

Review Article

New Stratigiedies in Therapeutics: Hypolipidemic Agents

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Abstract

High lipid accumulation and biomass productivity are the two manifestly desired phenotypes in algae for biodiesel production. However, various studies conducted under nutrient depleted conditions have demonstrated that biomass productivity and lipid accumulation are negatively related. These studies have established that stress conditions, which by definition reduce the biomass production, increase lipid content of algae. This problem was addressed by using a two-stage reactor where algal species such as *Oocystis* sp. and *amphora* sp. are grown in optimal conditions for maximum biomass, followed by stress conditions for maximum lipid accumulation. Within this context, nitrogen depletion can be still considered as a strategy for increasing lipid accumulation since it has been still defined as one of the best lipid accumulator stress condition in algae to date. However, the mechanistic insights of this phenomenon are still needed. 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±2.98mg/dl, means 31.7mg/dl LDL reduction was observed when compared with placebo group (Table 1). In Gemfibrozil group of patients LDL cholesterol decreased from 197.77±3.91mg/dl to 159.62±2.20mg/dl, means LDL reduction in mean values was 38.2mg/dl (Table 2), when compared with placebo group. These changes are highly significant with p-values of <0.001. We concluded from this study that herbal medicine *Nigella sativa* is as effective as traditionally used hypolipidemic drug Gemfibrozil.

Introduction

The idea of using biofuels has gained prominence, since they provide a cleaner alternative to the currently used fossil fuels. It has recently been estimated that utilization of biofuels will result in a 30% decrease in CO₂ emissions in the United States [1]. Biofuels can be derived from different kinds of resources including microalgae, animal fats, soybeans, corns and other oil crops. While none of these options currently has the efficiency to produce the required amounts of biofuel, microalgae are considered the most promising venue of biofuel production due to their ease of cultivation, sustainability, and compliance in altering their lipid content resulting in higher biofuel production [2]. Nitrogen depleted conditions trigger reactive oxygen species accumulation, increased cellular lipid content and protein production impairment. However, the temporal order and the causal links between these events are yet to be explored. Here, we aimed at finding the relationship between oxidative stress and increased cellular lipid content under nitrogen-depleted conditions in a hypersaline green alga in order to have a better understanding of this phenomenon. Use of saturated fats cause LDL oxidation in systemic circulation and formation of atherosclerosis and may develop coronary artery disease [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 [10]. *Dunaliella* genus is one of the microalgae genus that has been considered for lipid production. *Dunaliella* species are particularly attractive due to their strong resistance characteristics to various unfavorable environmental conditions such as high salinity [4,7].

Table 1: Showing Nigella Sativa group's values and significance.

LDL-C at day-0:191.14±3.45	at day-60: 159.40±2.98	(mean change=31.7mg/dl)	P-value= <0.001
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Table 2: Showing Gemfibrozil group's values and significance.

LDL-C at day-0:197.77±3.91	at day-60: 159.62±2.20	(mean change=38.2mg/dl)	P-value= <0.001
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Table 3: Showing Placebo group's values and significance.

LDL-C at day-0:163±1.45	at day-60: 159.40±1.77	(mean change=3.7mg/dl)	P-value= <0.05
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KEY: LDL-C= low-density lipoprotein cholesterol, all parameters are measured in mg/dl, P-value <0.01 stands for significant change, P-value >0.05 stands for non-significant change.

Patients and Method

Research study design was single blind placebo-controlled, and was conducted at Jinnah Hospital, Lahore from February 2012 to July 2012. 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 600mg 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 ($LDL\text{-Cholesterol} = Total\ Cholesterol - (Triglycerides/5 + HDL\text{-Cholesterol})$). 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±3.45mg/dl to 159.40±2.98mg/dl. This change in mean values was 31.7mg/dl with highly significant p-value of <0.001. Gemfibrozil decreased LDL cholesterol from 197.77±3.91mg/dl to 159.62±2.20mg/dl. In mean values this change was 38.2mg/dl with highly significant p-value of <0.001. Placebo group showed LDL cholesterol reduction from 163.10±1.45mg/dl to 159.40±1.77mg/dl. This change in mean values was 3.7mg/dl, with non-significant p-value of >0.05 (Table 3).

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 31.7mg/dl. Statistically this change is highly significant. Our results match with results of study conducted by N. A. Zeggwagh et al [11] who proved 28.99mg/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 al [12] 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. F. R. Dehkordi also quotes this mechanism and A. F. Kamkhah [13]. In our study, Gemfibrozil decreased LDL cholesterol 38.2mg/dl that is highly significant change when analyzed statistically. These results match with results of study conducted by Vuorio A [14] who observed LDL reduction by 600mg 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 RP [15,16] 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; 300mg once daily for three months. In their results, LDL cholesterol reduction was only 18.53mg/dl. Research conducted by Dasgupta S et al proved that if Gemfibrozil is used in therapeutic dose for long-term therapy, it could 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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