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Research Article

Reduction of cholesterol and markers of oxidation in serum of hypercholestrolemic patients treated with lycosome formulation of simvastatin

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ABSTRACT

Background: Use of microencapsulated HMG-CoA reductase inhibitors (statins) might be extremely helpful in the prevention of their side effects.
Methods: 24 volunteers with hypercholesterolemia were given once daily 20 mg of lycosome-formulated Simvastatin fused with 7 mg lycopene (Lyco-Simvastatin) or the same amount of unmodified Simvastatin with no lycopene. Control patients received 7 mg of lycopene alone. Plasma lipids and oxidative markers were measured after 4 weeks of treatment.
Results: Both formulations of Simvastatin, but not lycopene, caused a reduction in serum total cholesterol and LDL at the intermediate (end of 2nd week) and final (end of 4th week) points of interventional period. Notably, reduction of total cholesterol and LDL in the 4th week of the trial was more profound in patients treated with Lyco-Simvastatin versus unmodified Simvastatin ($P<0.05$). Patients treated with Lyco-Simvastatin showed a reduction in serum Apo B level, which was not observed in other groups. Lycopene treatment caused a modest but statistically significant decrease in serum triglyceride. However, the triglyceride-lowering effect of Simvastatin was more profound in the case of Lyco-Simvastatin treatment. Lycopene as well as unmodified Simvastatin gave a marginal reduction of Inflammatory Oxidative Damage. Remarkably, the combined formulation of Simvastatin and lycopene gave a significant reduction in the values for oxidative damage (reduction of median by 112.5 µM, $P<0.05$). Similar synergistic effect was observed when levels of oxidized LDL were analyzed.
Conclusions: Lycosome-formulated microencapsulated Simvastatin has a better cholesterol-lowering and antioxidant capacity presumably due to enhanced bioavailability of the drug and synergism with lycopene.

Keywords: Simvastatin, Lycopene, Hypercholesterolemia, Oxidative stress

INTRODUCTION

Statins, known otherwise as HMG-CoA reductase inhibitors, are the most widely used drugs for primary and secondary prevention of atherosclerosis and cardiovascular disease in the world. Currently, over 25 million people worldwide take statins on regular basis.[1] Despite the indisputable clinical benefits of statins, there are some significant concerns over safety and side effects of HMG-CoA reductase inhibitors. These include increased risk of type 2 diabetes mellitus, nephropathies, cataracts, cognitive problems and venous thromboembolism.[2] Myopathies and potentially fatal rhabdomyolysis represent a dangerous side effect of statins.[3,4] Reduced and/or intermittent non-daily dosing of statin as well as the use of statins with other lipid-lowering strategies are most widely used approaches in the prevention of statin-induced myopathies.[5] Current

advances in the pharmacology of statins reveal that the lipid-lowering action of HMG-CoA reductase inhibitors and the subsequent clinical benefits of statin treatment develop strictly in a liver-specific manner. All statins inhibit within the liver conversion of HMG-CoA to mevalonate, a cholesterol precursor.[6] This process takes place in hepatocytes and the degree of hepatic HMG-CoA reductase inhibition predetermines the extent of the cholesterol-lowering effect of statins.[7] Inhibition of HMG-CoA reductase in extrahepatic cells and tissues is unlikely to affect lipid homeostasis and serum lipid level.[8] Therefore, hepatic bioavailability of statins has to be considered as a new and pivotal feature of statin biopharmacology.[9] Statins represent a heterogeneous class of chemical compounds with significant variation in physico-chemical features and bioavailability. Atorvastatin, lovastatin, simvastatin, and fluvastatin are lipophilic and tend to have lower bioavailability, whereas pravastatin and rosuvastatin are more hydrophilic substances having a better rate of intestinal absorption and hepatoselectivity.[10] So the search for new formulations of statins with increased bioavailability and hepatoselectivity has become an important task in modern cardiovascular pharmacology, addressing the prevention of statin toxicity and enhancement of their hypolipidemic activity.

In the present paper we report that a proprietary lycosome-simvastatin formulation designated in our study as Lyco-Simvastatin (Lycotec Ltd, Cambridge, UK) has a superior effect on reduction of serum lipid levels in patients with hypercholesterolemia when compared to the regular formulation of the drug.

METHODS

Study design

The study was conducted at the Institute of Cardiology, the Ministry of Health of the Russian Federation (Saratov, RF). The protocol was registered (ACTRN222333448) and approved by the local ethics committee. All patients were fully informed about the purpose of the study and had given written consent to their participation in the study.

Inclusion/exclusion criteria

The present study was part of a larger multi-arm trial which included 94 patients with hyperlipidemia. Hypercholesterolemia was defined as a state with total serum cholesterol level exceeding 200 mg/dl.[11] Hypercholesterolemic patients were further screened for parameters of oxidative stress and inflammatory markers. Patients positive for oxidation/inflammation markers were selected for the study and underwent thorough clinical and anamnestic investigation. After randomization, patients were asked to withdraw from intake of any drugs or supplements which may have affected serum lipid profile while maintaining their habitual diet. After a 2 week wash out period all patients were rescreened for serum lipid level as well as oxidative and inflammatory markers. 24 individuals who met the inclusion/exclusion criteria were randomized into 3 study groups (8 patients per group) and were given a 2 week supply of study products. All patients were screened for laboratory values (serum lipids, oxidative and inflammatory markers) at an intermediate time point (14 days after intake of investigational products) and at the completion of the study (28th day of the study). Four patients were unable to complete the study for various reasons not related to the intake of the test products and were replaced with qualifying individuals from the pre-screened pool. Patient legibility was determined by the following inclusion/exclusion criteria:

Inclusion criteria

Caucasian male or female subjects 40-65 years old, elevated total serum cholesterol (between 200 and 300 mg/dl), elevated serum LDL (>150 mg/dl), serum markers for oxidative stress LDL-Px ELISA $\times 103 \geq 250$ and IOD ≥ 40 μM/mL, absence of concomitant intake of anti-hypertensive, lipid-lowering or any other cardio-vascular drugs.

Exclusion criteria

Unwillingness to sign the informed consent, inability to comply with the protocol, significant medical condition that would impact safety considerations (severe cardiovascular disease, hepatitis, severe dermatitis, uncontrolled diabetes, cancer, severe GI disease, fibromyalgia, renal failure, recent cerebrovascular accident, pancreatitis, respiratory diseases, epilepsy, HIV/AIDS, compulsive alcohol abuse (>10 drinks weekly) or regular exposure to other substances of abuse.

Study products

Each volunteer took daily in the evening 20 mg of lycosome-formulated simvastatin fused with 7 mg of lycopene (Lyco-Simvastatin, a proprietary formulation of Simvastatin, Lycotec Ltd, Cambridge, UK) or the same amount (20 mg) of unmodified simvastatin with no lycopene. Simvastatin was obtained from Bal Pharma Ltd (Bangalore, India). Control patients took 7 mg of lycopene (Lycored Inc, NJ, USA) alone with no simvastatin added. Control capsules of lycopene were made from the same batch of tomato oleoresin used for the preparation of the lycosome formulation of Simvastatin.

Blood collection, biochemistry and inflammatory markers

Blood was collected from the arm veins of patients between 8 and 10am following overnight fast. The serum was separated by centrifugation and aliquots were stored at −80°C prior to analysis. Glucose, total cholesterol, TC,

triglycerides, TG, high density cholesterol, HDL, low density cholesterol, LDL and C-reactive protein, CRP, were measured using commercially available analytical kits according to the manufacturers' instructions (Byo Systems, R&D Systems).

Inflammatory oxidative damage (IOD)

Serum samples were incubated overnight in 0.05 M PBS acetate buffer (pH 5.6) to imitate the type of oxidative damage that occurs after release of lysosomes following neutrophil degranulation. The following morning, the reaction was terminated using trichloroacetic acid. The concentration of the end products such as malonic dialdehyde (MDA) and other possible thiobarbituric acid reactive substances (TBARS) were then measured with colorimetric methods (12) using reagents and kits from Cayman Chemical (MC, USA).

LDL-Px

The activity of serum LDL peroxidase proteins, which include IgG with superoxide dismutase activity,[13] was measured as described earlier.[14,15]

Statistics

For the assessment of normally distributed parameters, the Shapiro-Wilk method was used. Student's t-test was then applied both for paired and unpaired samples. In cases where parameters were not normally distributed, the Mann-Whitney U- test and Kruskal-Wallis test were used. ANOVA and ANCOVA were used with post hoc analysis (Statistica 9 suit, StatSoft; Inc.). Statistical significance between two-tailed parameters was considered to be $P<0.05$.

RESULTS

Table 1 shows the basal characteristics of the patients enrolled in the trial. All patients were of similar age and had comparable values for BMI, systemic blood pressure and pulse rate. There was no statistically significant difference in serum levels of major lipid classes (total cholesterol, triglycerides, HDL and LDL) among the volunteers. Serum levels of glucose and CRP were similar among all three groups of the study. The study volunteers were therefore considered to have been successfully randomized.

The most significant changes in the study groups were observed in the serum lipid profile. As can be seen from Table 2, lycopene treatment did not affect most of the values for serum lipids. In particular, a minor reduction in medians for total cholesterol concentration in the serum of lycopene-treated patients was not statistically significant ($P>0.5$). However, Simvastatin treatment caused a statistically significant reduction in total cholesterol levels at the end of the 2nd and 4th weeks of intervention (Table 2). The most significant reduction took place in patients treated with Lyco-Simvastatin whose serum total cholesterol values were reduced by 56 mg/dl and 72.5 mg/dl after the 2nd and 4th weeks of treatment respectively. The difference between the Simvastatin and Lyco-Simvastatin groups in terms of total cholesterol reduction was statistically significant ($p<0.05$) only after completion of the treatment (at the end of the 4th week of intervention). Therefore, the lycosome formulation of Simvastatin was shown to have superior activity in regulation of serum cholesterol level when compared to unmodified Simvastatin. Similar changes were observed in serum LDL levels. Lycopene treatment alone did not affect serum LDL values.

Table 1: Baseline characteristics of the enrolled volunteers (Mean +/- SD).

Study groups			
Variable	***Lycopene***	***Simvastatin***	***Lyco-Simvastatin***
Number of Patients (n)	8	8	8
Age (years)	55.03±3.7	56.8±2.88	554.2±3.05
Gender			
Males	50%	50%	50%
Females	50%	50%	50%
Smokers	20%	12.5%	20%
BMI	27.32±1.32	26.59± 1.66*	27.27± 1.77*
Pulse Rate	75.1±4.61	71.22.5± 3.77	76.22± 4.22*
Blood Pressure			
Systolic	127.2±1.89	121.4± 1.94*	127.14± 1.89*
Diastolic	83.2±2.45	85.70± 1.41*	83.4±1.66*
CRP	6.11±1.21	4.57±1.19*	5.11±1.22*
Cholesterol, mg/dl	256.5±16.65	244.30± 17.24*	239.1± 14.56 *
Triglycerides mg/dl	120.65± 16.28	157.26± 19.22*	140.2± 21.2*
HDL mg/dl	42.50±1.55	43.10±2.0*	44.70± 1.44*
LDL mg/dl	188.2±14.53	158± 13.88*	155.1± 19.11*
Glucose mmol	5.66±0.81	5.9±0.74*	5.48± 0.88*

*- insignificant changes with $P>0.05$ as compared to the lycopene group

However, ingestion of both Simvastatin formulations gave a reduction of serum LDL in a time-dependent manner. Modest reduction of LDL values at the end of the second week of treatment (decrease of median values by 18 mg/dl and 14.5 mg/dl in Simvastatin and Lyco-Simvastatin groups) was accompanied by a more significant drop in serum LDL at the end of the interventional period (by 23.5 mg/dl and 38.5 mg/dl in Simvastatin and Lyco-Simvastatin groups respectively).

Once again Lyco-Simvastatin had a more distinct ability to reduce serum LDL as compared to unmodified Simvastatin (P<0.05).

Variations in Apo B level were in sensible agreement with the lipid profile changes. Lycopene treatment did not affect the Apo B levels at any time point of the study. Both formulations of Simvastatin caused reduction of Apo B after 4 weeks of treatment. The most profound changes in Apo B concentration were seen in the Lyco-Simvastatin group at the end of the interventional period (reduction of median by 24.4 mg/dl, P<0.05). At the same time point, Simvastatin alone gave only a marginal reduction of Apo B (reduction of median by 11.2 mg/dl. P=0.057). There was a statistically significant (P<0.05) between-group difference in Apo B level when the two formulations were compared.

Table 2: Median values with 5% and 95% CIs for lipid profile parameters.

Parameters in groups	Pre treatment			2 weeks			4 weeks		
	Median	5/95% CI	P	Median	5/95% CI	P	Median	5/95% CI	P
Total cholesterol									
LYC	254.5	288.7/225.5	–	250	277.9/217.4	>0.05	246	266.5/205.3	>0.05
SIMV	237.5	273.1/220.4	–	207	223.9/193.5	<0.05	174	205.6/160	<0.05
LYC-SIMV	234.5	275.9/210.3	–	178.5	213.1/161.3	<0.05	162	210.5/148.2	<0.05
LDL									
LYC	183	297.2/171.7	–	184	202.8/168.4	>0.05	188.5	200/170.7	>0.05
SIMV	158	183.0/154.5	–	140	175.7/130	<0.05	134.5	162.1/116.3	<0.05
LYC-SIMV	159.5	175.4/150.3	–	145	165.3/127	<0.05	121	154/103.1	<0.05
HDL									
LYC	42	50.3/37	–	43	50.3/37.3	>0.05	43	50.9/38	>0.05
SIMV	43.5	50.3/37	–	43.3	50.3/37	>0.05	42	50.9/38	>0.05
LYC-SIMV	44.5	52.9/38.7	–	45	53.3/40	>0.05	43.5	53.5/40.7	>0.05
Triglycerides									
LYC	122	147.9/94.4	–	117	138.2/92.1	>0.05	98.5	119.9/90.7	<0.05
SIMV	175	226.3/81.8	–	146	209.1/76.6	<0.05	110.5	191.5/58.5	<0.05
LYC-SIMV	147.5	152.7/78.5	–	86.5	97.9/71.8	<0.05	84	94.5/72.8	<0.05
APO B									
LYC	162	177.1/148	–	161	177.2/144.8	>0.05	166	173.9/142.8	>0.05
SIMV	161.2	179.5/143.1	–	157.7	176.1/143.8	>0.05	150	171.7/141.4	>0.05
LYC-SIMV	155	165.9/111	–	147.5	160/107.6	.>0.05	141.5	156/104.4	>0.05
Apo A									
LYC	120.5	130/103.8	–	119.5	128.2/105.2	>0.05	120.5	130.6/105.1	>0.05
SIMV	104.5	123.2/87	–	110.5	121.9/85.9	>0.05	112.5	122.6/90	>0.05
LYC-SIMV	118	128.8/104	–	119	128.8/105.2	>0.05	120	127.9/105.4	>0.05

Table 3: Median values with 5% and 95% CIs for parameters of oxidation.

Parameters in groups	Pretreatment			2 weeks			4 weeks		
	Median	5/95% CI	P	Median	5/95% CI	P	Median	5/95% CI	P
IOD									
LYC	124.5	236.2/66.8	–	119.5	216.6/66.5	>0.05	110.5	186.2/56.8	>0.05
SIMV	118	163.5/56.9	–	97.5	154.5/65	>0.05	97	143.4/72.7	>0.05
LYC-SIMV	142	228.3/57.9	–	123	201.6/49.3	<0.05	29.5	62.5/1.05	<0.05
LDL-Px									
LYC	461	674.4/296.3	–	430.5	661.4/284.7	>0.05	343.5	520.3/225.3	<0.05
SIMV	406	572.6/260.1	–	382	545.9/236.4	>0.05	310	519.3/204	<0.05
LYC-SIMV	478.5	593.8/299.8	–	386.5	543/223.1	<0.05	193	352.4/97.7	<0.05

It seems that a different pattern of regulation took place in serum triglyceride levels. Lycopene gave a modest but statistically significant reduction in serum triglyceride at the end of the interventional period (decrease in median by 23.5 mg/dl) with no changes observed at the intermediate point of the trial. Both formulations of Simvastatin were effective in reducing serum triglyceride level at both the intermediate and final points of the study although the triglyceride-lowering effect of Lyco-Simvastatin was more profound (P2 weeks<0.05, P4 weeks<0.05) when between-group analysis was performed. No changes in HDL or Apo A levels were seen in the lipid profile of the patients during the study.

Some unexpected findings were obtained when LDL oxidation parameters of the patients were analyzed. As can be seen from Table 3, lycopene treatment gave some reduction in the intensity of Inflammatory Oxidative Damage (IOD). However, these changes were not statistically significant (P2week=0.067, P4week=0.054). Unmodified Simvastatin treatment gave a similar reduction in the median for this parameter but with a marginal level of statistical difference (P2week=0.061, P4week=0.053). However, the combined formulation of Simvastatin and lycopene produced a significant decline in values for oxidative damage by the end of the interventional period (Figure 1), a reduction of the median by 112.5 µM, P<0.05.

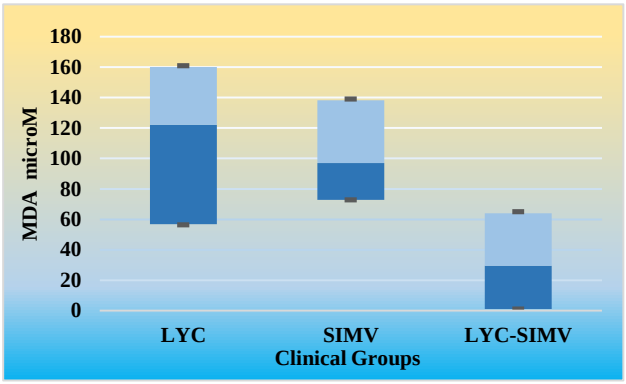

Figure 1: Inflammatory oxidative damage. 4th week of the trial.

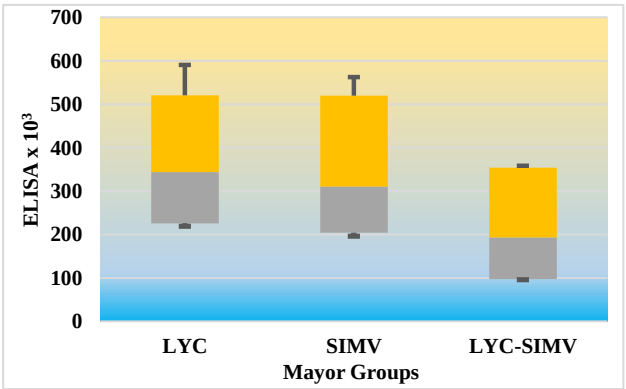

Figure 2: LDL-Px. 4th week of the trial.

Moreover, there was a step-wise reduction in levels of oxidized LDL (LDL-Px) in the serum of lycopene-treated and Simvastatin-treated patients which reached its peak at the end of the trial (Table 3). Interestingly, the combined formulation of lycopene and Simvastatin produced significant inhibition of LDL-Px values at the end of 4th week of treatment (Figure 2). Taken together these results suggest that the antioxidant effect of the lycosome formulation of Simvastatin arises from synergistic action of lycopene and Simvastatin on the oxidative status of the patients.

DISCUSSION

Statins are the best-selling pharmaceuticals of modern times. They have an indisputable efficacy in the prevention/treatment of cardiovascular disease, and their projected use is predicted to grow.[16] However, various adverse reactions take place in a large number of patients (reportedly from 5% to 20%) with more side effects occurring at higher doses.[17] So the search for new formulations of statins along with optimization of protocols for statin use and their delivery has become a significant challenge in modern biotechnology. Improvement of bioavailability of statins is a poorly explored option in statin pharmacology, although some attempts at the use of statin nanoformulations have been reported recently.[18]

In our recent study we show that lycosome formulation of Simvastatin has a superior ability to normalize serum lipid profile in hypercholesterolemic patients when compared to unmodified Simvastatin used with the same dose (20 mg) and intake regimen. The greatest effect of Lyco-Simvastatin was seen on serum LDL level, which is a major parameter known to be affected by statin treatment. As widely accepted inhibitors of HMG-CoA reductase activate the SREBP-2 pathway and enhance the hepatic expression of LDL-receptors thereby promoting hepatic clearance of pro-atherogenic Apo B-containing lipoproteins.[19] Therefore, other effects of Lyco-Simvastatin including a greater reduction of total cholesterol and Apo B levels should be considered as secondary phenomena reflecting its primary effect on serum LDL values. The triglyceride-reducing effect of simvastatin was also more pronounced in the Lyco-Simvastatin patients and might be considered as a direct consequence of LDL reduction, since LDL and VLDL are major forms of triglyceride transport.[20]

Perhaps the more effective ability of Lyco-Simvastatin to improve lipid profile parameters takes place due to enhanced bioavailability and hepatoselectivity of lycosome-formulated Simvastatin. The incorporation of bioactive compounds in the lycosome structure promotes their intestinal absorption and hepatic delivery. Lycopene, a major structural component of lycosome particles, is known to be preferentially incorporated into the structure of intestinal VLDL with further delivery of lycosome-containing lipoprotein particles directly to

hepatocytes via carotenoid receptors and possibly LDL-receptors.[21,22] Receptor-mediated uptake of lycosomes by hepatocytes minimizes exposure of extrahepatic tissues to lycosome-associated drugs and reduces the chance of extrahepatic toxicity of xenobiotics. Additional studies are required to gain a deeper insight into the mechanism of Lyco-Simvastatin pharmacology. However, regardless of mechanism, the enhanced modulating activity of Lyco-Simvastatin on lipid profile might be considered as a valuable development in the methodology of statin treatment. It would require further studies to see if lycosome formulations of other statins have a similarly enhanced biological activity.

Another exciting piece of scientific evidence comes from the results reflecting changes in oxidative status of hypercholesterolemic patients treated with Simvastatin formulations. Even in recent times there are some significant deficiencies in methodology for pharmacological control of oxidative status in cardiovascular patients.[23] Antioxidants of pharmacological grade are almost non-existent. As we have shown in our work, both lycopene and Simvastatin used separately are capable of reduction of oxidative stress markers in hypercholesterolemic patients. However, under the conditions used that effect was very modest. In particular, there was a 10.2% reduction in the parameters of Inflammatory Oxidative Damage (IOD) in the patients treated with lycopene formulation for 4 weeks, while Simvastatin treatment of similar duration gave a 17.7% decline in IOD values. Similarly, there was a 25.4% reduction in the concentration of oxidized LDL in lycopene-treated patients, while the corresponding parameter in Simvastatin-treated volunteers dropped by 23.6%. To our surprise, the Lyco-Simvastatin formulation gave a remarkable decrease in serum oxidative markers. As we found, IOD and LDL-Px values were reduced at the end of the interventional period by 79.2% and 59.6% respectively. Such a significant decline in markers of oxidative stress caused by Lyco-Simvastatin suggests a synergistic action of lycopene and Simvastatin on mechanisms of biological oxidation. Simvastatin has a limited ability to directly affect mechanisms of biological oxidation.[24] whereas lycopene is an antioxidant with a proven and well established record.[25] Additional studies are required to reveal the mechanism behind the cooperative action of both compounds on oxidative status. However, notwithstanding the molecular mechanism, the newly observed potentiation of antioxidative activities in lycopene and Simvastatin can be employed for the correction of oxidative status in cardiovascular patients.

CONCLUSIONS

Lycosome-formulated microencapsulated Simvastatin has a better cholesterol-lowering and antioxidant capacity presumably due to enhanced bioavailability of the drug and synergism with lycopene.

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REFERENCES

1. Alvarado CM, Marín SA, Lima RJ. Statins and autoimmunity. Med Clin (Barc). 2015;S0025-7753(14)00878-1.
2. Desai CS, Martin SS, Blumenthal RS. Non-cardiovascular effects associated with statins. BMJ. 2014;17:349.
3. Magni P, Macchi C, Morlotti B, Sirtori CR, Ruscica M. Risk identification and possible countermeasures for muscle adverse effects during statin therapy. Eur J Intern Med. 2015. pii: S0953-6205(15)00003-5.
4. Pasnoor M, Barohn RJ, Dimachkie MM. Toxic myopathies. Neurol Clin. 2014;32(3):647-70.
5. Rallidis LS1, Fountoulaki K, Anastasiou-Nana M. Managing the underestimated risk of statin-associated myopathy Int J Cardiol. 2012;6;159(3):169-76.
6. Yeganeh B, Wiechec E, Ande SR, Sharma P, Moghadam AR, Post M, et al. Targeting the mevalonate cascade as a new therapeutic approach in heart disease, cancer and pulmonary disease. Pharmacol Ther. 2014;143(1):87-110.
7. McKenney JM. Pharmacologic characteristics of statins. Clin Cardiol. 2003;26(4):III32-8.
8. Cui CJ, Li S, Li JJ. PCSK9 and its modulation. Clin Chim Acta. 2015;440C:79-86.
9. Petyaev IM, Improvement of hepatic bioavailability as a new step for statin future. Arch Med Sci. 2015.
10. Gazzerro P, Proto MC, Gangemi G, Malfitano AM, Ciaglia E, Pisanti S, et al. Pharmacological actions of statins: a critical appraisal in the management of cancer. Pharmacol Rev. 2012;64(1):102-46.
11. Stapleton PA, Goodwill AG, James ME, Brock RW, Frisbee JC. Hypercholesterolemia and microvascular dysfunction: interventional strategies.J Inflamm (Lond). 2010;7:54.
12. Gómez H, Mesquida J, Simon P. Characterization of tissue oxygen saturation and the vascular occlusion test: influence of measurement sites, probe sizes and deflation thresholds. Critical Care. 2009;13,(3):1-7.
13. Yagi K. Lipid peroxides and human diseases. Chemistry and Physics of Lipids. 1987;45,2-4:337-51.
14. Petyaev I, Mitchinson MMJ, Hunt JV, Coussons PJ. Superoxide dismutase activity of antibodies purified from the human arteries andatherosclerotic lesions. Biochemical Society Transactions. 1998;26(1):S43.
15. Petyaev IM, Coussons PJ. Superoxide dismutase activity of antibodies purified from human atherosclerotic lesions, in Superoxide Dismutase: Recent Advances and Clinical Applications. 1999:51-4.
16. Balakumar P, Mahadevan N. Interplay between statins and PPARs in improving cardiovascular

outcomes: a double-edged sword? Br J Pharmacol. 2012;165(2):373-9.
17. Olson EA, Hainsworth DP, Davis G, Hagan JC. Eye on statins: A comprehensive review. Mo Med. 2013;110(4):344-8.
18. Romana B, Batger M, Prestidge CA, Colombo G, Sonvico F. Expanding the therapeutic potential of statins by means of Nanotechnology enabled drug delivery systems. Curr Top Med Chem. 2014;14(9):1182-93.
19. Poirier S, Mayer G. The biology of PCSK9 from the endoplasmic reticulum to lysosomes: new and emerging therapeutics to control low-density lipoprotein cholesterol. Drug Des Devel Ther. 2013;7:1135-48.
20. Webb J, Gonna H, Ray KK. Lipid management: maximizing reduction of cardiac risk. Clin Med. 2013;13(6):618-20.
21. Carotenoid particles and uses thereof. GB Patent Application No. 1101669.8, PCT/GB2012/000075, 25.01.2012.
22. Bravo E, Napolitano M. Mechanisms involved in chylomicron remnant lipid uptake by macrophages. Biochem Soc Trans. 2007;35(3):459-63.
23. Nasri H, Baradaran A, Shirzad H, Rafieian-Kopaei M. New concepts in nutraceuticals as alternative for pharmaceuticals. Int J Prev Med. 2014;5(12):1487-99
24. Li Y, Fu J, Yuan X, Hu C. Simvastatin inhibits the proliferation of A549 lung cancer cells through oxidative stress and up-regulation of SOD2. Pharmazie. 2014;69(8):610-4.
25. Vance TM, Su J, Fontham ET, Koo SI, Chun OK. Dietary antioxidants and prostate cancer: a review. Nutr Cancer. 2013;65(6):793-801.

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