain is blocked, usually from a blood clot, an ischemic stroke can result.^{2,10} Hypolipidemic drugs can be used to treat hyperlipidemia, CAD, heart

arrhythmias and cardiac arrest. Allopathic drugs used to prevent or cure Hyperlipidemia include Statins, Fibrates, niacin and bile acid binding resins.^{3,8} Gemfibrozil increases plasma HDL levels by stimulating their synthesis. Increased transport (turnover) of HDL induced by gemfibrozil may be significant in increasing tissue cholesterol removal in hyperlipidemic patients.^{4,7} Furthermore Fibrates treatment results in the formation of LDL with a higher affinity for the LDL receptor, which are thus catabolized more rapidly.⁵⁻⁷ Nigella sativa or kalonji contains conjugated linoleic acid, thymoquinone, melanthin, nigilline, damascenine, and trans-anethole. Thymoquinone (TQ) extracted from Nigella sativa (kalonji) inhibits iron-dependent microsomal lipid peroxidation. Stimulation of polymorphonuclear leukocytes with thymoquinone works as protector against damaging effects of free radicals generated biochemically in human body. Hypolipidemic drugs can be used to treat hyperlipidemia, CAD, heart arrhythmias and cardiac arrest. Allopathic drugs used to prevent or cure Hyperlipidemia include Statins, Fibrates, niacin and bile acid binding resins¹⁰.

PATIENTS & METHOD

Research study design was single blind placebo-controlled, and was conducted at Jinnah Hospital, Lahore from February 2022 to July 2022. Seventy five hyperlipidemic patients were selected for research work. Written consent was taken

from all patients. Specific Performa was designed for the research work. Seventy five newly diagnosed primary hyperlipidemic patients were selected with age range from 18 to 70 years. Exclusion criteria were hypothyroidism, diabetes mellitus, alcohol addictive patients, peptic ulcer, any gastrointestinal upset, renal impairment, and any hepatic or cardiac problem. All patients were divided in three groups (group-A, group-B, group-C), 25 in each group. Their baseline experimental data was taken and filed in specifically designed Performa, at start of taking medicine, like lipid profile, blood pressure and pulse rate. The study period was eight weeks. Twenty five patients of group-A were advised to take one tea spoon of Nigella sativa (Kalonji), twice daily, i.e.; one tea spoon after breakfast and one tea spoon after dinner. Twenty five patients of group-B were advised to take Gemfibrozil 600 mg tablets, one after breakfast and one after dinner. Twenty five patients were provided placebo capsules, (containing grinded wheat), taking one capsule after breakfast and another before going to bed. All participants were advised to take these medicines for eight weeks. They were also advised for 20 minutes brisk walk at morning or evening time. Patients were called every 2 weeks for follow up to check blood pressure, weight, pulse rate and general appearance of the individual. Drug compliance to the regimen was monitored by interview and counseling at each clinical visits. Serum LDL-cholesterol was calculated by Friedwald formula (LDL-

Cholesterol = Total Cholesterol-(Triglycerides/5 +HDL-Cholesterol). Data were expressed as the mean \pm SD and "t" test was applied to determine statistical significance as the difference. A probability value of <0.05 was considered as non-significant and $P<0.001$ was considered as highly significant.

RESULTS

When results were compiled and statistically analyzed, it was observed that Nigella sativa and Gemfibrozil decreased LDL-cholesterol significantly. Nigella sativa decreased LDL cholesterol from 191.14 ± 3.45 mg/dl to 159.40 ± 2.98 mg/dl. This change in mean values was 31.7 mg/dl with highly significant p-value of <0.001 . Gemfibrozil decreased LDL cholesterol from 197.77 ± 3.91 mg/dl to 159.62 ± 2.20 mg/dl. In mean values this change was 38.2 mg/dl with highly significant p-value of <0.001 . Placebo group showed LDL cholesterol reduction from 163.10 ± 1.45 mg/dl to 159.40 ± 1.77 mg/dl. This change in mean values was 3.7 mg/dl, with non-significant p-value of >0.05 .

DISCUSSION

From a young age, cholesterol-laden plaque due to increase level of LDL cholesterol can start to deposit in the blood vessel walls. As individual get older, the plaque burden builds up, inflaming the blood vessel walls and raising the risk of blood clots and heart attack. The plaques release chemicals that promote the process of healing but make the inner

walls of the blood vessel sticky. Then, other substances, such as inflammatory cells, lipoproteins, and calcium that travel in bloodstream start sticking to the inside of the vessel walls. To escape from victimization of heart attack or heart arrhythmias, blood cholesterol levels must be kept at normal range. Hypolipidemic drugs include Statins, Fibrates, Niacin, and Bile acid binding resins. These drugs have low patient and doctor compliance due to their side effects. So herbal medicine is going to be popular even in western world. Nigella sativa is one of those medicinal herbs which is used in more than 100 diseases all over the world. In this study we have compared LDL cholesterol lowering effects of traditional drug Gemfibrozil with medicinal herb Nigella sativa. Nigella sativa when used by 25 hyperlipidemic patients for two months, it reduced LDL cholesterol 31.7 mg/dl. Statistically this change is highly significant. Our results match with results of study conducted by N. A. Zeggwagh et al¹¹ who proved 28.99 mg/dl reduction in LDL cholesterol in 45 hyperlipidemic patients. Their results support our study results. Change in LDL cholesterol in our results are in contrast with results of study conducted by Han SH et al¹² who proved much less reduction in LDL cholesterol when Nigella sativa was used in 100 hyperlipidemic patients for one month. Reason for this contrast may be due to their large sample size and less exposure of patients to take Nigella sativa for only four weeks. They have also explained mechanism of action of Nigella sativa that

how these agents act as antioxidant. Nigella Sativa oil with its potent free radical scavenging properties, inhibits subarachnoid-haemorrhage-(SAH-) induced lipid peroxidation of the brain tissue against the reactive hydroxyl, peroxy, and superoxide radicals. This mechanism is also quoted by F. R. Dehkordi and A. F. Kamkhah.¹³ In our study Gemfibrozil decreased LDL cholesterol 38.2 mg/dl which is highly significant change when analyzed statistically. These results match with results of study conducted by Vuorio A¹⁴ who observed LDL reduction by 600 mg of Gemfibrozil used by 10 patients for 2 weeks. Their results support our results. They explained five mechanisms that how Fibrates make plasma cholesterol levels at normal range. No:1. By induction of lipoprotein lipolysis 2. By induction of hepatic fatty acid (FA) uptake and reduction of hepatic triglyceride production. 3. by increased removal of LDL particles. 4. By reduction in neutral lipid (cholesteryl ester and triglyceride) exchange between VLDL and HDL may result from decreased plasma levels of triglyceride rich lipoproteins (TRL). 5. By increase in HDL production and stimulation of reverse cholesterol transport. Our results do not match with results of study conducted by Dellavalle RP¹⁵ who proved that LDL reduction by Gemfibrozil is not significant if used even for three months. Reason for this contrast may be due to lesser dose of Gemfibrozil ie; 300 mg once daily for three months. In their results LDL cholesterol reduction was only 18.53 mg/dl.

Research conducted by Dasgupta S et al proved that if Gemfibrozil is used in therapeutic dose for long term therapy, it can reduce LDL cholesterol and prevent hyperlipidemic patients from being victimized by CAD, cardiac arrest and cardiac arrhythmias.

CONCLUSION

We concluded from this research that patient compliance for hypolipidemic agents of herb origin may be good due to their less intensity and frequency of side effects, as observed and experienced by taking traditional hypolipidemic drug Gemfibrozil.

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