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Active ingredients of the herb decrease Apo proteins synthesis required for structural existence of LDL Particles

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Abstract

Introduction: Hyperglycemia and hyperlipidemia are main risk factors for coronary artery disease like syndrome leading to morbidity, and mortality. This syndrome may be prevented by allopathic as well as herbal medicines like *Nigella sativa* and fibrates. Conventional allopathy related drugs have unwanted effects. Herbal therapy for hyperlipidemia well as diabetes mellitus type-2 (DMT2) is getting attention due to their less frequent side effects. In this study we have compared hypolipidemic effects of Fenofibrate 40 mg with *Nigella sativa*.

Sample size and study area: Seventy five hyperlipidemic and DM type-2 patients from National Hospital Lahore were enrolled for study.

Consent, grouping in sample size and Advise to patients: 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 600 mg BD plus Glibenclamide 5 mg BD and third group was on placebo therapy. They were advised to take drugs for two months.

Results: 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. Fasting Blood Sugar (FBS) in this group decreased from 210 mg/dl to 180 mg/dl in two months which is significant change in this parameter. In Fenofibrate 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 . FBS in this group decreased from 219.65 ± 1.10 to 171.76 ± 2.04 mg/dl which is highly significant change in the parameter.

Conclusion: We concluded from this study that herbal medicine *Nigella sativa* is as effective hypoglycemic/hypolipidemic agent as traditionally used hypolipidemic drug Fenofibrate, and hypoglycemic drug Glibenclamide.

Keywords: Ingredients, structural, LDL, FBS

Introduction

Sometimes, atherosclerotic plaques burst open and cause the blood cells that form clots (called "platelets") to rush into the artery around the plaque. This then causes blood clots and further luminal narrowing. These blood clots can become large enough to block arterial blood flow to your heart, which leads to a heart attack. In the event of a heart attack, your heart muscle will start to die within the territory downstream from the blocked coronary artery. Increased blood sugar, and blood lipids levels can cause metabolic syndrome leading to develop coronary artery disease (CAD) syndrome. This syndrome can lead to morbidity and mortality due to myocardial infarction (MI) [1]. Increased blood sugar and lipid levels cause oxidative stress leading to damage various tissues of vital organs like liver, kidney, brain, heart, and lungs [2]. Increased sugar levels in blood can cause damage to renal, and cardiac microcirculation leading to cause cardiac and renal impairment, finally to failure of these organs [3]. High lipids levels in blood initiate oxidation of LDL particles leading to formation of atherosclerotic plaques and CAD [4]. In allopathy Glibenclamide is widely used to decrease blood sugar level which binds to ATP-sensitive K channels and inhibit sulfonylurea receptors in pancreatic beta cells leading to opening of Ca-channels which consequence to release insulin in blood circulation [5]. Gemfibrozil is used in allopathy as hypolipidemic agent which decrease synthesis of triacylglycerol (TGs), VLDL, and LDL in blood.

This phenomenon causes decrease in LDL oxidation. This drug also enhances formation of apoproteins required to mature high density lipoproteins (HDL) in blood [6-8]. Allopathy related drugs compliance is narrow so herbal medications are being used to treat dyslipidemia and DMT2 [9]. One of the important herb used to treat DMT2, and dyslipidemia is *nigella sativa* (Kalwanji). Extracts of this herb contains transanethole, thymoquinone, linoleic acid, melanthin, Nigilline, and damascenine [10-13]. These active ingredients of the herb decrease apoproteins synthesis required for structural existence of LDL particles, and increases those apoproteins which give structural potential to good lipid carrier lipoproteins; Eg HDL. These active ingredients also work as allopathy related drug used in DMT2 ie; Glibenclamide [14].

Patients & Method

National Hospital Lahore was area of research conducted from February to July 2015. Seventy five hyperlipidemic and DMT2 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, and hyperglycemic patients were selected with age range from 18 to 70 years. Exclusion criteria were hypothyroidism, 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 sugar (fasting) 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*, 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 + Glibenclamide 5 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 [7] (LDL-Cholesterol = Total Cholesterol-(Triglycerides/5 +HDL-Cholesterol). Blood Sugar (fasting) was estimated by Glucometer provided by Acon laboratories Ltd. Data were expressed as the mean ± 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

Table 1: Illustrating LDL-cholesterol, fasting blood sugar (FBS) values before and after treatment with *Nigella sativa*, Gemfibrozil 600 mg, Glibenclamide 5 mg and placebo with their p-values.

Drug Group	At day-0	At day-90	Change in mg/dl	BS Significance (p-value)
NS	LDL=191.14±3.45	LDL=159.40±2.98	31.7	<0.001
	FBS=200.81±0.91	FBS= 181.99 ±2.17	18.82	<0.05
GF	LDL=197.77±3.91	LDL=159.62±2.20	38.2	<0.001
GC	FBS = 210.84±2.34	FBS = 180.66±1.63	30.13	<0.001
PL	LDL=163.10±1.45	LDL=159.40±1.77	3.7	>0.05
	FBS= 188.11 ±1.90	FBS= 184.32±1.94	3.79	>0.05

Key: NS stands for *Nigella sativa*, GF stands for Gemfibrozil, GC stands for Glibenclamide, PL stands for placebo group. FBS stands for fasting blood sugar. All parameters are measured in mg/dl, P-value <0.01 stands for significant change, P-value >0.05 stands for non-significant change.

Discussion

Allopathic drugs used in treatment of primary, secondary hyperlipidemia, and diabetes mellitus type-2 are going to reduce their popularity due to their adverse effects. For prevention of dyslipidemia, and DMT2 herbal medications are effective. Because DMT2, and dyslipidemia are major risk factors in development of coronary artery disease (CAD), so prescription of herbs with lower adverse effects are replacing allopathic agents used in these illnesses. When we used two allopathic drugs for reduction of hyperglycemia and hyperlipidemia these agents worked effectively as mentioned in the text. To prevent coronary artery disease (CAD), it is much necessary to keep blood lipid levels in normal range. In allopathy 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. In this study we have compared LDL cholesterol lowering effects of traditional drug Fenofibrate 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 Foosaw J *et al.* [15] who proved 28.99 mg/dl reduction in LDL cholesterol in 45 hyperlipidemic patients. Change in LDL cholesterol in our results are in contrast with results of study conducted by Lemoav A *et al.* [16] 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. This is also quoted by JH Lungrra C *et al.* [17] 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 Melladw E *et al.* [18] who observed LDL reduction by 40 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 Johan U *et al.* [19] who proved that LDL reduction by fenofibrate is not significant if used even for three months. Reason for this contrast may be due to lesser dose of Fenofibrate ie; 20 mg once daily for three months. In their results LDL cholesterol reduction was only 18.53 mg/dl. Research conducted by Zwaserr S *et al.* [20] stated that Fenofibrate enhances lipolysis and causes elimination of TG-rich lipoproteins from systemic circulation. This mechanism is due to activation of lipoprotein lipase. Fenofibrates also reduces synthesis of apoprotein C-III which is responsible for inhibition of lipoprotein lipase activity. Qeetwav J *et al.* [21] and Jayasee L *et al.* [22] described mechanism resemblance of hypolipidemic agents used in allopathy with Nigella sativa that both reduce TG synthesis, VLDL, IDL, LDL particles by decreasing lipoprotein lipase activity in adipose tissues, liver and blood. Thymoquinone found in Nigella sativa (NS) has more potential to scavenge free radicals in blood circulation, so are known as antioxidant compounds in NS [23]. Linoleic acid, and melanthin found in NS act as free radical scavenger agents as well as sensitize beta cells of pancreas to release insulin [24].

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