PHARMACOLOGICAL EFFECTS OF GEMFIBROZIL ON SOME CARDIOVASCULAR PREPARATIONS OF EXPERIMENTAL ANIMALS

By

Enass Abd El-Aty Ouda*

FROM

Assistant Professor of Pharmacology Faculty of Medicine (Girls) – Al-Azhar University

ABSTRACT

Background:

Gemfibrozil (member of fibrates) is Peroxisome proliferator activated receptors (PPAR-α) agonist which improves lipid profiles particulary very low density lipoprotein and high density lipoprotein in patients with dyslipidemia. **Objective:** Studying the pharmacological effects of Gemfibrozil on some cardiovascular preparations of experimental animals. **Materials and Methods:** The experiments were conducted to study the effect of different doses of gemfibrozil on isolated perfused rabbit heart & coronary flow, isolated rabbit aortic spiral strip and mean arterial blood pressure of anaesthetized cats. Each experiment was done on six preparations. **Results:** ***In-vitro study:*** on isolated perfused rabbit heart, gemfibrozil (25-800µg/ml) produced a dose-dependent reduction on the amplitude of myocardial contractions. The inhibitory effect of gemfibrozil (100µg/ml) was not abolished after complete blockade of nicotinic and muscarinic receptors while it was completely abolished after inhibition of nitric oxide synthase by N-methyl L-arginine. On the other hand the stimulatory effects of calcium gluconate, isoprenaline, histamine and serotonin were not abolished after administration of gemfibrozil (100µg/ml). On coronary flow of isolated perfused rabbit heart, gemfibrozil (25-800µg/ml) produced also a dose-dependent reduction of coronary flow. On isolated spiral aortic strips of rabbit , gemfibrozil produced dose-dependent significant reduction on nor-epinpherine (NE) induced contraction. ***In-vivo study*** gemfibrozil produced a dose-dependent significant reduction in mean arterial blood pressure (MABP) of anaesthetized cats. **Conclusion:** Gemfibrozil produced a negative inotropic effect through nitric oxide release with a decrease in coronary flow. It also reduced NE-induced contractions of aortic spiral strips with reduction in mean arterial blood pressure. So it must me used cauciously in cases of heart failure, but it could be beneficial in hypertensive patient with atherosclerosis.

Key words:

Gemfibrozil, Isolated Prefused Rabbit Heart, Aortic Spiral Strips Anaesthetized cats .

*The experiment in this study on isolated rabbit heart and coronary flow is part of MSC thesis presented by Azza El-kassas . Under supervision of Fatma Sabry , Azza Ezzo & Enass Ouda

INTRODUCTION

Peroxisome proliferator activated receptors (PPARs) are steroid receptors that exhibit broad tissue expression pattern ***(Mandard et al., 2004 and Fuentes et al., 2013).*** They regulate the expression of a wide array of genes that are involved in fatty acids uptake and oxidation, inflammations and vascular function ***(Steals and Fruchart, 2005).*** The intensive studies of PPARs have revealed their importance in both normal physiology and pathology of various tissues ***(Ehrmann, 2002)***.

The heart contains high levels of all PPARs, little is known about how PPARs ligands affect cardiac functions ***(Brandt et al., 1998).*** Nothing is known about the role of PPARs in cardiac diseases ***(Bailey, 2000)***. It is still unclear whether PPARs agonists are beneficial or harmful for heart failure cases ***(Chen et al., 2008).*** In addition to that ***Robins et al. (2001)*** reported that fibrates (PPARs agonists) produce a significant reduction in coronary heart disease in patients with low HDL cholesterol levels.

The cardiovascular effect of fibrates was studied by many authors who mentioned that fibrates exert beneficial effects in prevention of cardiovascular diseases through activation of PPAR-α which seems to protect the heart from ischemia/reperfusion myocardial injury ***(Yue et al., 2003)***. PPAR-α ligands not only reduce the incidence of cardiovascular diseases but also their cardioprotective efficacy is higher in dyslipidemic patient with diabetes or hyperinsulinemia, in which the cardiovascular diseases are the major cause of mortality ***(Steiner, 2001, Rubins et al., 2002 and Israelian-Konaraki and Reaven, 2005)***. Gemfibrozil is one of the most widely used antihyperlipidemic drugs in the world and has been shown to be effective in preventing coronary heart diseases in hyperlipidemic patients and in patients with low level of HDL cholesterol and normal or low level of LDL cholesterol ***(Vosper et al., 2002)***.

From another point of view, the effect of PPARs activation on diseased heart was mentioned by ***Schiffrin (2005)*** who reported that, PPAR-α is expressed in cardiomyocytes and regulates gene expression of key proteins involved in myocardial lipid and energy metabolism. PPAR-α activity may significantly contribute to cardiac hypertrophy and overall cardiovascular remodeling. In addition, ***Goikoetxea et al. (2004)*** reported that, under conditions of pressure overload, there is suggestion of a potential role of PPAR-α in the transition from compensated heart hypertrophy to heart failure in hypertensive heart disease.

Moreover It was concluded that, PPAR-α agonists have demonstrated significant anti-inflammatory activity that seem to play not only a role in their protective actions within the cardiovascular system ***(Berger et al., 2005)***, but also may have benefits in therapeutic intervention in other inflammatory diseases ***(Murphy and Holder, 2000 and Moore et al., 2001)***.

So this work was performed to study the pharmacological effect on some cardiovascular preparation including experiments on isolated cardiac muscle, coronary flow, spiral aortic strips & arterial blood pressure . Its possible mechanism of action was also done .

MATERIALS AND METHODS

Gemfibrozil was supplied in the form of tablets which were film coated Each tablet contained 600mg gemfibrozil which was dissolved in distilled water **. *It was tested on the following strips:***

I- In-vitro study

- **Experiments on isolated perfused rabbit heart and coronary flow: *(The staff of the department of pharmacology, Edinburgh, 1970).***

The effect of test drug on cardiac contractions was obtained using gradually increasing doses of gemfibrozil (25-800µg/ml) and coronary flow. **For site of action** of gemfibrozil (100µg/ml), the effect of test drug (100µg/ml) on the amplitude of myocardial contractions was recorded before and after complete blockade of nicotinic and muscrinic cholinergic receptors by appropriated doses of nicotinic (10µg/ml) and atropine (10µg/ml). Also the effect of gemfibrozil was tested on calcium channels using calcium glucoicate (300 µg/ml) ; in addition its effect on isoprenaline (0.3µg/ml), histamine (0.05µg/ml), serotanine (0.1µg/ml) induced myocardial contractions and after L-arginine (inhibitor of nitric oxide synthase , NOS)

- **Experiments on isolated aortic spiral strips of rabbit *(Furchgott and Bhadrakom, 1984)*:**

The effect of gemfibrozil (25-800ug/ml) on the NE- induced contractions was tested after incubation 35 minutes. The experiment was done on six prepartions .

II- In-vivo study

- **Experiments on arterial blood pressure of anaesthetized cats *(The staff of the department of pharmacology, Edinburgh, 1970).***

The effect of gemfibrozil (1-8 mg/kg-iv) on mean arterial blood pressure of anaesthetized cats was recorded.

Statistical analysis: Statistical analysis was done using SPSS 14.0 for windows. Significant value was considered when p value <0.05. Student t-test of significant was used ***(Steel and Torrie, 1964).***

RESULTS

I- In-vitro study:

- **Experiments on isolated perfused rabbit heart and coronary flow:**

Gemfibrozil (25-800µg/ml) produced a dose-dependent reduction on the amplitude of myocardial contractions (Fig.1). The mean percent reduction ± SEM ranged from 22.97 ± 1.87 to 85.65 ± 3.81 and was found to be statistically significant Table (1), (Fig.2). On coronary flow (ml/min) Gemfibrozil (25-800µg/ml): Gemfibrozil (25-800µg/ml) produced a dose-dependent reduction of coronary flow. The mean percent reduction ± SEM ranged from 20.92 ± 2.83 to 87.48 ± 2.94 and was found to be statistically significant (Table 2). { Gemfibrozil (100µg/m)} produced reduction of the amplitude of myocardial contractions

after complete blockade of nicotinic and muscarinic receptors. The stimulant effect of either calcium gluconate (300µg/ml), Isoprenaline (0.3µg/ml), histamine (0.05µg/ml), or serotonin (0.1µg/ml), on the amplitude of myocardial contractions was not abolished after administration of gemfibrozil (100µg/ml). On the other hand , the inhibitory effect of gemfibrozil (100µg/ml) on the amplitude of myocardial contractions was completely abolished after inhibition of nitric oxide synthase by N-methyl L- arginine (100µg/ml) (Fig.2-8).

- **Experiments on isolated rabbit aortic spiral strips:**

Gemfibrozil (25-800µg/ml) produced a dose-dependent significant reduction on the NE-induced contractions. The mean percent reduction ± SEM ranged from 5.31 ± 1.42 to 65.14 ± 5.32 and was found to be statistically significant while the first dose (25ug/ml) has no effect Table (3), (Fig.9).

II- In-vivo study:

- **Experiments on mean arterial blood pressure of anaesthetized cats:**

Gemfibrozil (5-160mg/kg-iv) produced a dose-depended reduction on the mean arterial blood pressure of anaesthetized cats. The mean percent reduction ± SEM ranged from 8.17 ± 1.40 to 58.2 ± 3.1 and was found to be statistically significant Table (4), (Fig. 10).

Table (1): Mean % reduction caused by gemfibrozil (25-800 µg/ml) on the amplitude of myocardial contractions (cm) of isolated perfused rabbit heart (Mean % ± SEM).

Doses / Ug / ml	25	50	100	200	400	800
Mean%	22.97	38.86	50.52	63.00	74.42	85.65
±SEM	1.87	2.38	2.51	1.86	1.78	3.81
P	*<0.001	*<0.001	*<0.001	*<0.001	*<0.001	*<0.001

% Red: percent reduction. ±SEM: standard error of mean. * : significant (P < 0.05)

Table (2): Mean % reduction caused by gemfibrozil (25-800µg/ml) on coronary flow (ml/min) of isolated perfused rabbit heart (Mean % ± SEM).

Doses / Ug/ml	25	50	100	200	400	800
Mean%	20.92	35.42	46.77	63.10	75.76	87.48
±SEM	2.83	2.41	2.02	2.41	2.96	2.94
P	*<0.001	*<0.001	*<0.001	*<0.001	*<0.001	*<0.001

% Red: percent reduction. ±SEM: standard error of mean. *: significant (p < 0.05)

Table (3): Mean % reduction caused by gemfibrozil (25-800µg/ml) of nor-epinephrine-induced contractions (cm) of rabbit aortic spiral strips (Mean % ± SEM).

[1]Doses / Ug/ml	25	50	100	200	400	800
Mean%	0.00	5.31	8.57	15.32	37.67	65.14
±SEM	0.00	1.42	2.5	3.7	3.92	5.32
P	0.00	*<0.05	*<0.001	*<0.001	*<0.001	*<0.001

% Red: percent reduction. ±SEM: standard error of mean *: significant ($p < 0.05$)

Table (4): Mean % reduction caused by gemfibrozil (5-160mg/kg) on mean arterial blood pressure (mmHg) of anaesthetized cats (Mean % ±SEM).

Doses / Mg/kg	5	10	20	40	80	160
Mean%	8.17	14.73	19.12	28.21	35.2	58.2
±SEM	1.40	1.08	1.02	1.3	2.1	3.1
P	*<0.05	*<0.001	*<0.001	*<0.001	*<0.001	*<0.001

% Red: percent reduction. ±SEM: standard error of mean. *: significant ($p < 0.05$)

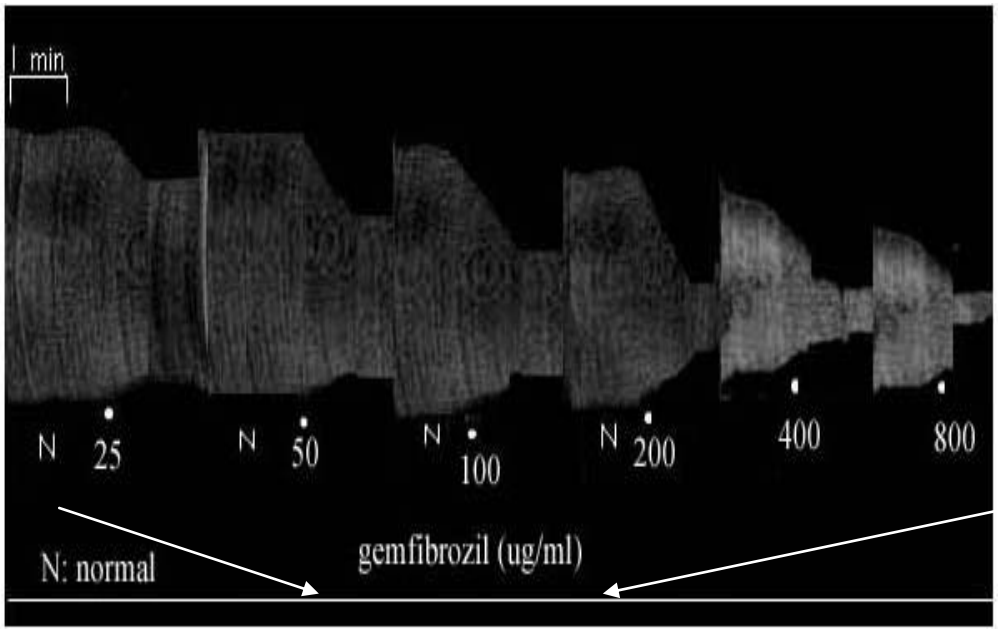

Figure (1): Effect of gemfibrozil (25-800µg/ml) on the amplitude of myocardial contractions of isolated perfused rabbit heart.

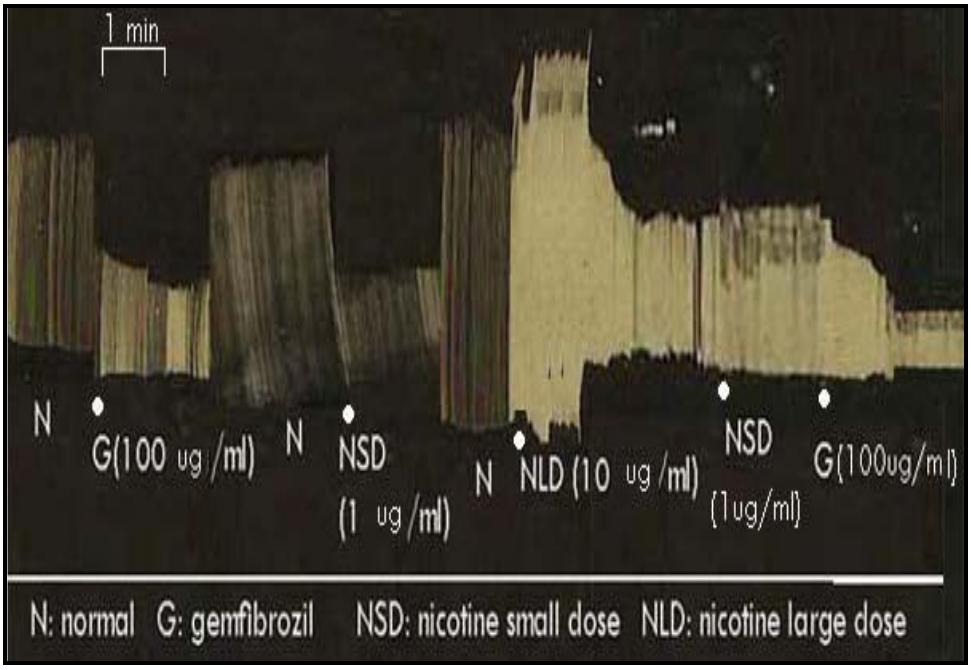

Figure (2): Effect of gemfibrozil (100µg/ml) on the amplitude of myocardial contractions of isolated perfused rabbit heart after complete blockade of nicotinic receptors.

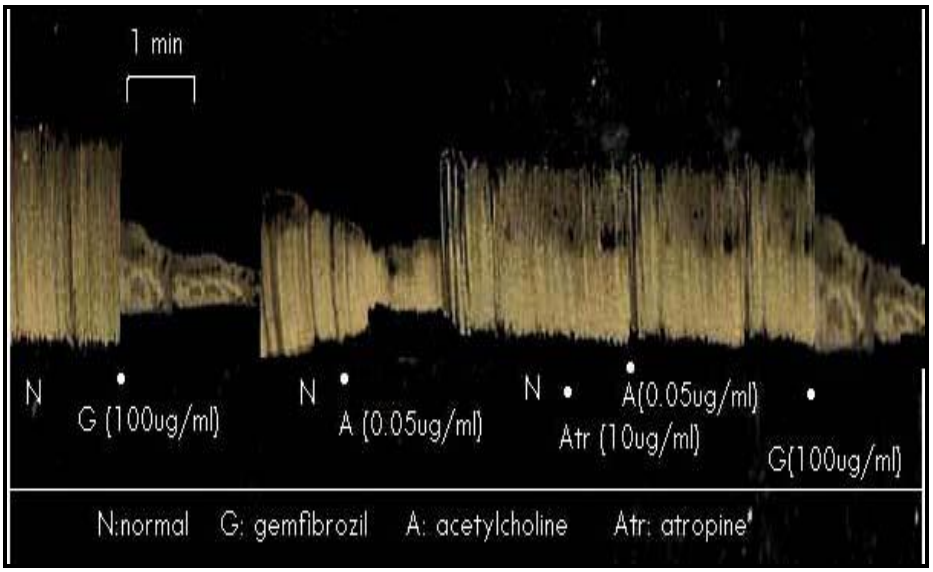

Figure (3): Effect of gemfibrozil (100µg/ml) on the amplitude of myocardial contractions of isolated perfused rabbit heart after complete blockade of muscarinic receptors.

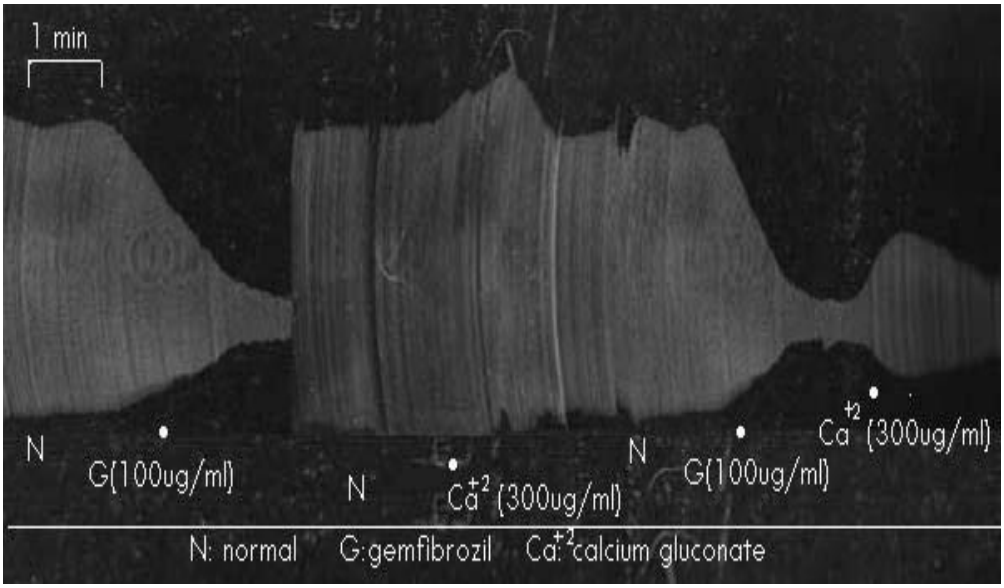

Figure (4): Effect of gemfibrozil (100µg/ml) on calcium gluconate-induced contraction of isolated
perfused rabbit heart.

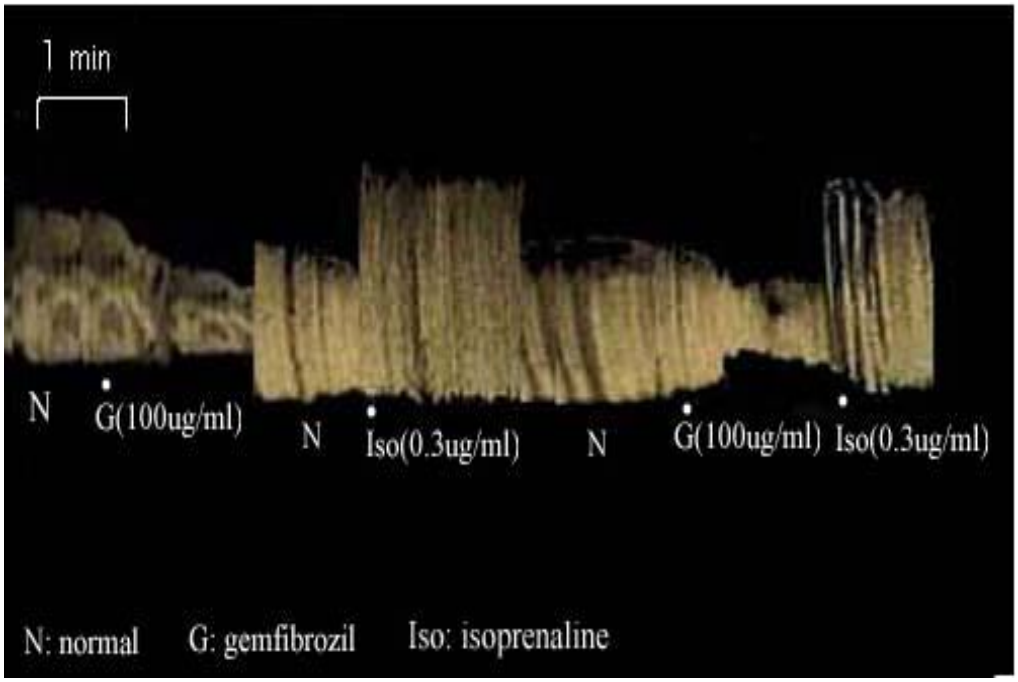

Figure (5): Effect of gemfibrozil (100µg/ml) on isoprenaline-induced contraction of isolated perfused rabbit heart.

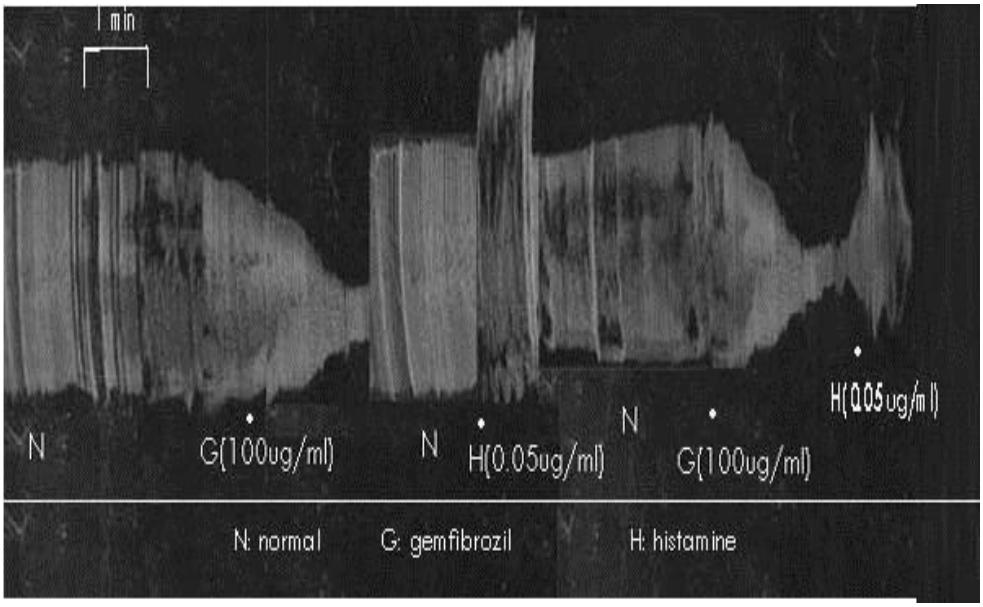

Figure (6): Effect of gemfibrozil (100µg/ml) on histaminie induced contraction of isolated perfused rabbit heart.

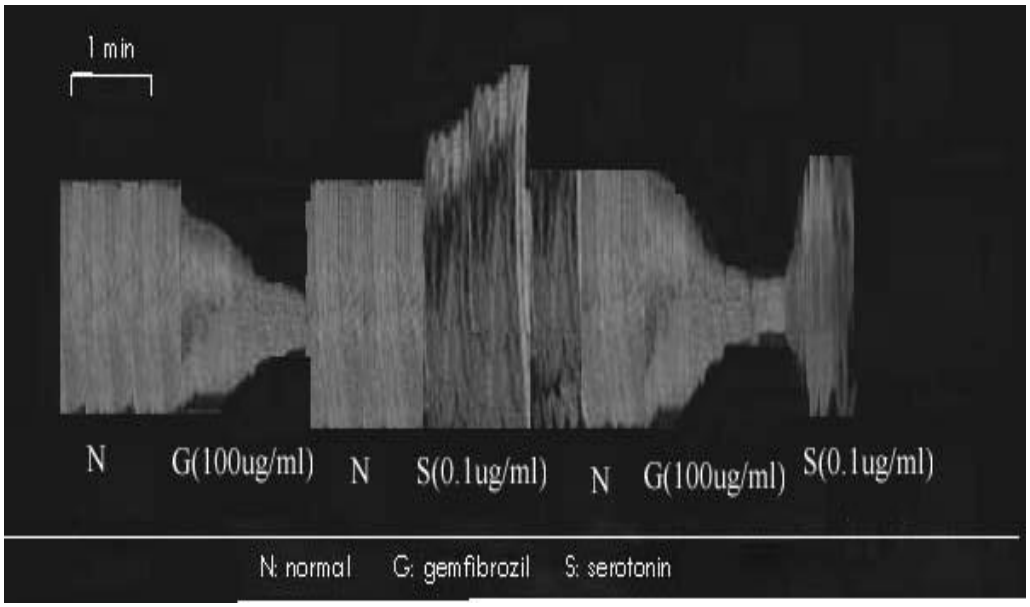

Figure (7): Effect of gemfibrozil (100µg/ml) on 5-HT induced contraction of isolated perfused rabbit heart.

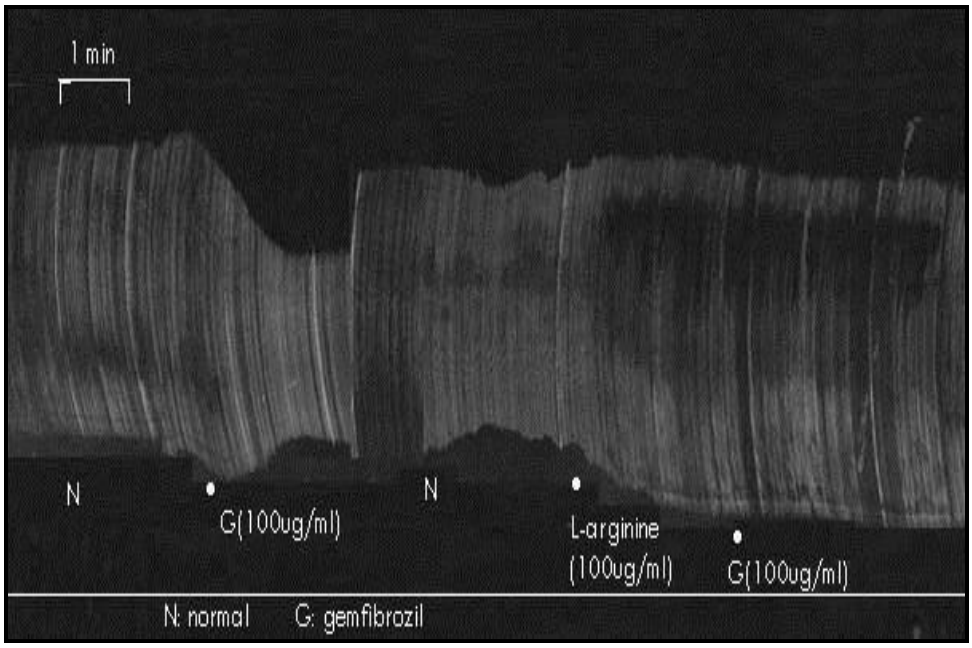

Figure (8): Effect of gemfibrozil (100µg/ml) on the amplitude of myocardial contractility of isolated perfused rabbit heart after inhibition of nitric oxide synthase by N-methyl L- arginine (100µg/ml).

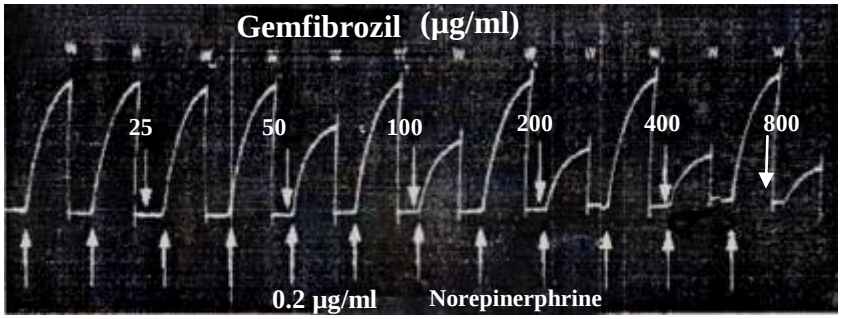

Figure (9): Effect of gemfibrozil (25-800µg/ml) on nor-epinerphrine(0.2ug/ml)-induced contractions of isolated rabbit aortic spiral strip.

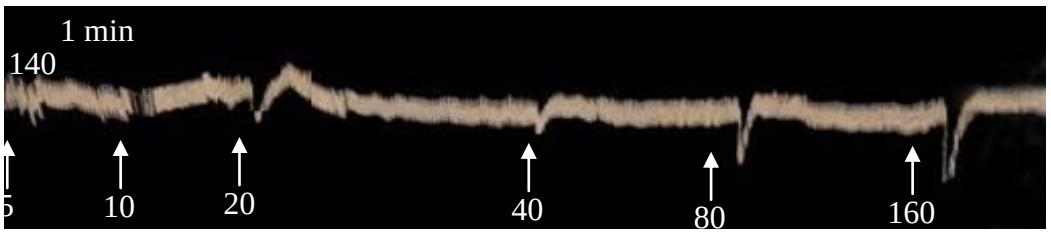

Figure (10): Effect of gemfibrozil (5- 160 mg/kg) on the arterial blood pressure (mmHg) of anesthetized cats.

DISCUSSION

In the present work, the experiments on isolated perfused rabbit heart showed that, gemfibrozil (fibrate, PPAR-α agonist) (25-800µg/ml) produced a significant reduction on the amplitude of myocardial contractions in a dose dependant manner. This negative inotropic effect is in agreement with ***Vikramadithyan et al. (2005)*** who

reported that the experimental studies revealed that chronic activation of PPAR-α could lead to ventricular dysfunction and the treatment of cardiomyopathic mice with fenofibrate (PPAR-α agonist) worsened cardiac function. In addition, ***Goikoetxea et al. (2004)*** reported that there was a potential role by PPAR-α agonists in the transition from compensated heart hypertrophy to heart failure. ***Kang et al. (2007)*** supported also the previous results, where they reported that PPAR-α activation in murine model of pressure induced cardiac hypertrophy resulted in sever left ventricular dysfunction. ***Duerr et al. (2014)*** demonstrated also that during brief repetitive ischemia reperfusion episodes, cardiomyocytes showed PPAR-α overexpression which lead to irreversible cardiomyocytes loss with deteriorated ventricular function. The increased apoptosis, deranged antioxidative capacity and maladaptation of contractile elements were observed by the same authors as major contributors involved in the modulation of post-ischemic inflammation and remodeling. The negative inotropic effect of gemfibrozil was likewise that observed by rosiglitazone (PPAR-γ agonist) which had also negative inotropic effect on the heart and inhibits the positive inotropic effect of digoxin ***(Said and Nader, 2013)***.

Moreover, clinically, ***Zambon et al. (2006)*** reported that clinical trials with PPAR-α agonists had shown a significant reduction in cardiovascular events. ***Kang et al. (2007)*** supported this study by reporting that fibrates may be beneficial for decreasing the rate of clinical cardiovascular events in a specific population and particularly among those patients suffering from metabolic syndrome and atherogenic dyslipidemia.

In the present study, the mechanism of the negative inotropic effect of gemfibrozil showed that the effect was completely abolished after inhibition of nitric oxide synthase (NOS) suggesting that it may be mediated through stimulation of NOS. The depressant effect of rosiglitazone; (another PPAR agonist which stimulate γ type) was attributed also to increasing NO production ***(Kim and Cheon, 2006)*** or activation of K^+ channel leading to hyperpolarization of membrane potential and thus closing voltage dependant Ca^{2+} channels responsible for Ca^{2+} influx ***(Knock et al., 1999, Eto et al., 2001 and Kim and Cheon, 2006)*** or inhibiting Ca^{2+} channel in high concentration ***(Knock et al., 1999)***.

From another point of view the study of ***Goya et al. (2004)*** had reported that PPAR-α activators upregulate endothelial NOS (eNOS) expression which explain one of the mechanisms of PPAR-α mediated cardiovascular protection. ***Zambon et al. (2006)*** in addition referred the cardioprotection effect of PPAR-α agonists to their metabolic and anti-inflammatory mechanisms.

The role of NO on heart function was discussed by many authors. A study by ***Massion et al. (2003)*** had reported that all three isoforms of NOS (endothelial, neural and inducible) are expressed in cardiomyocytes themselves and NO regulates cardiac function through direct effect on several aspects of cardiomyocytes contractility, starting from the fine regulation of excitation-contraction coupling to modulation of (presynaptic and postsynaptic) autonomic signaling and mitochondrial respiration. The same authors added also that, excessive NO delivery may result in profound cellular disturbances leading to heart failure. ***Drexler and Hornig (1999) and Anker and Haehling (2004)*** have supported what mentioned before by reporting that high concentration of NO in the failing myocardium may cause loss of myocytes and inhibit

myocyte contractility. In addition ***Chen et al. (2002) and Dobutovic et al. (2011)*** confirmed the above results by reporting that inhibition of NO synthase increased left ventricular contractility.

Azatian et al. (1998) referred the negative inotropic effect of NO donor to activation of cyclic guanidine mono phosphate (cGMP) dependant Na^{+}:Ca^{2+} exchange. In addition, it was reported by ***Brunner et al. (2001)*** that large concentrations of NO depress cardiac function through cGMP and protein kinase G (PKG) mediated desensitization of cardiac myofilaments. On the other hand, ***Adachi (2010)*** mentioned that S-glutathiolation of various proteins by NO can explain redox-sensitive cGMP independent actions and the oxidative inactivation of target proteins by NO can be associated with the pathogenesis of cardiovascular diseases.

Concerning the effect of gemfibrozil on coronary flow of isolated perfused rabbit heart, the present study revealed that gemfibrozil (25-800µg/ml) reduced the coronary flow significantly in a dose dependant manner. This result seems to disagree with other studies which support the beneficial effect of gemfibrozil in coronary heart disease and the reduction in coronary flow may be attributed to the significant reduction in myocardial contractility as illustrated by ***Ramanathan and Skinner (2005)*** who reported that in case of heart failure there is impaired ejection that results in large diastolic volume which cause elevation in the left ventricular end diastolic pressure (LVEDP) so the coronary perfusion pressure is reduced. The relation between LVEDP and coronary perfusion pressure is mentioned also by ***Kaplan et al. (1999)*** who mentioned that the coronary perfusion pressure is the difference between the aortic diastolic pressure and LVEDP. So when LVEDP is elevated due to reduction in myocardial contractility caused by gemfibrozil, the coronary blood flow is reduced. In addition to what mentioned before ***Mohri et al. (1997)*** supported the present result when said that the reduction in NO dependant coronary reserve is proportional to impairment of cardiac function.

Concerning the effect of gemfibrozil on rabbit arotic spiral strips

Gemfibrozil (25-800µg/ml) reduced NE-induced contractions. This results in agreement with ***Staels and Fruchart (2005)*** who reported that relaxation of thoracic aorta by fibrtate drugs correlation with their potency in disturb intracellular calcium of vascular smooth muscle contractions. ***Diep et al. (2002)*** reported that the direct beneficial effects of PPAR-α activator generally on the vascular wall is discussed through **inhibition of oxidative stress** generation and **anti-inflammatory** action in addition to its involvement in **lipid metabolism**. As regard to the **antioxidative** action of gemfibrozil, ***Roy and Pahan (2009)*** demonstrated that gemfibrozil reduces the burden of superoxide, lipid peroxidation products by down-regulating the expression of different subunits of NADPH oxidase (a membrane-bound enzyme that generates superoxide) and gemfibrozil fortifies also the cellular defense by stimulating the activity of anti-oxidant proteins such as paraxonase. In addition, ***Deans and Sattar (2006)*** demonstrated that treatment with gemfibrozil over longer period significantly reduced the size and swelling of atherosclerotic lesions in aortic blood vessel. ***Huber et al. (2001)*** had demonstrated also that fibrates modulate factors which promote thrombosis as plasminogen activator inhibitor type 1 ([PAI]-1) which is associated with high risk of acute coronary syndrome.

In this work the experiments on mean arterial blood pressure in anaesthetized cats revealed that gemfibrozil produced a dose-dependent reduction in mean arterial blood pressure of anaesthetized cats. This results was supported by ***Diep et al. (2002)*** who reported that PPAR α- activator reduces blood pressure in some hypertensive models. Further study by the same author reported that PPAR-α activator decosahexaenoic (DHA) attenuated the development of hypertension, correct structural abnormalities and improved inflammation in vascular wall. On the other hand the mechanism may be independent of changes in HDL concentration as ***Fruchart et al. (1999)*** mentioned. ***Staels and Fruchart (2005)*** reported also that PPAR-α agonist may improve endothelial function in vivo. It may be through increase of NO expression and release from vascular endothelial cells as reported by ***Calnek et al. (2003) and Goya et al. (2004)***. ***Phelps and Peuler (2007)*** who concluded that gemfibrozil has direct smooth muscle relaxant properties. In addition, ***Phelps and Peuler (2010)*** reported that gemfibrozil can directly inhibit the force of spontaneously occurring phasic rhythmic smooth muscle contractions and its primary site of action is the smooth muscle itself, either by inhibiting its responsiveness to endogenous contractile substances and/or its inherent ability to contract spontaneously on its own. Finally the NO mediated mechanism of gemfibrozil in this study is supported by different studies of many authors. ***Omae et al. (2012)*** reported that fenofibrate induced endothelium dependent vasodilatation mediated by NO release. In addition ***Khazaei et al. (2012)*** reported also that benzafibrate (pan-PPAR agonist) significantly increased serum nitrite concentration which is the main metabolite of NO. This study seems to be in agreement with ***Eberhadt et al. (2002)*** who reported that, the inhibitory effect of PPAR-α agonists on some inflammatory process are indirect and primarily due to super induction of iNOS with high levels of NO.

So our results concluded that gemfibrozil which is a member of fibrate and one of the most drugs in hypertiglyceridemias can be effective in hypertensive atherosclerotic patient . However it must be used cautiously in patients with impaired myocardiam .

REFERENCES:

Adachi T (2010): Modulation of vascular sarco/ endoplasmic reticulum calcium ATPase in cardiovascular pathophysiology. Adv. Pharmacol, 59:165-195.

Anker SD and Haehling SV (2004): Inflammatory mediators in chronic heart failure: an overview. Heart, 90:464-470.

Azatian KV, White AR, Walker RJ and Ayrapetyan SN (1998): Cellular and molecular mechanisms of nitric oxide-induced heart muscle relaxation. Gen. Pharmacol, 30(4):543-553.

Bailey DB (2000): Peroxisome proliferator-activated receptors in cardiovascular system. Br. J. Pharmacol, 129(5)**:** 823-834.

Berger JP, Akiyama TE and Meinke PT (2005): PPARs: therapeutic targets for metabolic disease. Trends Pharmacol Sci, 26(5):244-251.

Brandt JM, Djouadi F, Kelly DP (1998): Fatty acids activate transcription of the muscle arnitine palmitoyltransferase I gene in cardiac myocytes via peroxisome proliferator-activated receptor-α J. Biol. Chem, 273:23786–23792.

Brunner F, Andrew P, Wolkart G, Zechner R and Mayer B (2001): Myocardial contractile function and heart rate in mice with myocyte-specific overexpression of endothelial nitric oxide synthase. Circulation, 104:3097-3102.

Calnek DS, Mazzella L, Roser S, Roman J and Hart CM (2003): peroxisome proliferator-activated receptor gamma ligands increase release of nitric oxide from endothelial cells. Arteriosclerosis, Thrombosis and vascular biology, 23: 52-57.

Chen R, Liang F, Moriya J, Yamakawa J, Takahashi T, Shen L and Kanda T (2008): Peroxisome proliferator-activated receptors (PPARs) and their agonists for hypertension and heart failure: Are the reagents beneficial or harmful? International journal of cardiology, 130(2):131-139.

Deans KA and Sattar N (2006): Anti-inflammatory drugs and their effects on type 2 diabetes. Diabetes technology and therapeutics, 8(1):18–27.

Diep QN, Amiri F, Touyz RM, Cohn JS, Endemann D, Neves MF and Schiffrin EL (2002): PPARα activator effects on ang Π induced vascular oxidative stress and inflammation. American heart association hypertension, 40: 866-871.

Dobutovic B, Smiljanic K, Soskic S, Dungen HD and Isenovic ER (2011): Nitric oxide and its role in cardiovascular diseases. The open nitric oxide journal, 3:65-71.

Drexler H and Hornig B (1999): Endothelial dysfunction in human disease. J. Mol. Cell. Cardiol, 31:51-60.

Duerr GD, Heinemann JC, Arnoldi V, Feisst A, Kley J, Ghanem A, Welz A and Dewald O (2014): Cardiomyocyte specific peroxisome proliferator-activated receptor-α overexpression leads to irreversible damage in ischemic murine heart. Life Sci, 102(2):88-97.

Ehrmann JJ, Vavrusova N, Collon Y and Kolar Z (2002): Peroxisome proliferator-activated receptors in health and disease. Biomed. 146(2): 11-14.

Eto K, Ohya Y, Nakamura Y, Abe I and Fujishima M (2001): Comparative actions of insulin sensitizers on ion channels in vascular smooth muscle. Eur. J. Pharmacol, 423:1-7.

Fruchart JC, Duriez P and Steals B (1999): Peroxisome proliferator-activated receptor-alpha activators regulate genes governing lipoprotein metabolism, vascular inflammation and atherosclerosis. Current Opinion in Lipidology, 10 (3):240-257.

Fuentes E, Fuentes F, Vilahur G, Badimon L and Palomo I (2013): Mechanisms of chronic state of inflammation as mediators that link obese adipose tissue and metabolic syndrome. Mediators Inflamm, 2013: 136584.

Goikoetxea MJ, Beaumont J and Diez J (2004): peroxisome proliferator- activated receptor alpha and hypertensive heart disease. Drugs, 64: 9-18.

Goya K, Sumitani S, Xu X, Kitamura T, Yamamoto H, Kurebayashi S, Saito H, Kouhara H, Kasayama S, Kawase I (2004): Peroxisome proliferator-activated receptor alpha agonists increase nitric oxide synthase expression in vascular endothelial cells. Arteriosclerosis, Thrombosis and Vascular Biology, 24: 658-663.

Huber K, Chris G, Wojita J and Gulba D (2001): plasminogen activator inhibitor type-1 in cardiovascular disease. Status report Thromb. Res, 103(2):103-107.

Israelian-Konaraki Z and Reaven PD (2005): Peroxisome proliferator-activated receptor-alpha and atherosclerosis: from basic mechanisms to clinical implications. Cardiology, 103:1-9.

Kang YR, Kwak CH and Hwang JY (2007): Safety and efficacy of peroxisome proliferator-activated receptor-α agonist for treating cardiovascular disease. Korean Circ. J, 37:599-608.

Kaplan JA, Reich DL, Konstadt SN and Saunders PW (1999): ECG exercise testing, Hurst's The Heart. Anesthesiology, 96(2):359-400.

Khazaei M, Salehi E and Rashidi B (2012): Pan-PPAR agonist, benzafibrate, restores angiogenesis in hindlimb ischemia in normal and diabetic rats. international journal of peptides, 2012:1-5.

Kim KY and Cheon HG (2006): Antiangiogenic effect of RGN is mediated via peroxisome proliferator-activated receptor γ activated maxi-K+ channel opening in human umbilical vein endothelial cells. J. Biol. Chem, 281:13503-13512.

Knock GA, Mishra SK and Aaronson PI (1999): Differential effects of insulin sensitizers Troglitazone and rosiglitazone on ion currents in rat vascular myocytes. Eur. J. Pharmacol, 368: 103-109.

Mandard S, Muller M and Kersten S (2004): Peroxisome proliferator-activated receptor alpha target genes. Cell Mol Life Sci. 61:393-416.

Massion PB, Feron O, Dessy C and Balligand JL (2003): Nitric oxide and cardiac function ten years after, and continuing. Cir Res, 93: 388-398.

Mohri M, Egashirak K, Tagawa T, Kuga T, Tagawa H, Harasawa Y, Shimokawa H and Takeshita A (1997): Basal release of NO is decreased in coronary circulation in patient heart failure. Hypertension, 30:50-56.

Moore KJ, Rosen ED, Fitzgerald ML, Randow F, Andersson LP, Altshuler D, Milstone DS, Mortensen RM, Spiegelman BM and Freeman MW (2001): The role of PPAR-gamma in macrophage differentiation and cholesterol uptake. Nat. Med, 7(1):41-7.

Murphy GJ and Holder JC (2000): PPAR-gamma agonists: therapeutic role in diabetes, inflammation and cancer. Trends Pharmacol Sci, 21(12):469-474.

Omae T, Nagaoka T, Tanano I, Kamiya T and Yosbida A (2012): Fenofibrate, an anti-dyslipidemia drug, elicits the dilation of isolated porcine retinal arterioles: role of nitric oxide and AMP- activated protein kinase. Investigative ophthalmology and visual science, 53(6): 2880-2886.

Ramanathan T and Skinner H (2005): Coronary blood flow. British journal of anaesthesia; Critical Care and Pain, 5(2):61-64.

Robins SJ, Collins D, Wittes JT, Papademetriou V, Deedwania PC, Schaefer EJ, McNamara JR, Kashyap ML, Hershman JM, Wexler LF and Rubins HB (2001): Relation of gemfibrozil treatment and lipid levels with major coronary events, VA-HIT, a randomized controlled trial. JAMA, 285(12):1585–1591.

Roy A and Pahan K (2009): Gemfibrozil, stretching arms beyond lipid lowering. Immunopharmacol Immunotoxicol, 31(3): 339–351.

Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, Faas FH and Anderson JW (2002): Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Archives of Internal Medicine, 162(22):2597–2604.

Said SA and Nader MA (2013): Myocardial depression and inhibition of positive inotropic effect of digoxin by rosiglitazone. Journal of food and pharmaceutical sciences, 1(2.13):35-42.

Schiffrin EL (2005): Peroxisome proliferator-activated receptors and cardiovascular remodeling. Am. J. physiol heart circ. Physiol, 288:1037-1043.

Staels B and Fruchart JC (2005): Therapeutic roles of peroxisome proliferator-activated receptor agonists. American Diabetes association, 54: 2460-2470.

Steel and Torrie (1960): Principal and procedures of statistics; P.37. McGraw Hill Book Company INC London.

Steiner G (2001): Effect of fenofibrate on progression of coronary artery disease in type 2 diabetes. The diabetes atherosclerosis intervention study, a randomized study. Lancet, 357:905-910.

The staff of the department of pharmacology, University of Edinburgh (1970): Experiments with heart muscle. The isolated perfused rabbit heart. In Pharmacological experiments on isolated preparations. 2nd edition. Chapter 6. P116-118. Publishers (Churchill Livingstone, 23 Ravelston Terrace, Edinburgh). Printed in Great Britain.

Tian XY, Wong WT, Wang N, Ye LU, Cheang WS, Liu J, Liu L, Liu Y, Lee SS, Chen ZY, Cooke JP, Yao X and Huang Y (2012): pparδ activation protects endothelial function in diabetic mice. Diabetesjournals; Diabetes, 61: 3285-3293.

Vikramadithyan RK, Hirata K, Yagyu H, Hu Y, Augustus A, Homma S and Goldberg IJ (2005): Peroxisome proliferator-activated receptor agonists modulate heart function in transgenic mice with lipotoxic cardiomyopathy. J. Pharmacol. Exp. Ther, 313(2):586–593.

Vosper H, Khoucloli GA, Graham TL and Palmer CN (2002): Peroxisome proliferator-activated receptor agonists, hyperlipidemia and atherosclerosis. Pharmacol Ther, 95(1):47-62.

Yue TL, Bao W, Jucker BM, Gu JL, Romanic AM, Brown PJ, Cui J, Thudium DT, Boyce R, Burns-Kurtis CL, Mirabile RC, Aravindhan K and Ohlstein EH (2003): Activation of peroxisome proliferator-activated receptor-alpha protects the heart from ischemia/reperfusion injury. Circulation, 108(19): 2393-2399.

Zambon A, Gervois P, Pauletto P, Fruchart JC and Staels B (2006): Modulation of hepatic inflammatory risk markers of cardiovascular diseases by PPAR-α activators. American heart association; Arterioscler Thromb Vasc Boil, 26: 977-986.

Furchgott RT and Bhadrakom S (1984): The rabbit aortic spiral strip. In: text book of in vitro practical pharmacology, edited by kitchen IP; p. 113-115, Blackwell Scientific Publications. London Edinburgh.

The staff of the department of pharmacology (1970): Phamacolgocial experiments on intact preparations, pp:18-21, E & S Livingstone, edinburgh London.

Chen R, Liang F, Moriya J, Yamakawa JI, Takahashi T, Shen L and Kanda T (2008): Peroxisome proliferator-activated receptors (PPARs) and their agonists for hypertension and heart failure: are the reagents beneficial or harmful?. International Journal of Cardiology; 130(2):131-9.

Diep QN, El Mabrouk M, Touyz RM and Schiffrin EL (2002): Expression of Cell Cycle Proteins in Blood Vessels of Angiotensin II–Infused Rats Role of AT1 Receptors. Hypertension; 37(2):604-8.

دراسه تأثير دواء الجيمفيوبروزيل علي بعض اجزاء الجهاز الدوري .

للسيد الدكتور

ايناس عبد العاطي عوده

مـــــــــن

استاذ مساعد بقسم الفارماكولوجي بصيدلة الازهر بنات

خلفيه البحث : جيمفيبروزيل واحد من الفيبرات و الذي يعمل مناهض علي مستقبلات الفا بيروكزام –بروفيبرات و التي تحسن من صوره الدهون و خصوصا الدهون الاقل و الاكثر كثافه وذلك في المرضي المصابين بخلل في نسبه الدهون.

الهدف من البحث: دراسه تاتير دواء الجيمفيوبروزيل علي بعض التجارب المعمليه الخاصه باجزاء الجهاز الدوري

. **طرق البحث** : اجريت التجارب لدراسه تأثير دواء الجيمفيروزيل فالجرعات العلاجيه المختلفه علي عضله القلب المعزوله من الارنب البلدي و ايضا قياس تدفق الدم في الشريان التاجي كما اجريت التجارب علي الشرائط الحلزونيه المعزوله من شريان الاورطي للارنب البلدي بالاضافه الي التجارب علي القطط المخدره لقياس ضغط الدم الشريان .

النتائج : اثبتت التجارب ان الجيمفيروبوزيل في الجرعات (٢٥ -٨٠٠ ميكروجرام \ ملليليتر)له تأثير مثبط علي عضله القلب المعزول للارنب البلدي وهذا التأثير ذو دلاله احصائيه و لقد اختفي هذا التأثير المثبط بعد غلق مستقبلات الكوينيلرجيه بينما اختفي هذا التأثير كليا بعد استخدام عقار ان –مثيل- ال –ارجينين بينما وجد ان الجيمفيروزيل (١٠٠ميكروجرام\ملليليتر) ليس له تأثير علي التأثير المنشط لكل من الكالسيوم جلوجنات و ايزوبرينالين و هيستامين و سيروتونين اثبتت التجارب ايضا ان الجرعات (٢٥-٨٠٠ ميكروجرام \ ملليليتر) أدت الي انخفاض تدفق الشريان التاجي تدريجيا مع زياده الجرعات وهذا الانخفاض ذو دلاله احصأيه اما عن التجارب التي اجريت علي الشرائط الحلزونيه من الشريان الاورطي فقد وجد ان الجيمفيروزيل ادي الي تثبيط التقلساط الناتجه من دواء النورابينفرين و ذو دلاله احصائيه . اثبت التجارب ان دواء جيمفيروزيل سبب انخفاضا تدريجيا في ضغط الدم مع الجرعات العلاجيه المختلفه وله دلاله احصائيه .**الخلاصه** : وجد ان دواء الجيمفيروزيل له تأثير مثبط لعضله القلب المعزول و ليضا ادي الي انخفاض سريان الدم في الشريان التاجي كما ان له تأثير مثبط للتقلصاط الناتجه للدواء النورابينفرين وسبب ايضا انخفاضا في ضغط الدم ولذلك ينصح استخدمه بحذر في حالات ضعف القلب ولكن له تأثير مفيد في حالات ضغط الدم المرتفع المسحوب بتصلب الشراين .