

**Athens Institute for Education and Research  
ATINER**



**ATINER's Conference Paper Series  
BIO2015-1659**

**Evaluation of Novel Compound  
Benzoylphenyl-Indole-Carboxamide Effect on  
Hyperlipidemic and Hyperglycemic Rat**

**Mahmoud Al-Shawabkeh  
Professor  
Applied Sciences University  
Jordan**

**Abdulrahim Al Jamal  
Professor  
Al-Hussein Bin Talal University  
Jordan**

**Omaymah Ghaleb Al-Jamal  
Research Assistant  
Al-Albait University  
Jordan**

An Introduction to  
ATINER's Conference Paper Series

ATINER started to publish this conference papers series in 2012. It includes only the papers submitted for publication after they were presented at one of the conferences organized by our Institute every year. This paper has been peer reviewed by at least two academic members of ATINER.

Dr. Gregory T. Papanikos  
President  
Athens Institute for Education and Research

This paper should be cited as follows:

**Al-Shawabkeh, M., Al Jamal, A. and Al-Jamal, O. G. (2015). "Evaluation of Novel Compound Benzoylphenyl-Indole-Carboxamide Effect on Hyperlipidemic and Hyperglycemic Rat", Athens: ATINER'S Conference Paper Series, No: BIO2015-1659.**

Athens Institute for Education and Research  
8 Valaoritou Street, Kolonaki, 10671 Athens, Greece  
Tel: + 30 210 3634210 Fax: + 30 210 3634209 Email: info@atiner.gr URL:  
www.atiner.gr

URL Conference Papers Series: [www.atiner.gr/papers.htm](http://www.atiner.gr/papers.htm)

Printed in Athens, Greece by the Athens Institute for Education and Research. All rights reserved. Reproduction is allowed for non-commercial purposes if the source is fully acknowledged.

ISSN: 2241-2891

26/10/2015

## **Evaluation of Novel Compound Benzoylphenyl-Indole-Carboxamide Effect on Hyperlipidemic and Hyperglycemic Rat**

**Mahmoud Al-Shawabkeh**

**Abdulrahim Al Jamal**

**Omaymah Ghaleb Al-Jamal**

### **Abstract**

Hyperlipidemia is one of the many risk factors involved in the development of cardiovascular diseases. As a consequence of hyperlipidemia treatment, a high demand for new oral antihyperlipidemic drugs is required. The present study was designed to investigate the potential effect of a novel compound N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide on diet-induced hyperlipidemic (prepared by mixing cholesterol 0.5%, 0.25 % cholic acid, 20% fat and 2% corn oil with standard powdered animal food for two months), triton-induced hyperlipidemic (by intraperitoneal injection of Triton WR-1339 250 mg/kg body weight) and alloxan-induced hyperglycemic rats (150 mg/kg body weight injected intraperitoneally). Lipid profiles [Total cholesterol (TC), Triglyceride (TG), Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL)] in all groups showed significant ( $p < 0.05$ ) changes ( $\pm$ ) before treatment. After 24 hrs of treatment with N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (15 mg/kg body weight), there was a significant decrease ( $p < 0.05$ ) in serum cholesterol level 60%, triglyceride 33-45%, LDL 32% and an increase in HDL 58% levels. Nevertheless, antihyperlipidemic fenofibrate - used as standard reference - showed parallel results to the novel compound. In addition, body weight of diet-induced hyperlipidemic rats decreased about 20%. On the other hand, the novel compound showed no significant effect on the glucose levels of hyperglycemic rats. In conclusion, the results indicate that N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide possesses significant antihyperlipidemic activity and may conserve a promising potential effect in the treatment of hyperlipidemia correlated to heart diseases.

**Keywords:** Alloxan, Hyperglycemia, Hyperlipidemia, Lipid Profiles, Triton, [4-Benzoylphenyl]-1*H*-Indole-2-Carboxamide

**Acknowledgments:** The authors greatly thank Dr. Alhiari and his team workers for supplying the novel organic compound used in this study. Thanks also to the biology department at Al-Albait University for their facilities to achieve this research.

## Introduction

Lipoproteins are large spherical complexes that transport lipids (primarily triglycerides, cholesteryl esters, and fat-soluble vitamins) through body fluids (plasma, interstitial fluid, and lymph) to be exchanged with tissues. Based on relative densities, plasma lipoproteins are classified into five major classes: chylomicrons, very low density lipoproteins (VLDL), intermediate-density lipoproteins (IDL), low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Most triglycerides are transported by chylomicrons or VLDL, and most cholesterol is carried as cholesteryl esters by LDL and HDL [1].

Abnormal high levels of cholesterol and triglycerides in the blood were identified as hyperlipidemia that can lead to severe health complications like congestive cardiac failure, atherosclerosis, pancreatitis and eventually strokes [2]. Mostly, hyperlipidemia is caused by life style habits (obesity, not exercising, and smoking) or treatable medical conditions (diabetes, kidney disease, pregnancy, and an under active thyroid gland). Other factors such as genetic, sex and age may also contribute to hyperlipidemia [3]

Interestingly, the risky effect of hyperlipidemia was postulated to alleviate vasomotor disturbances due to peroxides and free radical synthesized by the metabolic reactions of diet-derived lipids in the arterial wall and serum that hasten the progression of atherosclerosis [4]. Progressively, these compounds induce endothelial cell injury by oxidizing low density lipoproteins (LDLs) that will damage the arterial walls [5].

Antihyperlipidemic drugs or lipid-lowering strategies which mainly act as antioxidants, may have a beneficial role in normalizing vascular function and greatly decreasing the frequency of clinical events associated with atherosclerosis. Several classes of drugs are used to treat hyperlipidemia. These classes have different mechanisms of action in reducing types and magnitudes of lipids. For example, Statins - the most common group of antihyperlipidemic drugs- lowers cholesterol by interrupting the cholesterol biosynthetic pathway [5, 6]. More or less, the Fibrate group decreases fatty acids and triglyceride levels by stimulating the peroxisomal *b*-oxidation pathway [7, 8]. Apart from these drugs, other groups selectively inhibit intestinal cholesterol absorption or esterification [9], microsomal triglyceride transfer proteins or sequestering bile acids [10]. Virtually, Triton WR-1339 (Tyloxapol), a non-ionic detergent, has been widely used to induce acute hyperlipidemia in animal models through inhibition of the clearance of triglyceride-rich lipoproteins [11]. Since hyperlipidemia is mostly associated with hyperglycemia and both are considered major risk factors for the development of cardiovascular diseases [12], researchers are focusing toward discovering new drugs capable of reducing or regulating glucose levels and lipid profile parameters [total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and high density lipoproteins (HDL)]. Optimistic attempts of using some medicinal plants such as bay leaves, fenugreek, rosemary and cinnamon were reported to

reduce the level of either glucose or/and lipid profiles in mice, rats and humans as well [13-16].

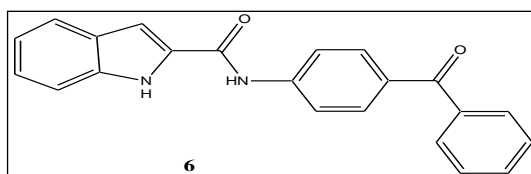
Pharmaceutical reports mention that indole-2-carboxamide derivatives are also known as hypolipidemic agents [17], and anti-allergics [18] in addition to their potential role as antioxidants [19-21].

The present work is based on the discovery of a novel synthesized benzoylphenylindole carboxamide compound [22-24] to illustrate its effect on hyperlipidemic and hyperglycemic rat models.

## Materials and Methods

### Material Preparations

- a. Hyperlipidemic diet: prepared as described by (25) for induction of hyperlipidemia experimental rats using 2% corn oil, 0.5% cholesterol, 0.25 % cholic acid, and 20% fat.
- b. Preparation of an antihyperlipidemic chemical compound:



N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) was newly prepared by using esterification of Ethyl-1H-Indole-2-Carboxylate treated with 4-aminobenzophenone in the presence of sodium ethoxide and DMF. The compound was dissolved in 4% dimethylsulfoxide (DMSO) [21, 22].

- c. Fenofibrate [(2-[4-(4-Chlorobenzoyl)phenoxy]-2-methylpropanoic acid isopropyl ester) Sigma-Aldrich, USA] dissolved in 4% DMSO.
- d. Triton WR-1339 (Tyloxapol, Sigma-Aldrich, USA) dissolved in 4% DMSO.
- e. Alloxan monohydrate (B.O.H chemical LTD England) dissolved in fresh normal saline.

### Animal Models

- a. Model of hyperlipidemia: hyperlipidemia in rats was induced either by a hyperlipidemic diet 2 months before starting treatment or by Triton WR-1339 administrated intraperitoneally as a 2.0 ml dose (250 mg/kg body weight) 24 hrs before treatment [21, 24].
- b. Model of hyperglycemia: Normal Rats were made hyperglycemic by injecting alloxan intraperitoneally as 1.0 ml dose (150 mg/kg body weight) 24 hrs before treatment [26].

### Experimental Design

Adult male Wister rats weighing 150-180 g obtained from the animal house of the Jordan University of Science and Technology were used in this

study. The rats were harbored in stainless steel cages under standard laboratory condition. The animals were maintained at a 12 h light-dark cycle. Water and food were provided *ad libitum*. The rats received intraperitoneal injections and were distributed into the following groups:

- The control groups received 2.0 ml of normal saline or 2.0 ml of 4% DMSO and were fed normally.
- The Hyperlipidemic and Hyperglycemic groups were injected either by 2.0 ml of N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (15 mg/Kg body weight) or 2.0 ml of fenofibrate (5 mg/kg body weight).

### *Experimental Analysis*

#### Acute Oral Toxicity Study

Acute oral toxicity assay was performed to estimate the lethal dose (LD<sub>50</sub>) concentration of the target compound N-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) using six different concentrations of the compound (200, 400, 600, 800, 1000 and 1200 mg/kg), which were orally administered to each group of the six rats that were carefully and daily recorded over a period of 72 hours.

#### Evaluating the Effect of BIC and Fenofibrate (FF) on Body Weight

The Hyperlipidemic group rats were injected daily either by 2.0 ml of BIC (15 mg/Kg body weight) or 2.0 ml of FF (5 mg/kg body weight) for 4 weeks consequently.

#### Determination of Serum Lipid Profiles

Blood samples of 2-3 ml were aspirated and collected in non-heparinized tubes from anesthetized rats through heart puncture and then centrifuged at 3000 rpm for 10 min at room temperature. The serum lipid profile levels of total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL) and high density lipoprotein (HDL) level were measured by using bio Merieux Kits specified for each parameter (bio Merieux Lab. reagent and product, France).

#### Determination of Blood Glucose Level

Whole blood samples from the lateral vein of the tail were collected in heparinized capillary tubes before and after 24 hrs of treatment, and the blood glucose levels were determined by a strip fast method (Infopia Co., Ltd.Korea). Only rats with blood glucose levels above 200 mg/100 ml were considered and employed in the study.

#### Statistical Analysis

All data were analyzed by using the Student's t-test and expressed as mean  $\pm$  SD where  $P < 0.05$  were considered statistically significant.

## Results

### *Lethal Dose Determination of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC)*

Acute oral toxicity results in Table 1 showed that the lethal dose (LD<sub>50</sub>) of the target compound N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) was estimated to be about 800 mg/kg which is equivalent to ≈ 200 mg for a rat weighing 250 g. However, the fenofibrate dose was 5 mg/kg based on literature recommendation [27].

### *Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) Derivative Compound and Fenofibrate (FF) on Body Weight*

Changes in the body weight of the experimental group are shown in (Table 2). The body weight of diet-induced hyperlipidemic group for two months was increased by 25% due to their diet. However, after 4 weeks of treatment, both BIC and FB showed a 23% decrease in the body weight of diet-induced hyperlipidemic animals but with no effect on the control or Triton groups.

### *Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) Derivative Compound and Fenofibrate (FF) on Lipid Profile Parameters*

The results indicate that BIC significantly affects all lipid parameters in both hyperlipidemic model animals. The reduction in the level of total cholesterol was 60 % (Table 2), triglyceride 33-45% (Table 3), and low density lipoprotein 32% (Table 4). However, the high density lipoprotein increased by 58% (Table 5). The BIC results showed an improved effect on lipid parameters especially HDL 2.5 folds more when compared with fenofibrate results.

### *Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide (BIC) Derivative Compound and Fenofibrate (FF) on Glucose Level*

The results in Table 6 showed that both BIC and fenofibrate showed no significant change in the glucose level in all animal models (hyperlipidemic and hyperglycemic).

**Table 1.** Toxicity Effect of N-[4-benzoylphenyl]-1H-indole-2-carboxamide on Rat Survival

Dose (mg/kg)	Survival rate %
200	100 %
400	100 %
600	83 %
800	50 %
1000	17 %
1200	0 %

**Table 2.** Effect of *N*-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) and Fenofibrate (FF) on the Body Weight of Hyperlipidemic Rats

	Normal rat			Diet Hyperlipidemic rat			Triton Hyperlipidemic rat		
	1 <sup>st</sup> day	After 4 weeks	Change %	1 <sup>st</sup> day	After 4 weeks	Change %	1 <sup>st</sup> day	After 4 weeks	Change %
DMSO	182.3 ± 1.8	190.6 ± 1.8	< 1	229.0±3.3*	226.5 ± 4.3*	+ 25	196.2 ± 2.2	192.2 ± 1.6	< 1
BIC	183.4 ± 1.5	195.2 ± 1.6	< 1	215.0±4.6	173.5 ± 4.7**	- 23	192.2 ± 3.4	191.6 ± 1.3	< 1
FF	185.7 ± 1.7	189.6 ± 1.4	< 1	214.6±5.2	172.2± 2.0**	- 23	193.8 ± 4.6	190.8 ± 1.6	< 1

> Values are means ± SEM.

> DMSO : dimethylsulfoxide

\* Statistically Significant when compared to the control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to the Hyperlipidemic group at  $P < 0.05$ .

**Table 2.** Effect of *N*-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) and Fenofibrate (FF) on Rat Serum Cholesterol

	Normal rat			Diet Hyperlipidemic rat		Triton Hyperlipidemic rat	
	1 <sup>st</sup> day	After 4 weeks	Change %	After 4 weeks	Change %	After 24 hrs	Change %
DMSO	85.3±3.8	87.3±4.8	< 1	315.4 ±5.5*	+270	313.4 ±5.5*	+268
BIC	83.3±5.5	78.3±3.7	< 1	119.2±3.4**	- 60	116.2±3.4**	- 60
FF	82.3±7.4	79.3±4.4	< 1	97.3±2.4**	- 66	99.3±2.4**	- 66

>Values are means ± SEM.

\* Statistically Significant when compared to the control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to the Hyperlipidemic group at  $P < 0.05$ .

**Table 3.** Effect of *N*-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) and Fenofibrate (FF) on Rat Serum Triglyceride

	Normal rat			Diet Hyperlipidemic		Triton Hyperlipidemic	
	1 <sup>st</sup> day	After 4 weeks	Change %	After 4 weeks	Change %	After 24 hrs	Change %
DMSO	82.1±2.2	84.1±2.2	< 1	125.1±4.6*	+ 55	189.1±4.6*	+55
BIC	80.1±3.6	83.1±5.7	< 1	83.1±5.7**	-33	106.5±2.6**	-45
FF	84.1±4.1	84.2±3.3	< 1	87.2±3.3**	30	20.1±602**	- 35

> Values are means ± SEM.

> DMSO: dimethylsulfoxide

\* Statistically Significant when compared to the control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to the Hyperlipidemic group at  $P < 0.05$ .



**Table 4.** Effect of *N*-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) and Fenofibrate (FF) on Rat Serum Low Density Lipoprotein (LDL)

	Normal rat			Diet Hyperlipidemic		Triton Hyperlipidemic	
	1 <sup>st</sup> day	After 4 weeks	Change %	After 4 weeks	Change %	After 24 hrs	Change %
DMSO	29.2±1.4	31.1±1.9	< 1	62.3±2.5	< 1	62.3±2.5	< 1
BIC	31.2±1.9	29.4±2.1	< 1	41.3±1.5**	- 32	41.3±1.5**	-32
FF	28.9±1.1	30.1±1.2	< 1	39.7±1.2**	-32	39.7±1.2**	-32

> Values are means ± SEM.

> DMSO: dimethylsulfoxide

\* Statistically Significant when compared to the control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to the Hyperlipidemic group at  $P < 0.05$ .

**Table 5.** Effect of *N*-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) and Fenofibrate (FF) on Rat Serum High Density Lipoprotein (HDL)

	Normal rat			Diet Hyperlipidemic rat		Triton Hyperlipidemic rat	
	1 <sup>st</sup> day	After 4 weeks	Change %	After 4 weeks	Change %	After 24 hrs	Change %
DMSO	41.2±1.2	42.1±1.3	< 1	31.2±2.1	< 1	31.2±2.1	< 1
BIC	42.1±1.7	45.3±1.5	< 1	49.5±1.1**	+58	49.5±1.1**	+58
FF	44.3±1.4	42.4±1.1	< 1	40.2±1.4**	+23	36.2±1.4**	+23

> Values are means ± SEM.

> DMSO: dimethylsulfoxide

\* Statistically significant when compared to the control group at  $P < 0.05$ .

\*\* Statistically significant when compared to the Hyperlipidemic group at  $P < 0.05$ .

**Table 6.** Effect of *N*-[4-benzoylphenyl]-1*H*-indole-2-carboxamide (BIC) and Fenofibrate (FF) on Rat Plasma Glucose

	Normal rat			Diet Hyperlipidemic			Hyperglycemic		
	1 <sup>st</sup> day	After 4 weeks	Change %	1 <sup>st</sup> day	After 4 weeks	Change %	1 <sup>st</sup> day	After 4 weeks	Change %
NS	95.3±2.5	94.4±3.5	< 1	95.4±1.5	97.4±4.5	< 1	322.4±2.2	325.4±4.2	< 1
DMSO	93.2±2.4	95.5±2.5	< 1	94.3±4.2	96.3±4.6	< 1	320.4±6.3	323.4±6.3	< 1
BIC	96.3±3.3	97.4±4.5	< 1	96.4±3.5	94.4±4.5	< 1	331.2±3.7	335.2±3.7	< 1
FF	94.4±4.5	93.3±4.6	< 1	98.3±4.6	99.3±4.6	< 1	325.4±4.5	328.4±4.7	< 1

> Values are means ± SEM.

> NS: normal saline

> DMSO: dimethylsulfoxide

\* Statistically Significant when compared to the control group at  $P < 0.05$ .

\*\* Statistically Significant when compared to the Hyperlipidemic group

## Discussion

Hyperlipidemia is a major contributor for health problems and leads to atherosclerosis, and the induction of various tissues damage, which in turn, alters the cellular functions resulting to many pathological conditions [28]. A high-fat diet was demonstrated to be a major factor in uprising hyperlipidemia. In this study, hyperlipidemic-induced animal models showed high levels of lipid profiles. In addition, their body weight was significantly increased indicating that a high-fat diet may cause hyperlipidemia which ultimately leads to obesity. These results agree with previous studies who declared that the addition of corn oil increased the level of TG and decreased in serum HDL [29]. Increasing the level of lipid profiles in diet- induced hyperlipidemic rats may be attributed to the presence of corn oil, which increases the synthesis and release of LDL and VLDL from the liver into the circulation and decreases the activity of mitochondrial carnitine palmitoyl transferase-1 (PTS-1), which weakens fatty acid oxidation and lipid accumulation [25]. It has been reported that the administration of Triton WR-1339 to adult rats produces hyperlipidemia in which cholesterol, triglycerides and phospholipids increase to a maximum in about 24 hours and decrease thereafter in about 20 hours of treatment with other BIC derivatives [22, 23] Triton WR-1339 was found to act as a surfactant that suppresses the action of lipase and the increase of VLDL secretion by the liver and blocks the uptake of lipoproteins from the circulation by extra hepatic tissues causing an increase in the levels of the circulating lipid [26]. The present results showed significant increase in lipid profile (TC, TG, and LDL) and significant decrease in HDL in the animals 24 hours after the Triton WR-1339 treatment. Interestingly, the results of the present study show that the used dose of N-[4-benzoylphenyl]-1H-indole-2-carboxamide at dose (15 mg/Kg body weight) was able to reverse the drastic effect induced by Triton WR-1339 in rats within a 24 hour treatment. Other lipid-lowering agents were found to exert their outcomes via affecting the catabolism of apo-B lipoproteins [27, 30]. Meanwhile, HDL was found to facilitate the mobilization of triglycerides and cholesterol from plasma to the liver where it is catabolized and eliminated in the form of bile acids [28]. Hence, this may interpret the inverse relation between LDL and HDL [31]. On the other hand, the fenofibrate also showed significant changes of the lipid profile as shown in our results. The fenofibrate compound used in our experiment, showed coincide results with previous studies which have examined the effects of fenofibrate on daily food intake, body weight, and the lipid profile in rodent models of obesity [27].

Alloxan was reported to induce diabetes by damaging the insulin secreting cells of the pancreas leading to hyperglycemia [26, 32, 33]. In the present study, alloxan-induced animals showed hyperglycemic levels. However, our results in this concern showed that N-[4-benzoylphenyl]-1H-indole-2-carboxamide didn't employ any significant changes. Nevertheless, Diabetes mellitus is known to cause hyperlipidemia through various metabolic derangements, in which insulin deficiency has been known to stimulate

lipolysis in the adipose tissue and gives rise to hyperlipidemia and fatty liver [34].

## Conclusions

A hyperlipidemic diet can increase body weight and levels of the lipid profile (TC, TG, and LDL). The newly prepared compound was found to reverse this increase in our animal models without showing any significant effect on the hyperglycemic glucose level. Further studies are needed to elucidate and assess the mechanism of action of this newly prepared compound as a lipid-lowering agent.

## References

1. Reilly M, Rader DJ. Apolipoprotein E and coronary disease: A puzzling paradox. *PLoS Medicine*. 2006. p. 0736–8.
2. Ueshima K, Akihisa-Umeno H, Nagayoshi A, Takakura S, Matsuo M, Mutoh S. Implitapide, a microsomal triglyceride transfer protein inhibitor, reduces progression of atherosclerosis in apolipoprotein E knockout mice fed a Western-type diet: involvement of the inhibition of postprandial triglyceride elevation. *Biol Pharm Bull*. 2005;28:247–52.
3. Ruixing Y1, Jinzhen W, Weixiong L, Yuming C, Dezhai Y SP. The environmental and genetic evidence for the association of hyperlipidemia and hypertension. *J Hypertens*. 2009;27(2):251–8.
4. Chien C-T, Chang W-T, Chen H-W, Wang T-D, Liou S-Y, Chen T-J, et al. Ascorbate supplement reduces oxidative stress in dyslipidemic patients undergoing apheresis. *Arterioscler Thromb Vasc Biol* [Internet]. 2004 Jun [cited 2014 Dec 1];24(6):1111–7. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/15072991>.
5. Harman D. Free radical theory of aging. *Mutat Res*. 1992;275:257–66.
6. Krukemyer JJ, Talbert RL. Lovastatin: a new cholesterol-lowering agent. *Pharmacotherapy*. 1987;7:198–210.
7. Hebert PR, Gaziano JM, Hennekens CH. An overview of trials of cholesterol lowering and risk of stroke. *Arch Intern Med*. 1995;155:50–5.
8. Bard J-M, Parra H, Camare R, Luc G, O Z, C D, et al. A multicenter comparison of the effects of simvastatin and fenofibrate therapy in severe primary hypercholesterolemia, with particular emphasis on lipoproteins defined by their apolipoprotein composition. *Metabolism*. 1992;41:498–503.
9. Gauthier A, Lau P, Zha X, Milne R, McPherson R. Cholesteryl ester transfer protein directly mediates selective uptake of high density lipoprotein cholesteryl esters by the liver. *Arterioscler Thromb Vasc Biol*. 2005;25:2177–84.
10. Steinmetz KL. Colesevelam hydrochloride. *American Journal of Health-System Pharmacy*. 2002. p. 932–9.
11. Ågren JJ, Kurvinen JP, Kuksis A. Isolation of very low density lipoprotein phospholipids enriched in ethanolamine phospholipids from rats injected with Triton WR 1339. *Biochim Biophys Acta - Mol Cell Biol Lipids*. 2005;1734:34–43.

12. Frishman W. Biologic markers as predictors of cardiovascular disease. *Am J Med.* 1998;104:18S – 27S.
13. Aljamal A. Effects of Bay Leaves on Blood Glucose and Lipid Profiles on the Patients with Type 1 Diabetes. 2010;211–4.
14. Eidi A, Eidi M, Sokhteh M. Effect of fenugreek (*Trigonella foenum-graecum* L) seeds on serum parameters in normal and streptozotocin-induced diabetic rats. *Nutr Res.* 2007;27:728–33.
15. Aljamal A, Ibrahim A, Al-fararjeh MA, Alqadi T. Effects of rosemary on lipid profile in diabetic rats. *African J Plant Sci* [Internet]. 2012 Apr 6 [cited 2014 Nov 29];6(7):222–5. Available from: [http://www.academicjournals.org/ajps/abstracts/abstracts/abstract2012/6April/Aljamal et al.htm](http://www.academicjournals.org/ajps/abstracts/abstracts/abstract2012/6April/Aljamal%20et%20al.htm)
16. Mang B, Wolters M, Schmitt B, Kelb K, Lichtinghagen R, Stichtenoth DO, et al. Effects of a cinnamon extract on plasma glucose, HbA<sub>1c</sub>, and serum lipids in diabetes mellitus type 2. *Eur J Clin Invest.* 2006;36:340–4.
17. Gurkan AS, Karabay A, Buyukbingol Z, Adejare A, Buyukbingol E. Syntheses of novel indole lipoic acid derivatives and their antioxidant effects on lipid peroxidation. *Arch Pharm (Weinheim).* 2005;338:67–73.
18. Ezeamuzie CI, El-Hashim AZ, Renno WM, Edafiohio IO. Antiallergic and antiasthmatic effects of a novel enhydrizinone ester (CEE-1): inhibition of activation of both mast cells and eosinophils. *J Pharmacol Exp Ther* [Internet]. 2014;350:444–54. Available from: <http://jpet.aspetjournals.org.ezproxy.is.ed.ac.uk/content/350/2/444>
19. Suzen S, Cihaner SS, Coban T. Synthesis and comparison of antioxidant properties of indole-based melatonin analogue indole amino acid derivatives. *Chem Biol Drug Des.* 2012;79:76–83.
20. Olgen S, Kiliç Z, Ada AO, Coban T. Synthesis and evaluation of novel N-H and N-substituted indole-2- and 3-carboxamide derivatives as antioxidants agents. *J Enzyme Inhib Med Chem.* 2007;22:457–62.
21. Prabhakar PK, Doble M. Mechanism of action of natural products used in the treatment of diabetes mellitus. *Chin J Integr Med.* 2011;17(8):563–74.
22. Al-Qirim T, Shahwan M, Shattat G, Al-Hiari Y, Sheikha GA, Zaidi S. Pharmacological evaluation of novel indole-2-carboxamides as potent lipid-lowering agents in triton-WR-1339-induced hyperlipidemic rats. *Zeitschrift fur Naturforsch (Journal of Natural Sciences) - Sect C J Biosci.* 2009;64:619–25.
23. Al-Hiari Y, Shattat G, Al-Qirim T, El-Huneidi W, Sheikha GA, Hikmat S. Antihyperlipidemic properties of novel N-(benzoylphenyl)-5-substituted-1H-indole-2-carboxamides in Triton WR-1339-induced hyperlipidemic rats. *Molecules.* 2011;16:8292–304.
24. Shattat G, Al-Qirim T, Sweidan K, Shahwan M, El-Huneidi W, Al-Hiari Y. The hypolipidemic activity of novel benzofuran-2-carboxamide derivatives in Triton WR-1339-induced hyperlipidemic rats: a comparison with bezafibrate. *J Enzyme Inhib Med Chem.* 2010;25:751–5.
25. Baddar NWA-H, Aburjai TA, Taha MO, Disi AM. Thujone corrects cholesterol and triglyceride profiles in diabetic rat model. *Nat Prod Res.* 2011;25:1180–4.
26. Kianbakht S, Hajiaghvaei R. Anti-hyperglycemic effects of saffron and its active constituents, crocin and safranal, in alloxan-induced diabetic rats. *J Med Plants.* 2011;10(39):82–9.
27. Kadian S, Mahadevan N, Balakumar P. Differential effects of low-dose fenofibrate treatment in diabetic rats with early onset nephropathy and established

- nephropathy. *Eur J Pharmacol* [Internet]. 2013 Jan 5 [cited 2014 Dec 1];698(1-3):388–96. Available from:  
<http://www.sciencedirect.com/science/article/pii/S0014299912008588>
28. Chander R, Kapoor K SC. Lipid peroxidation of hyperlipidemic rat serum in chronic ethanol and acetaldehyde administration. *J Biosci.* 2003;13:289–274.
  29. Ismael OE, Hashish EA, Ali HA. Lipid Profile and Lipogenesis Following Corn Oil, Truffle Oil or Wheat Germ Oil Administration in Albino Rat. 2014;12(4):461–9.
  30. Z. Yunke, L. Guoping CZ. Triglyceride-to-HDL cholesterol ratio. *Herz.* 2014;39(1):105–10.
  31. Pati HN, Das U, Quail JW, Kawase M, Sakagami H, Dimmock JR. Cytotoxic 3,5-bis(benzylidene)piperidin-4-ones and N-acyl analogs displaying selective toxicity for malignant cells. *Eur J Med Chem* [Internet]. 2008 Jan [cited 2014 Dec 3];43(1):1–7. Available from:  
<http://www.sciencedirect.com/science/article/pii/S0223523407001456>
  32. Anila L, Vijayalakshmi NR. Antioxidant action of flavonoids from *Mangifera indica* and *Embllica officinalis* in hypercholesterolemic rats. *Food Chem.* 2003;83:569–74.
  33. Sharma US, Kumar A. Original Article : Anti-diabetic effect of *Rubus ellipticus* fruit extracts in alloxan induced diabetic rats. 2011;(June):2–7.
  34. Greene CM, Zern TL, Wood RJ, Shrestha S, Aggarwal D, Sharman MJ, et al. Human Nutrition and Metabolism Maintenance of the LDL Cholesterol : HDL Cholesterol Ratio in an Elderly Population Given a Dietary Cholesterol Challenge 1. 2005;(August):2793–8.