

# Comparative effects of pioglitazone, $\alpha$ -lipoic acid, taurine and chromium picolinate and their combinations on hyperglycemic, lipid profile and oxidative stress parameters in fructose-induced insulin resistant rats

Mohammed H. Moawad, Hala F. Zaki, Ezz-El-Din S. El-Denshary

Pharmacology & Toxicology Department, Faculty of Pharmacy, Cairo University, Kasr EL-Eini Street, P.O. Box 11562, Cairo, Egypt.

**Abstract-** The potential of pioglitazone and certain micronutrients, namely,  $\alpha$ -lipoic acid, taurine and chromium or their combinations to improve glycemic status and insulin resistance (IR), and their role in treating oxidative stress insults and dyslipidemia were studied.

Seven groups of rats (n=8) were fed on fructose enriched diet (FED) for 18 weeks. One group served as FED-control, groups were daily treated with pioglitazone (7mg/kg),  $\alpha$ -lipoic acid (600 mg/kg), taurine (600mg/kg), chromium (500mg/kg), and combination of pioglitazone with each of such micronutrients during the last 6 weeks of treatment. Another group was fed on normal laboratory chow (normal control group). At the end of the experiment, blood samples were taken by retro-orbital technique for estimation of markers related to IR. Induction of IR was associated with increased body weight gain (23.5%) coupled with elevated fasting blood glucose (134%), glycated hemoglobin (64%), triglycerides (6%), total cholesterol (29%), low density lipoprotein (62%). The level of high density lipoprotein was reduced (26%). Fructose-induced IR was accompanied by reduction of superoxide dismutase (85%) and glutathione (74%), whereas malondialdehyde was elevated (145%). Body weight gain was enhanced after treatment with pioglitazone, taurine and their combinations. Fasting blood glucose was lowered after treatment with pioglitazone,  $\alpha$ -lipoic acid or taurine. It was normalized after co-administration of pioglitazone and chromium. Glycated hemoglobin was reduced by pioglitazone, taurine or chromium alone or in combination. Lipid profile and oxidative stress parameters were improved after pioglitazone administration, alone or along with each of the tested micronutrients.

In conclusion, this study proves the benefits of co-administration of  $\alpha$ -lipoic acid, taurine or chromium with pioglitazone in FED-induced IR models in rats.

**Index Terms-** FED-fed rats, insulin resistance, oxidative stress, pioglitazone.

## I. INTRODUCTION

Metabolic syndrome (MS) is a constellation of risk factors for cardiovascular diseases and type II diabetes mellitus, characterized by obesity, dyslipidemia, IR and hyperglycemia (Hall et al., 2006). Changes of dietary habits including increased intake of simple sugar, mainly fructose commonly used in food

industry and as a sweetener of soft drinks (Isomaa et al., 2001), contribute to the growing worldwide prevalence of MS.

Oxidative stress has been reported to play an important role in type II diabetes mellitus (Siddiqui et al., 2005; Shukla et al., 2007).

In animal models, excessive fructose intake is associated with IR, impaired glucose tolerance, hyperinsulinemia and hyperlipidemia (Elliot et al., 2002).

Enhancement of insulin action might be an effective approach in alleviating MS. Insulin sensitizers increase peripheral tissue sensitivity to insulin without stimulating its release (Vekramadithyan et al., 2000). Thiazolidinediones, including pioglitazone are used for the treatment of IR and management of type II diabetes mellitus (Bailey, 1999; Dey et al., 2002). Pioglitazone is used for improvement of insulin sensitivity in muscles and adipose tissue (Georios et al., 2013).

Micronutrients are effective in treating IR syndrome complications. Alpha lipoic acid is reported to be a necessary co-factor in mitochondrial energy metabolism. It also possesses an antidiabetic action (Liu et al., 2002; Suh et al., 2004).

Taurine was reported to improve insulin sensitivity in fructose-fed rats (Nandhini et al., 2005), an action that was attributed to combating the destructive effects of free radicals on the pancreas.

Chromium picolinate is an essential trace nutrient which is used as a nutritional supplement (Sawyer, 1994) with a central role in glucose metabolism. Chromium improves glucose tolerance by decreasing hepatic extraction in pigs (Guan et al., 2000). Its deficiency may lead to diabetes mellitus (Wada et al., 1983; Striffler et al., 1998). Chromium was reported to improve insulin sensitivity and modulate lipid metabolism in peripheral tissues (Anderson, 2008).

Therefore, there is a need to search for a better alternative therapy for IR syndrome that is more effective and less toxic. The present work was therefore, carried out to investigate the possible beneficial effects of  $\alpha$ -lipoic acid, taurine or chromium in fructose-induced insulin resistant syndrome alone or in combination with pioglitazone.

## II. MATERIALS AND METHODS

### Animals

Adult male albino rats weighing about 180 gm/each were purchased from National Research Centre, Cairo, Egypt and left

to accommodate in the animal house of Faculty of Pharmacy, Cairo University for one week before being subjected to experimental work. All animals were provided with diet and water ad libitum. The study was carried out according to the guide lines of Ethics commity of Faculty of Pharmacy, Cairo University.

#### Drugs and chemicals

Fructose was purchased from EL-Nasr Pharma, Egypt. Pioglitazone (Glaxo Smithkline, Beechow, Harlow, MK) was dissolved in normal saline and kept at 4°C (7mg/kg/day; p.o; **Zinn et al.,2008**). Alpha lipoic acid (Thiotacid®, 600mg/kg/day; p.o; **Androne et al., 2000**) was suspended in 1% tween 80. Taurine (Nutra Planet, Advanced Platinum series, GMP, 111 Bethea Rd, St 101, Fayetteville, GA 30214, USA) was dissolved in normal saline solution just before use (600mg/kg/day; p.o; **Anitha Nandhini et al., 2002; Penget al., 2005**). Chromium picolinate (E Merk, Dramstadt, Germany) was suspended in 1% Tween 80 (500µg/kg/day; p.o; **Moony et al., 1995**).

#### Induction of insulin-resistance syndrome

Insulin resistance was induced in rats by oral administration of 10% fructose in drinking water for 12 weeks(**Sanchez-Lozada et al., 2007**). To insure that metabolic syndrome was induced, fasting blood glucose level was determined at different time intervals.

#### Experimental design

Animals that showed elevated MS parameters were selected and randomly allocated into various groups and treated as follows: normal control group, received water and solvent vehicle; FED-control group, continued on 10% fructose in drinking water and solvent vehicle. Other drug-treated groups were given 10% fructose in drinking water plus pioglitazone (7mg/kg), α-lipoic acid (600mg/kg), taurine (600mg/kg), chromium picolinate (500mg/kg) and a combination of pioglitazone with α-lipoic acid, taurine or chromium picolinate. Drugs were orally administered starting from the 13<sup>th</sup> week after initiation of the diet and continued for extra 6 weeks. Another group was fed on normal diet and served as normal control group and received solvent vehicle. Animal weights were recorded throughout the period of study for calculation of body weight gain. By the end of the treatment period, animals were fasted for 12 h and blood samples were collected from the retro-orbital sinus and used for biochemical analysis.

#### Determination of body weight gain

The percentage of body weight gain was mathematically calculated using the following formula:

Body weight gain%=

$$\frac{\text{Final body weight(after treatment)} - \text{Initial body weight}}{\text{Initial body weight}} \times 100$$

#### Biochemical estimations

Serum glucose level was estimated using glucose kit (Spinreact, Spain, **Trinder, 1969**) and expressed as mg/dl. Serum glycated hemoglobin (HbA1c) was determined by the method of **Trivelli et al. (1971)** using HbA1c kit (Teco Diagnostics). The percentage HbA1c was determined by measuring the absorbance

at 415nm of both HbA1c fragment and total hemoglobin. The ratio of both absorbances represents percent glycated hemoglobin. Serum triglycerides (TG) were determined colorimetrically by the method of **Schettler (1980)** and calculated as mg/dl. Total serum cholesterol (TC) was determined spectrophotometrically by the method of **Richmond (1973)** and expressed as mg/dl. Serum high density lipoprotein (HDL) was determined by an enzymatic colorimetric method (**Burstein et al., 1970**) and expressed as mg/dl. Serum low density lipoprotein (LDL) was indirectly estimated by the method of **Fridewald et al. (1972)** and expressed as mg/dl. Serum malondialdehyde (MDA) was assayed as a measurement of lipid peroxidation according to the method of **Mihara and Uchiyama (1978)**. Concentration of MDA in serum was calculated as nmol/ml. Blood glutathione peroxidase (GPX) activity was determined by the method of **Paglia and Valentine (1967)**, which is based on oxidation of glutathione by GPX resulting into a decrease in absorbance at 340nm. GPX concentration is calculated as U/ml. Superoxide dismutase (SOD) was estimated according to the method of **Marklund and Marklund (1974)** and calculated as U/ml.

**Statistical analysis:** The values of the measured parameters were presented as mean ± S.E.M. Comparisons between different treatments were carried out using one way Analysis of Variance (ANOVA) followed by **Tukey-Kramer** as post ANOVA multiple comparisons test. Differences were considered statistically significant when p<0.05.

### III. RESULTS

**Effect of 6-week treatment with pioglitazone, α-lipoic acid, taurine or chromium picolinate and their combinations on body weight gain in fructose-enriched diet (FED) fed rats:** Induction of insulin resistance was associated with increased body weight gain (23.5%). Treatment with pioglitazone significantly increased body weight gain (28%). Treatment with α-lipoic acid or chromium did not affect body weight gain. Taurine significantly augmented body weight gain by 39%. This effect was synergized with pioglitazone (55%) (Fig.1).

**Effect of 6-week treatment with pioglitazone, α-lipoic acid, taurine or chromium picolinate and their combinations on fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) in fructose-enriched diet (FED) fed rats:**

Fructose-induced insulin resistance showed elevated levels of blood glucose (134%) and HbA1c (64%). Treatment with pioglitazone, αlipoic acid, taurine or chromium resulted in a significant reduction of elevated FBG by 65%, 45%, 54% and 55% respectively. Combination of pioglitazone with α-lipoic acid or taurine significantly reduced FBG by 64% and 67% respectively, whereas combination of pioglitazone with chromium normalized FBG. Treatment with pioglitazone, taurine or chromium significantly reduced HbA1c by 44% and 47% and 34% respectively. Combination of pioglitazone with α-lipoic acid, taurine or chromium significantly reduced HbA1c by 57%, 50% and 47% respectively (Table 1).

**Effect of 6-week treatment with pioglitazone, α-lipoic acid, taurine or chromium picolinate and their combinations on lipid profile in fructose-enriched diet (FED) fed rats:** Fructose-induced metabolic syndrome resulted in significant

increase in serum TG, TC, and LDL level almost by 16%, 29%, and 62% respectively. The level of HDL was reduced (26%). Treatment with pioglitazone significantly decreased serum TG, TC, and LDL by 20%, 13%, and 22% respectively, while increased HDL by 28%. Similarly  $\alpha$ -lipoic acid reduced TG, TC by 15% and 5% with a significant increase in HDL by 30%. Taurine reduced TG, TC, and LDL by 22%, 81%, and 11% respectively, while normalizing HDL. Chromium reduced TG and LDL by 8% and 21% respectively without affecting TG level but normalized HDL. Co-administration of pioglitazone and  $\alpha$ -lipoic acid significantly reduced TG, TC, and LDL by 48%, 12%, and 14% respectively, while augmented HDL by 25%, which reflects a considerable improvement of lipid profile. Combination of pioglitazone with taurine significantly decreased LDL by 11%, elevated TG by 9% but did not change TC level. Meanwhile, HDL was normalized (Table 2).

**Effect of 6-week treatment with pioglitazone,  $\alpha$ -lipoic acid, taurine or chromium picolinate and their combinations on oxidative stress parameters in fructose-enriched diet (FED) fed rats:** Insulin-resistant rats showed a significant reduction in SOD, GPX by 85% and 74% respectively, whereas MDA was elevated by 145% (Fig.2,a,b&c). Treatment with pioglitazone significantly increased SOD by 10% while both GPX and MDA were normalized. Treatment with  $\alpha$ -lipoic acid reduced MDA content and normalized both SOD and GPX. Taurine significantly increased SOD and GPX by 21% and 76% respectively and normalized MDA. Chromium significantly increased serum SOD by 8% but it normalized MDA. Administration of pioglitazone and  $\alpha$ -lipoic acid normalized GPX and MDA but did not change SOD activity. Co-administration of pioglitazone with taurine elevated both SOD and GPX and reduced MDA content. Administration of both pioglitazone and chromium normalized all parameters, namely, SOD, GPX and MDA (Fig.2,a,b&c).

In conclusion, this study proves the benefits of co-administration of  $\alpha$ -lipoic acid, taurine or chromium with pioglitazone in FED-induced insulin resistance models in rats.

#### IV. DISCUSSION

The investigation of agents of possible value in amelioration of serious problems of metabolic syndrome (MS) has become very important for the management of MS. An oxidant-antioxidant imbalance exists in diabetes mellitus (DM) so that an inverse correlation exists between blood glucose level and antioxidant status. A lower antioxidant defense is a common factor of uncontrolled DM. Antioxidants have thus received a great deal of attention with respect to their efficacy in treating the insulin resistance syndrome (IR) complications (Nirmala et al., 2015).

Fructose-enriched diet (FED) - fed rats model for induction of MS in rats is an ideal means of investigating IR syndrome. This model provides a convincing evidence that dietary imbalance may initiate the development of MS (Huang et al., 1997). Male rats were used in this study because of their higher susceptibility towards development of insulin resistant diabetes as compared to female rats (Santure et al., 2002; Brenner et al., 2003).

In the present study, there was a significant increase in body weight gain of rats maintained on FED for 16 weeks. This is in harmony with the reports of other investigators that fructose promotes obesity more than glucose as it enhances food intake without stimulating thermogenesis (Levine, 1986; Miller et al., 2002). Moreover, fructose is favored by the liver to be metabolized into lipids which leads to weight gain, increased abdominal obesity and insulin resistance (Elliott et al., 2002). Increased body weight gain was associated with hyperglycemia, dyslipidemia and pronounced oxidative stress. FED-fed rat model provides a convincing evidence that dietary imbalance may initiate the development of MS (Huang et al., 1997). Indeed, FED increases fasting glycemia leading to hepatic insulin resistance in healthy men (Faeh et al., 2005; Rizkalla, 2010). In the current study, FED-fed rats showed elevated levels of serum TG, TC, and LDL associated with a decreased level of HDL. These results are in harmony with Ackermann et al. (2005) and Nakagawa et al. (2006). On the other hand, HDL level was lowered in FED-fed rats. This finding is in agreement with that of Ohmori et al. (2004) who observed that FED reduced serum HDL in rats.

Hyperglycemia produces ROS via glucose auto-oxidation and protein glycation causing local oxidation damage (Maxwell et al., 1997). So, measurement of total anti-oxidant status is likely to be valuable for understanding the relationship of oxidative stress and insulin resistance (Yaworsky et al., 2000). Measurement of MDA is a reliable marker of oxidative stress in diabetes (Zadeh et al., 1997; Nacitarhan et al., 1995). In the present study, a significant increase in serum MDA along with a significant inhibition of blood SOD and GPX enzyme activities were demonstrated in IR-diabetic rats. This is in accord with previous studies reporting similar changes in alloxan and streptozotocin- diabetic rats (Coldiron et al., 2002). Furthermore, Martin-Gallan et al. (2003) demonstrated a lower activity of GPX with a higher level of MDA and lipid peroxides in young type I diabetic patients. The anti-oxidant status was diminished by high fructose consumption and improved by bread, rice and macaroni consumption (Santure et al., 2002). Furthermore, the results of the current study revealed that FED feeding reduced the activities of the anti-oxidant enzymes, GPX and SOD. This is in agreement with Delbosc et al. (2005) who reported that FED increases oxidative stress in rodents. Prolonged exposure of rats to hyperglycemia leads to inhibition of SOD and other anti-oxidant enzymes (Nadhini et al., 2005).

The results of the present study indicate that pioglitazone normalized glucose and glycated hemoglobin values. As an insulin sensitizer, pioglitazone has been effective in lowering blood glucose level in IR rats. This is supported by Ding et al. (2005) who found that treatment with pioglitazone improved insulin sensitivity in streptozotocin (STZ) and high sucrose-fed diet induced obesity in rats. A potential mechanism by which pioglitazone improves insulin action includes direct stimulation of glucose uptake or oxidation and disposal in skeletal muscles, facilitation of glucose transport and enhancement of glycogen synthesis (Smith et al., 2001). Thiazolidinediones ameliorate IR in muscle tissues by suppression of muscle lipid storage and the activity of a protein kinase isoforms (Zinn, 2008). Improvement of glucose homeostasis by pioglitazone may be achieved by systemic insulin sensitization or by direct action of a nuclear

peroxisome proliferator-activated receptor-  $\gamma$  (PPAR- $\gamma$ ) on the transcription of genes involved in glucose disposal (**Kalofoutis et al., 2007**).

In the present study, treatment of IR rats with  $\alpha$ -lipoic acid produced a significant lowering of blood glucose as well as MDA levels. On the other hand, serum SOD and GPX activities were increased. This is in accordance with **Borcea et al. (1999)** who observed that  $\alpha$ -lipoic acid lowered plasma peroxide level in diabetic patients; **Ziegler (2003)** who reported that  $\alpha$ -lipoic acid reduced the symptoms of diabetic peripheral neuropathy; **Arivazhangan et al. (2001)** who found that  $\alpha$ -lipoic acid reduced MDA in the brain regions of aged rats, and **Evans and Golder (2000)** who reported that alpha lipoic acid improves insulin sensitivity in patients with type II diabetes. Co-administration of pioglitazone and  $\alpha$ -lipoic acid markedly reduced serum TC and LDL levels, but HDL was increased. This may be attributed to an augmented effect of both agents on lipid profile parameters so that peroxidation of lipids by free radicals burdened in diabetic oxidative stress could be ameliorated by ROS scavenging capability of  $\alpha$ -lipoic acid (**Smith et al., 2004**).

The results of the present study revealed that taurine reduced blood glucose and glycated hemoglobin levels together with considerable enhancements of lipid profile and oxidative stress biomarkers. Other studies reported that taurine treatment produced similar effects. Taurine treatment resulted in a reduction of the elevated blood glucose, glycated end products, diabetes-evoked oxidative stress and lipid profile biomarkers (**Huang et al., 2008; Lin et al., 2010; Das et al., 2012**). It could be effective in removing fatty liver deposits in rats (**Mc Call, 2005**). It also could act as an antioxidant (**Sinha et al., 2008**) and prevent exercise-induced oxidative stress (**Zang et al., 2004**), and lowered blood cholesterol and LDL contents. Taurine was demonstrated as a potent antioxidant that improves drug-induced type I diabetes in rats and that it could ameliorate metabolic alterations in insulin resistance (**Das et al., 2012**).

Reports by **Murakami et al. (1999)** indicated that taurine administration to mice lowered serum LDL and elevated HDL. This effect might have been due to taurine's ability to promote the degradation of detrimental cholesterol to relatively harmless bile acids (**Lim and Kang, 1998**). Dietary supplementation of taurine is able to correct abnormal elevations of MDA and depletion of glutathione in diabetes (**Lim et al., 1998**).

Administration of chromium picolinate produced significant reductions in blood glucose and glycated hemoglobin levels of IR rats. It has been reported that chromium deficiency in rats may result in glucose intolerance in diabetics (**Person et al., 2008**). According to **Striffler et al. (2001)**, a biologically active form of chromium enhances the effect of insulin on glucose metabolism through enhancement of insulin receptor sensitivity towards glucose utilization. Chromium was found to work closely with insulin by facilitating the uptake of glucose in cells (**Anderson et al., 2001; Jain and Kannan, 2001**). Chromium has been reported to increase insulin binding to cells, insulin receptor number and activate insulin receptor kinase leading to enhancement of insulin sensitivity (**Krejpcio, 2001; Krol and krejpcio, 2010**). Since chromium picolinate reduced insulin resistance, this essential trace element could therefore have wide effects on abnormal blood lipids together with lowering of blood glucose levels (**Striffler et al., 2001**). Besides, the free radical

parameters namely GPX and SOD activities were normalized. Chromium treatment of IR rats resulted into marked reduction of TG level. This is in agreement with **Sahin et al. (2007)** who observed that blood TG of STZ-diabetic rats were markedly reduced after chromium supplementation. **Feng et al. (2015)** reported that chromium malate produced a better enhancement of glycometabolism and lipid metabolism as compared to other chromium compounds in type II diabetic rats.

The current investigation has proved the antioxidant potential of chromium whether given alone or along with pioglitazone. This study also demonstrated that chromium administration to FED-fed rats was associated with elevation of plasma GPX activity. Moreover, chromium administration resulted into reduction of elevated levels of MDA in IR-rats. In line with these findings, **Esen et al., (2009)** found that supplying rats with high chromium diet elevated the activities of antioxidant enzymes such as catalase, SOD, and GPX. Furthermore, **Martin et al. (2006); Hummel et al. (2007)** reported that chromium levels in diabetic subjects are lower as compared to normal subjects and that a correlation exists between plasma insulin and plasma chromium levels, so that a low chromium level would lead to incidence of type II diabetes.

## V. CONCLUSION

The findings of the present study prove the benefits of co-supplementation of pioglitazone and chromium picolinate as an insulin sensitizer micronutrient as well as with the tested antioxidants, namely  $\alpha$ -lipoic acid and taurine. Pioglitazone along with each of the tested compounds offer further improvements to the markers of IR, including hyperglycemia, dyslipidemia and exaggerated oxidative stress.

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#### AUTHORS

**First Author** – Mohammed H. Moawaḍ, Pharmacology & Toxicology Department, Faculty of Pharmacy, Cairo University, Kasr EL-Eini Street, P.O. Box 11562, Cairo, Egypt.

**Second Author** – Hala F. Zaki, Pharmacology & Toxicology Department, Faculty of Pharmacy, Cairo University, Kasr EL-Eini Street, P.O. Box 11562, Cairo, Egypt.

**Third Author** – Ezz-El-Din S. El-Denshary, Pharmacology & Toxicology Department, Faculty of Pharmacy, Cairo University, Kasr EL-Eini Street, P.O. Box 11562, Cairo, Egypt.

**Correspondence Author** – Mohammed H. Moawaḍ, Pharmacology & Toxicology Department, Faculty of Pharmacy, Cairo University, Kasr EL-Eini Street, P.O. Box 11562, Cairo, Egypt., Tell: (002)010 637 980 56, E-mail address: mhelmy@misrinternationalcompany.com

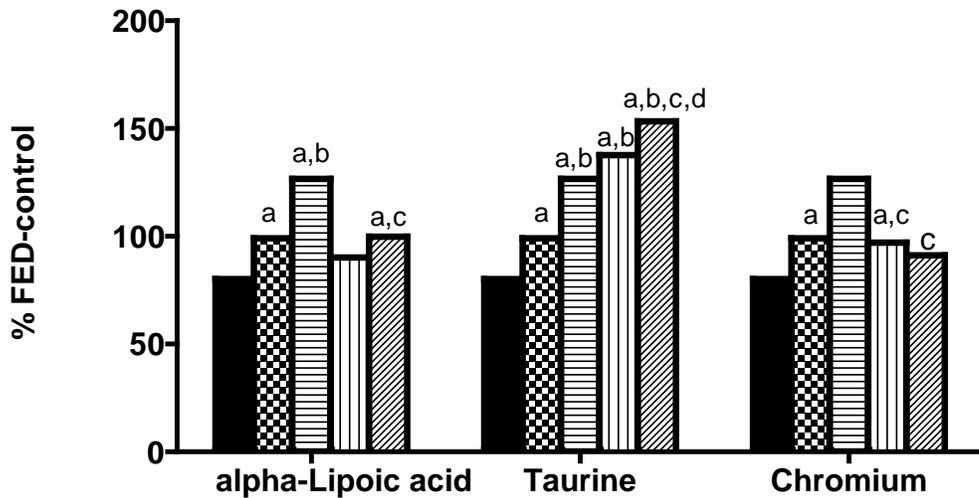


Figure (1): Effect of 6-week treatment with pioglitazone, alpha-lipoic acid, taurine, chromium picolinate and their combinations on body weight gain, in fructose enriched diet (FED) fed rats.

N=6-8 rats per group. Each value represents the mean ± SE of the mean.

Statistics were carried out by one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test.

<sup>a</sup>Significantly different from normal group at p<0.05.

<sup>b</sup>Significantly different from FED control group at p<0.05.

<sup>c</sup>Significantly different from pioglitazone-treated group at p<0.05.

<sup>e</sup>Significantly different from taurine-treated group at p<0.05

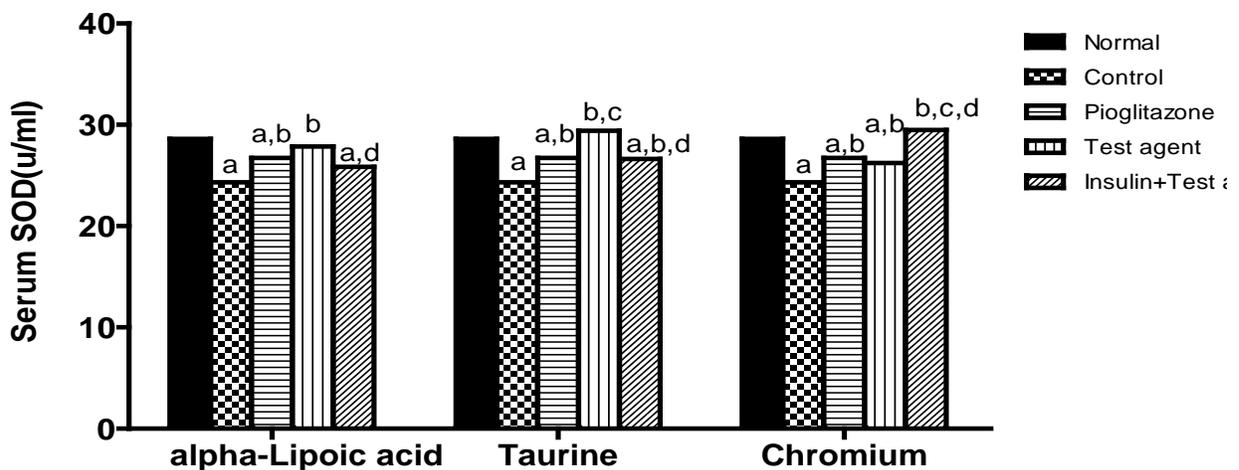


Figure (2-a): Effect of 6-week treatment with Pioglitazone, alpha-lipoic acid, taurine and chromium picolinate and their combinations on SOD, in fructose enriched diet (FED) fed rats.

N=6-8 rats per group. Each value represents the mean ± SE of the mean.

Statistics were carried out by one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test.

<sup>a</sup>Significantly different from normal group at p<0.05.

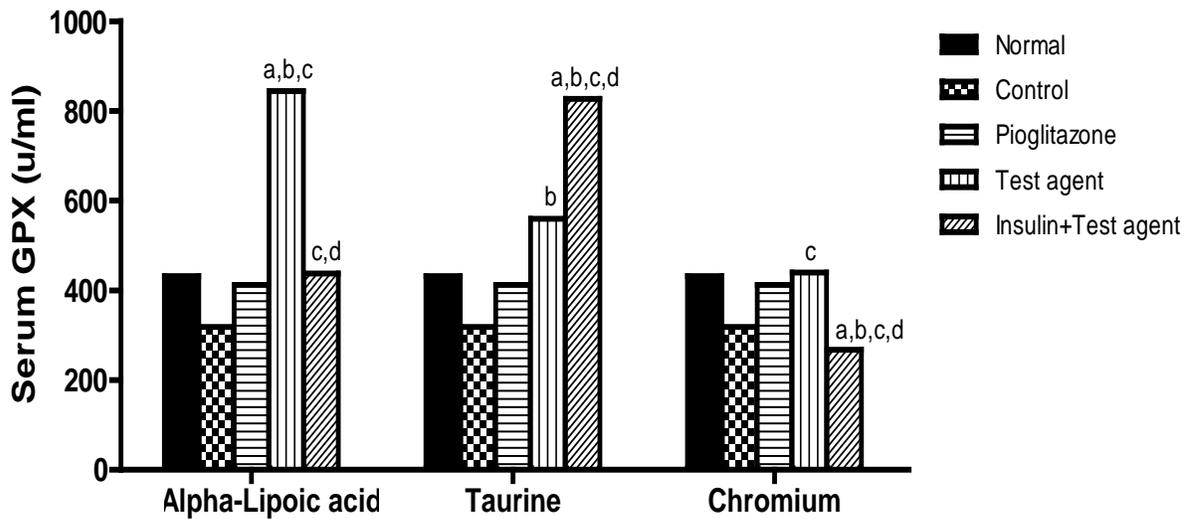
<sup>b</sup>Significantly different from FED control group at p<0.05.

<sup>c</sup>Significantly different from pioglitazone-treated group at p<0.05.

<sup>d</sup>Significantly different from Lipoic acid-treated group at p<0.05.

<sup>e</sup>Significantly different from taurine-treated group at p<0.05.

<sup>f</sup>Significantly different from chromium-treated group at p<0.05.



**Figure (2-b):** Effect of 6-week treatment with Pioglitazone, alpha-lipoic acid, taurine and chromium picolinate and their combinations on GPX, in fructose enriched diet (FED) fed rats.

*N=6-8 rats per group. Each value represents the mean  $\pm$  SE of the mean.*

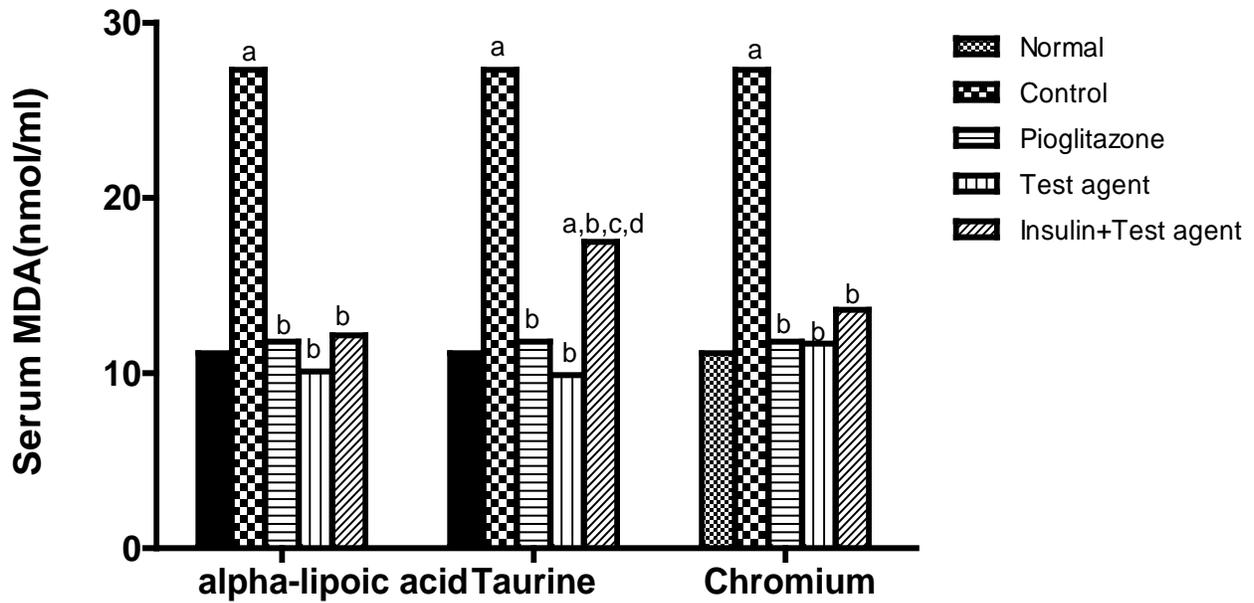
*Statistics were carried out by one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test.*

*<sup>a</sup>Significantly different from normal group at  $p < 0.05$ .*

*<sup>b</sup>Significantly different from FED control group at  $p < 0.05$ .*

*<sup>c</sup>Significantly different from pioglitazone-treated group at  $p < 0.05$ .*

*<sup>e</sup>Significantly different from taurine-treated group at  $p < 0.05$ .*



**Figure (2-c): Effect of 6-week treatment with Pioglitazone, alpha-lipoic acid, taurine and chromium picolinate and their combinations on MDA, in fructose enriched diet (FED) fed rats.**

*N=6-8 rats per group. Each value represents the mean ± SE of the mean.*

*Statistics were carried out by one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test.*

<sup>a</sup>*Significantly different from normal group at  $p < 0.05$ .*

<sup>b</sup>*Significantly different from FED control group at  $p < 0.05$ .*

<sup>c</sup>*Significantly different from pioglitazone-treated group at  $p < 0.05$ .*

<sup>d</sup>*Significantly different from Lipoic acid-treated group at  $p < 0.05$ .*

<sup>e</sup>*Significantly different from taurine-treated group at  $p < 0.05$ .*

<sup>f</sup>*Significantly different from chromium-treated group at  $p < 0.05$ .*

**Table (1): Effect of 6-week treatment with pioglitazone, alpha-lipoic acid, taurine, chromium picolinate and their combinations on fasting blood glucose (FBG) level and glycosylated hemoglobin (HbA1c) in fructose enriched diet (FED) fed rats.**

*N=6-8 rats per group. Each value represents the mean ± SE of the mean.*

Parameters/drugs & doses	FBG (mg/dl)	HbA1c (mg%)
Normal control (Saline; p.o.)	122.0 ± 1.95	4.73±0.11
Control (Saline; p.o.)	285.71±16.32 <sup>a</sup>	7.76±1.97 <sup>a</sup>
Pioglitazone (7mg/kg; p.o.)	98.75 ± 8.33 <sup>b</sup>	4.31 ± 0.15 <sup>b</sup>
Lipoic acid (600 mg/kg; p.o.)	155.9 ± 9.85 <sup>b</sup>	7.35 ± 0.18 <sup>a</sup>
Taurine (600 mg/kg; p.o.)	130.4 ± 4.54 <sup>b</sup>	4.08 ± 0.1 <sup>b</sup>
Chromium (500 mg/kg; p.o.)	127.3 ± 5.2 <sup>b</sup>	5.13 ± 0.16 <sup>b</sup>
Pioglitazone + Lipoic acid	102.5 ± 7.64 <sup>b,d</sup>	3.35 ± 0.13 <sup>b,d</sup>
Pioglitazone + Taurine	94.5 ± 3.83 <sup>b,d</sup>	3.88 ± 0.18 <sup>b</sup>
Pioglitazone + Chromium	84.25 ± 6.93 <sup>a,b,d</sup>	4.1 ± 0.14 <sup>b</sup>

*Statistics were carried out by one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test.*

<sup>a</sup>*Significantly different from normal group at p<0.05.*

<sup>b</sup>*Significantly different from FED control group at p<0.05.*

<sup>d</sup>*Significantly different from Lipoic acid-treated group at p<0.05.*

<sup>e</sup>*Significantly different from taurine-treated group at p<0.05.*

<sup>f</sup>*Significantly different from chromium-treated group at p<0.05.*

**Table (2): Effect of 6-week treatment with Pioglitazone, alpha-lipoic acid (LA), taurine, chromium picolinate and their combinations on serum lipid profile in fructose enriched diet (FED) fed rats.**

Parameters/ drugs & doses	TG mg/dl	TC mg/dl	HDL mg/dl	LDL mg/dl
Normal control (Saline;p.o.)	30.58±0.48	57.37±0.93	29.54±0.29	24.59±0.48
Control (Saline;p.o.)	35.47±0.16 <sup>a</sup>	74.43±0.72 <sup>a</sup>	21.89±0.31 <sup>a</sup>	39.93±0.2 <sup>a</sup>
Pioglitazone (7mg/kg;p.o.)	28.53±0.27 <sup>b</sup>	64.98±0.32 <sup>a,b</sup>	28.06±0.39 <sup>a,b</sup>	31.20±0.45 <sup>a,b</sup>
Lipoic acid (600mg/kg;p.o.)	30.08±0.78 <sup>b</sup>	70.93±0.43 <sup>a,b,c</sup>	28.43±0.14 <sup>b</sup>	37.15±0.35 <sup>a,c</sup>
Taurine(600mg/kg/day;p.o.)	27.71±0.38 <sup>a,b</sup>	68.89±0.49 <sup>a,b,c</sup>	28.19±0.26 <sup>b</sup>	35.55±0.51 <sup>a,b,c</sup>
Chromium(500mg/kg/day;p.o.)	34.64±0.27 <sup>a,c</sup>	68.73±0.28 <sup>a,b,c</sup>	30.33±0.21 <sup>b,c</sup>	31.53±0.39 <sup>a,b</sup>
Pioglitazone + Lipoic acid	18.29±0.29 <sup>a,b,c,d</sup>	65.24±0.39 <sup>a,b,d</sup>	27.36±0.23 <sup>a,b</sup>	34.31±0.09 <sup>a,b,c,d</sup>
Pioglitazone + Taurine	38.5±0.51 <sup>a,b,c,d</sup>	72.20±0.59 <sup>a,c,d</sup>	28.65±0.22 <sup>b</sup>	35.73±0.68 <sup>a,b,c</sup>
Pioglitazone + Chromium	31.64±0.81 <sup>b,c,e</sup>	67.49±0.26 <sup>a,b,c</sup>	25.38±0.31 <sup>a,b,c,d</sup>	38.98±0.17 <sup>a,c,d</sup>

*N=6-8 rats per group. Each value represents the mean  $\pm$  SE of the mean.*

*Statistics were carried out by one way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparisons test.*

*<sup>a</sup>Significantly different from normal group at  $p<0.05$ .*

*<sup>b</sup>Significantly different from FED control group at  $p<0.05$ .*

*<sup>c</sup>Significantly different from pioglitazone-treated group at  $p<0.05$ .*

*<sup>d</sup>Significantly different from Lipoic acid-treated group at  $p<0.05$ .*

*<sup>e</sup>Significantly different from taurine-treated group at  $p<0.05$ .*

*<sup>f</sup>Significantly different from chromium-treated group at  $p<0.05$ .*