Print ISSN: 2319-2003 | Online ISSN: 2279-0780

IJBCP International Journal of Basic & Clinical Pharmacology

DOI: http://dx.doi.org/10.18203/2319-2003.ijbcp20181170

Original Research Article

Effect of Lutein in the expression of PPARα and LDLR in hypercholesterolemic male Wistar Rats

Soundarya Priyadharsini K.[1]*, Nirmala P.[2], Ashok Kumar P.[3], Krishna Prasad T.[4]

[1]Department of Pharmacology, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Kancheepuram, Tamilnadu, India
[2]Department of Pharmacology, Rajah Muthaih Medical College, Annamalai University, Chidambaram, Tamilnadu, India
[3]Department of Biochemistry, Rajah Muthaih Medical College, Annamalai University, Chidambaram, Tamilnadu, India
[4]Department of Anaesthesia, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Kancheepuram, Tamilnadu, India

Received: 02 January 2018
Revised: 23 February 2018
Accepted: 27 February 2018

***Correspondence to:**
Dr. Soundarya Priyadharsini K.,
Email: sowmimbbs@yahoo.com

ABSTRACT

Background: Hyperlipidemia is a well known risk factor for cardiovascular disease, especially atherosclerotic coronary artery disease. Peroxisome proliferator activated receptor α (PPARα), a member of this nuclear receptor family, has emerged as an important player in this scenario, with evidence supporting a central co-ordinated role in the regulation of fatty acid oxidation, lipid and lipoprotein metabolism and inflammatory and vascular responses, all of which would be predicted to reduce atherosclerotic risk. The low-density lipoprotein (LDL) receptor (LDLR) is the primary pathway for removal of cholesterol from the circulation, and its activity is meticulously governed by intracellular cholesterol levels. Hence in this study we investigated the effect of Lutein on PPARα and LDLR expression in liver of wistar rats.
Methods: Male Wistar rats were divided into 6 groups of 6 each. Group I served as control. Group II III, IV, V and VI rats were received high cholesterol diet. Group III was treated with Atorvastatin 5mg/kg. Group IV, V and VI rats were treated with 25mg/kg, 50mg/kg and 100mg/kg of Lutein. After 16 weeks, liver tissue samples were collected from all the groups of animals to evaluate the expression of PPARα and LDLR.
Results: The expression of Peroxisome proliferator activated receptor α and low-density lipoprotein (LDL) receptor (LDLR) was significantly increased in Lutein treated hypercholesterolemic male wistar rats.
Conclusions: The results of this study indicate that Lutein activates LDL receptor and PPARα in hypercholesterolemic male wistar rats.

Keywords: Hypercholesterolemia, LDL receptor, Liver, Lutein, PPARα

INTRODUCTION

Cardiovascular disease is a leading cause of morbidity and mortality world-wide. The burden of disease is increasing as a result of the global epidemics, diabetes and obesity.[1]

The peroxisome proliferator-activated receptors (PPARs) are ligand-activated transcription factors that belong to the superfamily of nuclear hormone receptors.[2] It was first discovered in the early 1990s and since then has been identified as the master regulator of hepatic lipid metabolism.[3] Synthetic agonists of PPARα lower plasma triglycerides and increase plasma high-density lipoprotein (HDL) levels and are thus used clinically in the treatment of dyslipidemia.[4]

The peroxisome proliferator-activated receptor alpha (PPARα) is a ligand activated transcription factor involved in the regulation of a variety of processes, ranging from inflammation and immunity to nutrient metabolism and energy homeostasis. PPARα serves as a molecular target for hypolipidemic drug fibrates.[1] The receptor has a central role in fatty acid oxidation, lipid and lipoprotein metabolism, inflammatory responses, and oxidative stress.

Peroxisome proliferator–activated receptors (PPARs) are activated by fatty acids and derivatives. PPARα mediates hypolipidemic action and PPARγ mediates the antidiabetic action of drugs. PPARα is highly expressed in liver, muscle, kidney, and heart, where it stimulates the β-oxidative degradation of fatty acids.[5]

Activation of the PPAR is initiated by binding of an agonist, either an endogenous substance (e.g., fatty acids, eicosanoids, or oxidized phospholipids) or a drug to the ligand binding domain of the nuclear receptor forming heterodimers with retinoid X receptor (RXR), another nuclear receptor activated by its own ligand (purported to be 9 *cis*-retinoic acid).

The PPAR–RXR complex subsequently binds to DNA at sequence specific regions on target gene promoters, known as PPAR response elements (PPRE), thereby activating their expression.[6] PPARs need to form heterodimers with RXR upon ligand binding to regulate gene transcription.[7] The PPAR/RXR heterodimer binds the PPRE site in the 5' promoter regions of target genes.[8]

PPARα and lipid metabolism

Activation of PPARα leads to increased tissue-specific expression of key genes involved in fatty acid uptake and β oxidation. This includes acyl-Coenzyme A synthetase, an enzyme which plays a key role in esterification of fatty acids thereby preventing their efflux from cells, in the liver and kidney, and carnitine palmitoyltransferase type 1 (CPT-1), a pivotal enzyme involved in fatty acid catabolism within mitochondria in metabolically active tissue such as the heart, skeletal muscle and brown adipose tissue, which contains a PPRE in its promoter region.[9] The net effect of this is reduction in the availability of free fatty acids for synthesis and secretion of very-low-density lipoproteins (VLDL).[10]

PPARα on triglyceride and low-density lipoprotein (LDL)

Metabolism

Activation of PPARα decreases triglycerides (TG) by stimulating free fatty acid β oxidation, hepatic lipoprotein lipase expression, and expression of apolipoprotein V (apoV), and by inhibiting expression of apolipoprotein CIII (apoCIII).[11] In vitro studies imply repression of apoCIII expression via interaction with a PPRE in the Rev-erb-α promoter, given that mice deficient in this protein exhibit increased plasma concentrations of TG and apoCIII.[12]

An increase in apoCIII content of VLDL particles causes an increase in small dense LDL particles. PPARα activation leads to a reduction in the levels of atherogenic dense LDL-cholesterol that has poor affinity to LDL receptor while increasing large buoyant LDL particles that have a high affinity for this receptor.[13]

PPARα, high-density lipoprotein (HDL) metabolism and reverse cholesterol transport

Regulation of HDL metabolism through PPARα occurs through the stimulating of hepatic expression of apoA-I and apoA-II leading to increased HDL production by liver, This result in HDL-mediated cholesterol efflux from macrophages, via enhanced expression of scavenger receptor and the ATP-binding cassette transporter A1 (ABCA1).[14] This inhibits cellular cholesteryl ester formation and limits accumulation of cholesteryl ester in vascular macrophages, preventing foam cell formation.[15] PPAR activation also regulates cholesterol mobilisation, leading to enhanced availability of plasma membrane cholesterol for cholesterol efflux, which together with regulation of ABCA1 and SR-BI expression, stimulate reverse cholesterol transport.[16]

PPARα on atherosclerosis

PPAR is expressed in inflammatory cells involved in the process of atherogenesis, such as monocytes, macrophages and lymphocytes implying a regulatory role in the early stages of atherosclerosis. PPAR activators inhibit cytokine-induced expression of vascular cell-adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule-1 (ICAM-1), both playing a critical role in the recruitment of leukocytes and monocytes to the atherosclerotic lesion, by down-regulation at the transcriptional level, mediated in part by inhibition of the NF-B signalling pathway.[17] PPAR ligands also repress thrombin-induced expression of endothelin-1 (ET-1), by negatively interfering with the AP-1 signalling pathway.[18]

LDL receptor

The low-density lipoprotein (LDL) receptor (LDLR) is the primary pathway for removal of cholesterol from the

circulation, and its activity is meticulously governed by intracellular cholesterol levels.[19] Goldstein and Brown (2009) evaluated the molecular mechanism of LDLR in familial hypercholesterolemia (FH), an autosomal dominant metabolic disorder in patients with plasma cholesterol levels ranging from 300 mg/dL to 1500 mg/dL.[20] Patients with FH are at increased risk of cardiovascular disease and high cholesterol levels often results in advanced atherosclerosis within a time span of 10 years.[21]

The low-density lipoprotein (LDL) receptor mediates the specific uptake of LDL from circulation and its intracellular degradation and this process is known as LDL receptor pathway. LDL receptor gene expression is regulated by intracellular sterol content of liver. Mutations in LDLR, the gene encoding the LDL receptor, cause familial hypercholesterolaemia (FH), a dominantly inherited disease where accumulation of LDL in circulation increases the risk of coronary heart disease. Defects in other genes, including APOB, encoding the ligand for the LDL receptor, ARH, encoding a protein required for its internalisation and proprotein convertase subtilisin/kexin type 9 (PCSK9), encoding a protein that reduces LDL receptor protein levels, cause a similar disorder because the encoded proteins are involved in the LDL receptor pathway. FH can readily be treated with cholesterol-lowering drugs to reduce cardiovascular risk effectively, and identification of the causal genetic defect allows unequivocal and early diagnosis.[22]

The LDL-receptor pathway for uptake and degradation of LDL

The LDL receptor specifically binds to apolipoprotein B in LDL particles present in the extracellular fluid. The receptor–ligand complex is then internalized by endocytosis. The complex is transported to late endosomal compartment, where the acidic environment causes dissociation of the receptor–ligand complex. The receptor is again recycled to the cell surface while the LDL particle is degraded in the lysosomal compartment. Accumulation of free cholesterol released by hydrolysis of cholesteryl esters inactivates sterol regulatory element binding protein (SREBP), a transcription factor that drives expression of genes for enzymes involved in cholesterol synthesis and the LDL receptor. Mutations in LDLR, APOB, LDLRAP1 or PCSK9 are known to result in familial hypercholesterolemia.[23]

METHODS

This study was done at Central Animal House, Rajah Muthiah Medical College and Hospital, Annamalai University, Annamalai Nagar. All studies were conducted in accordance with CPCSEA guidelines. The study was approved by the Animal Ethical Committee of Rajah Muthiah Medical College and Hospital [Registration No.160/1999/(CPCSEA)] Annamalai University, Annamalai Nagar, Tamilnadu, India (Proposal No.1064, dated 29.11.2013).

Materials

Chemicals and reagents

Lutein (4-[18-(4-Hydroxy-2,6,6-trimethyl-1-cyclohexenyl)-3,7,12,16-tetramethyloctadeca-1,3,5,7,9,11,13,15,17-nonaenyl]-3,5,5-trimethyl-cyclohex-2-en-1-ol) was purchased from MP Biomedicals India Private Limited, Mumbai, Maharashtra. Cholesterol pure was purchased from Himedia, India. Cholic acid sodium salt, Pure was purchased from Himedia, India. Trizol reagent was purchased from Invitrogen, Calif., U.S.A. PCR primers (forward and reverse), and PCR Master Mix was purchased from Promega, N.Y., U.S.A. All reagents used in this study were of analytical grade.

Preparation of drug

Lutein 50mg/ml. Atorvastatin powder were dissolved in dimethyl sulfoxide (DMSO) to make a solution of 10mg/ml.

Animals

Healthy adult male rats of Wistar strain weighing 150-200gms were used in the present study. They were purchased from the Central Animal House, Rajah Muthiah Medical College and Hospital, Annamalai University, Annamalai Nagar, Tamil Nadu, India. Animals were housed in polypropylene cages [28cm x 22cm x 14cm] bedded with husk in groups of six under controlled environmental conditions [Temp-23±2^{0}C, Humidity 65-70% and 12 hrs light/dark cycles] at Central Animal House, Rajah Muthiah Medical College and Hospital, Annamalai University. Animals were fed with standard pellet diet VRK Nutritional Solutions, Baramati Agro Limited, Sangli, Maharashtra, India] and water ad libitum.

Induction of hypercholesterolemia

Hypercholesterolemia was induced in all groups except control group by feeding cholesterol diet (1% cholesterol, 0.5% sodium cholate, 1% coconut oil) in rat chow.[24]

Study design

The rats were divided into 6 groups of six each (n=6).

- Group I (n=6) = Control.
- Group II (n=6) = High cholesterol diet.
- Group III (n=6) = Atorvastatin 5mg/kg p.o daily with high cholesterol diet.
- Group IV (n=6) = Lutein 25mg/kg p.o daily with high cholesterol diet.
- Group V (n=6) = Lutein 50mg/kg p.o daily with high cholesterol diet.

- Group VI (n=6) = Lutein 100mg/kg p.o daily with high cholesterol diet.[25]

The drug treatment was carried out every day morning using intra-gastric tube for a period of 16 weeks.

Tissue sampling

At the end of the study, the animals were sacrificed by cervical dislocation and the Liver from all the groups of rats were dissected out and We stored tissues in RNA Later (Ambion), extracted total RNA with Trizol (Invitrogen) and they were processed for PPARα and LDLR gene expression through Q-RT-PCR.

RNA extraction

A volume of 1 cm^3 rat liver tissue was homogenized, and 500µL of Trizol reagent (Invitrogen, Calif., U.S.A.) was used to extract RNA. RNA was precipitated by mixing with isopropyl alcohol. The RNA pellet was washed twice with 75% ethanol and dissolved in diethylpyrocarbonate-treated water to a final concentration of 2.5µg/µL.

Table 1: Primer sets used for reverse-transcription PCR.

Gene	Forward primer	Reverse primer
PPAR - α	5'-TTCGTGGAGTCCTGGAACTG-3'	5'-TGTCGTACGCCAGCTTTAGC-3'
LDLr	5'-CTGTGGTCACCACATCAGCTGC- 3'	5'-CAGGCTGACCATCTGTCTCGA-3'
β –actin	5'-GCACCACACCTTCTACAATG- 3'	5'-TGCTTGCTGATCCACATCTG-3'

Quantitative -Reverse-transcription PCR Q (RT-PCR)

A mass of 2.5µg of total liver RNA from each rat liver tissue was used for the 1st-strand cDNA synthesis (Fermentas, Ontario, Canada). In short, total RNA was mixed with oligo (dT)18, Moloney Murine Leukemia Virus (M-MuLV) reverse transcriptase, dNTPs, and RNase inhibitor to a final reaction volume of 20µL. The reaction was carried out at 25◦C for 10 min, followed by 50◦C for 15 min, and was terminated at 85◦C for 5 min. PCR was then performed using 1µg of the 1st-strand c-DNAs, 50nM of the PCR primers (forward and reverse), and PCR Master Mix (Promega, N.Y., U.S.A.). The primer sets used are shown in Table. The expression levels of the gene transcripts of interest were related to those of an internal standard housekeeping gene (Beta actin [β-actin]) to correct differences in quantity and quality among different RNA samples. The PCR amplification protocol consisted of a 1-step denaturation for 3min at 94◦C, followed by 35 cycles of 1-min denaturation at 94◦C, 1-min annealing at 55◦C, and 1-min extension at 72◦C. The PCR products were run on 0.8% agarose gel and stained with (Ethidium bromide (EtBr). The light intensity of each band was measured by the freeware Image J (ver.1.42). The expression levels of various genes were expressed as the ratios of the measured intensity of the gene of interest to that of β - actin.

RESULTS

This study results show that PPARα mRNA expression in liver tissue in Lutein treated male wistar rats increase in a dose dependant manner. The expression of PPARα in rat liver tissue was significantly decreased in high cholesterol fed rats. Atorvastatin 5mg/kg body weight (group 3) showed statistically significant difference in comparison with high cholesterol fed rats in expression of PPARα.

Figure 1: Expression of PPARα and LDLR gene.

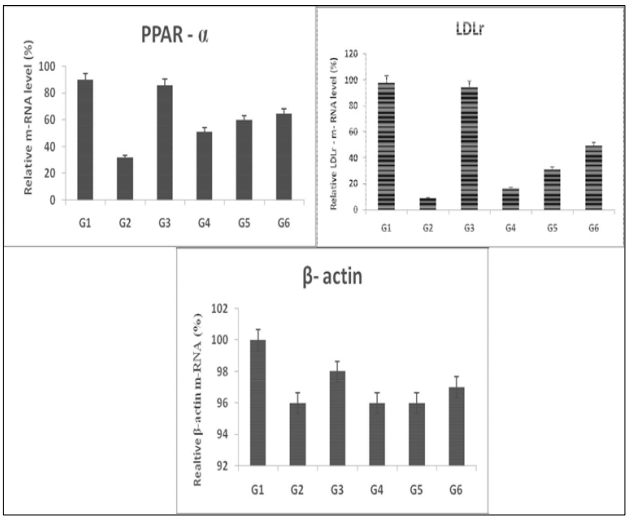

Figure 2: m-RNA quantification.

This study results show that PPARα mRNA expression in liver tissue in Lutein treated male wistar rats increase in a dose dependant manner. The expression of PPARα in rat liver tissue was significantly decreased in high cholesterol fed rats. Atorvastatin 5mg/kg body weight (group 3) showed statistically significant difference in comparison with high cholesterol fed rats in expression of PPARα.

The LDLR expression in rat liver tissue in Lutein treated groups was significantly increased in a dose dependent manner. Atorvastatin 5mg/kg body weight showed significant increase in expression of LDLR in comparison with high cholesterol fed rats.

DISCUSSION

Peroxisome proliferator activated receptor α (PPARα) also known as NR1C1 (Nuclear receptor subfamily 1 group c member 1) is a nuclear receptor protein and is encoded by PPAR α gene.[26] It is a transcription factor and major regulator of lipid metabolism in liver. It activates ketogenesis in conditions of fasting.[27] Activation of PPARα leads to uptake, utilisation and catabolism of fatty acids.[28] PPARα is expressed highly in tissues involved in fatty acid oxidation in liver and brown adipose tissue in rodents.[29] PPAR expression ligand binding can be analysed with PCR (polymerase chain reaction). PCR is a biochemical technology in molecular biology. It is used to amplify a single copy or a few copies of a piece of DNA across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence.

Primers are short DNA fragments containing sequences complementary to target region along with a DNA polymerase. PPARα expression and ligand binding was increased in a dose dependant manner for lutein. The highest interaction was seen in lutein 100mg/kg group (group VI) suggesting its possible mechanism of action. Although atorvastatin acts mainly through inhibition of HMG CoA reductase enzyme, studies have reported the upregulation of the expression of PPARα by Atorvastatin.[30] In this study reports also showed that Atorvastatin increased the expression of PPARα.

LDL receptors mediate endocytosis of cholesterol rich LDL. It is a cell surface receptor. Mutations of LDL receptor gene causes autosomal dominant hypercholesterolemia. Plasma clearance of LDL particals is mediated primarily by LDL receptor. Targeting LDL receptor expression is the most effective strategy in the management of hyperlipidemia as regulation of LDL receptor expression is a process by which cells regulate their free cholesterol content. Oxidation of LDL is a prerequisite for atherogenesis LDL becomes atherogenic when modified by oxidation, a step required for LDL uptake by scavenger receptor of macrophages forming foam cells. Maximum number of LDL receptor are present in the liver and 75% of plasma LDL is removed by hepatic LDL receptors. Statins increase expression of LDL receptors in liver.[31] Manipulation of hepatic LDL receptor gene expression is the most effective way of modulating plasma LDL-C levels. In this present study we evaluated the effect of lutein on LDL receptor in liver. Atorvastatin resulted in increased expression of LDL receptors to near normal level. LDL receptors were drastically reduced in high cholesterol diet group (group II) explaining the high level of LDL in this group. The carotenoid Lutein resulted in moderate increase in LDL receptors in a dose dependant manner. Although the upregulation of LDL receptor by Lutein is not comparable to atorvastatin group (group III) or control group (group I), it resulted in increased expression of LDL receptor compared to high cholesterol diet group (group II). This indicates the hypolipidemic potential of lutein.

CONCLUSION

This study proved that Lutein potentiates the expression of PPARα and LDLR gene in hypercholesterolemic male wistar rats compared to high cholesterol fed rats. In this preclinical study, the prophylactic effect of lutein in hyperlipidemia, was evaluated and compared with Atorvastatin. Its possible mechanism of action was found to be through the activation of PPARα and further extensive clinical studies are needed to prove this claim.

ACKNOWLEDGEMENTS

Authors would like to thank the Biochemistry Department, (R.M.M.C.H, Chidambaram) and Micro Therapeutic Research Labs Private Limited, Chennai for providing laboratory assistance in analyzing the samples used in this study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Animal Ethics Committee [160/1999/(CPCSEA)]. Proposal No - 1064

REFERENCES

1. Fruchart JC. Peroxisome proliferator-activated receptor-alpha (PPARalpha): at the crossroads of obesity, diabetes and cardiovascular disease. Atherosclerosis. 2009 Jul;205(1):1-8. Epub 2009 Mar 20.
2. Ravnskjaer K, Frigerio F, Boergesen M, Nielsen T, Maechler P, Mandrup S. PPARδ is a fatty acid sensor that enhances mitochondrial oxidation in insulin-secreting cells and protects against fatty acid-induced dysfunction. Journal of Lipid Research. 2010;51.
3. I.Issemann, Green S. Activation of a member of the steroid hormone receptor superfamily by peroxisome proliferators. Nature. 1990;347(6294):645-50.
4. Desvergne B, Wahli W. Peroxisome proliferator-activated receptors: nuclear control of metabolism. Endocrine Reviews. 1999;20(5):649-88.
5. Barbier O, Torra IP, Duguay Y, Blanquart C, Fruchart JC, Glineur C, Staels B. Pleiotropic actions of

peroxisome proliferator–activated receptors in lipid metabolism and atherosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2002 May 1;22(5):717-26.
6. Chinetti-Gbaguidi G, Fruchart JC, Staels B. Role of the PPAR family of nuclear receptors in the regulation of metabolic and cardiovascular homeostasis: new approaches to therapy. Curr Opin Pharmacol 2005;5:177-83.
7. IJpenberg A, Jeannin E, Wahli W, Desvergne B. Polarity and specific sequence requirements of peroxisome proliferator-activated receptor (PPAR)/retinoid X receptor heterodimer binding to DNA. A functional analysis of the malic enzyme gene PPAR response element. J Biol Chem. 1997;272:20108-17.
8. Feige JN, Gelman L, Michalik L, Desvergne B, Wahli W. From molecular action to physiological outputs: peroxisome proliferator-activated receptors are nuclear receptors at the crossroads of key cellular functions. Prog Lipid Res. 2006;45(2):120-59.
9. Martin G, Schoonjans K, Lefebvre AM, Staels B, Auwerx J. Coordinate regulation of the expression of the fatty acid transport protein and acyl-CoA synthetase genes by PPARalpha and PPARgamma activators. J Biol Chem. 1997;272:28210-7.
10. Chinetti-Gbaguidi G, Fruchart JC, Staels B. Role of the PPAR family of nuclear receptors in the regulation of metabolic and cardiovascular homeostasis: new approaches to therapy. Curr Opin Pharmacol. 2005;5:177-83.
11. Prieur X, Coste H, Rodriguez JC. The human apolipoprotein AV gene is regulated by PPAR and contains a novel FXR response element. J Biol Chem. 2003;278:25468-80.
12. Raspé E, Duez H, Mansén A, Fontaine C, Fiévet C, Fruchart JC, et al. Identification of Rev-erbα as a physiological repressor of apoC-III gene transcription. Journal of lipid research. 2002 Dec 1;43(12):2172-9.
13. Hiukka A, Fruchart-Najib J, Leinonen E, Hilden H, Fruchart JC, Taskinen MR. Alterations of lipids and apolipoprotein CIII in very low density lipoprotein subspecies in type 2 diabetes. Diabetologia. 2005 Jun 1;48(6):1207-15.
14. Chinetti G, Lestavel S, Remaley A, Neve B, Torra IP, Minnich A, Jaye M, Duverger N, Brewer HB, Fruchart JC, Clavey V. PPAR alpha and PPAR gamma activators induce cholesterol removal from human macrophage foam cells through stimulation of the ABC-1 pathway. Circulation. 2000 Oct 31;102(18):311.
15. Chinetti G, Lestavel S, Fruchart JC, Clavey V, Staels B. Peroxisome proliferator-activated receptor α reduces cholesterol esterification in macrophages. Circulation research. 2003 Feb 7;92(2):212-7.
16. Chinetti-Gbaguidi G, Rigamonti E, Helin L, Mutka AL, Lepore M, Fruchart JC, et al. Peroxisome proliferator-activated receptor α controls cellular cholesterol trafficking in macrophages. Journal of lipid research. 2005 Dec 1;46(12):2717-25.
17. Staels B, Koenig W, Habib A, Merval R, Lebret M, Torra IP, et al. Activation of human aortic smooth-muscle cells is inhibited by PPARα but not by PPARγ activators. Nature. 1998 Jun;393(6687):790.
18. Delerive P, Martin-Nizard F, Chinetti G, Trottein F, Fruchart JC, Najib J, et al. Peroxisome proliferator-activated receptor activators inhibit thrombin-induced endothelin-1 production in human vascular endothelial cells by inhibiting the activator protein-1 signaling pathway. Circulation research. 1999 Sep 3;85(5):394-402.
19. Slater HR, McKinney L, Packard CJ, Shepherd J. Contribution of the receptor pathway to low density lipoprotein catabolism in humans. New methods for quantitation. Arteriosclerosis, Thrombosis, and Vascular Biology. 1984 Nov 1;4(6):604-13.
20. Goldstein JL, Brown MS. The LDL receptor. Arteriosclerosis, thrombosis, and vascular biology. 2009 Apr 1;29(4):431-8.
21. Hobbs HH, Brown MS, Goldstein JL. Molecular genetics of the LDL receptor gene in familial hypercholesterolemia. Human mutation. 1992 Jan 1;1(6):445-66.
22. Soutar AK. LDL Receptor and Its Role in Inherited Disease. Medical Research Council Clinical Sciences; September 2010.
23. Soutar AK, Naoumova RP. Mechanisms of disease: genetic causes of familial hypercholesterolemia. Nature Reviews Cardiology. 2007 Apr;4(4):214.
24. Austin A, Elsie CS, Thirugnanasambantham P. Evaluating the clinical efficacy of a polyherbal formulation Arogh plus on stress a randomised clinical study. Journal of Stress Physiology & Biochemistry. 2011;7(1).
25. Hao H, Wei C, Danhong G, Bingquing H, Lin F. Oxygenated carotenoid Lutein supplementation against early atherosclerosis in apo-deficient mice through alleviation the dyslipidemia and attenuation the oxidative stress.
26. Sher T, Yi HF, McBride OW, Gonzalez FJ. cDNA cloning, chromosomal mapping, and functional characterization of human peroxisome proliferator activated receptor. Biochemistry. 1993;32(21):5598-604.
27. Kersten S, Seydoux J, Peters JM, Gonzalez FJ, Desvergne B, Wahli W. Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting; J Clin Invest. 1999;103(11):1489-98.
28. Kersten S. Integrated physiology and systems biology of PPARα. Molecular metabolism. 2014;3:354-71. PMC 4060217, PMID 24944896.
29. Braissant O, Foufelle F, Scotto C, Dauca M, Wahli W. Differential expression of peroxisome proliferator-activated receptors (PPARs) tissue distribution of PPAR-α, β, and γ in the adult rat. Endocrinology. 1995;137(1):354-66.
30. Sheng L, Ye P, Liu YX. Atorvastatin upregulates the expression of PPAR alpha/gamma and inhibits the

hypertrophy of cardiac myocytes in vitro; Zhonghua Xin Xue Guan Bing Za Zhi. 2005;33(12)1080-4.
31. Pocathikorn A, Taylor RR, Mamotte CD. Atorvastatin increases expression of low-density lipoprotein receptor mRNA in human circulating mononuclear cells; Clin. Exp. Pharmacol. Physiol. 2010;37(4):471-6.

Cite this article as: Soundarya PK, Nirmala P, Kumar AP, Krishna PT. Effect of Lutein in the expression of PPARα and LDLR in hypercholesterolemic male Wistar Rats. Int J Basic Clin Pharmacol 2018;7:684-90.