# The biochemical effect of curcumin and chromium administration on adiponectin secretion and metabolism in experimentally diabetic rats by streptozotocin.

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**A B S T R A C T**

In the present study, the potential therapeutic effect of Curcumin combined with Chromium administration on adiponectin secretion and its biochemical effects on serum glucose, total cholesterol, triglycerides, L-Malondialdehyde (MDA), reduced glutathione (GSH), Interleukin 6 (IL-6) and Peroxisome proliferator-activated receptor gamma (PPAR-γ) of adipose tissue in experimentally diabetic rats by streptozotocin (STZ) have been evaluated. Fourty male Albino rats were divided into four equal groups of 10 rats each. Group I (Control group): received no drugs. Group II :( normal rats treated with curcumin and chromium): Group III : (Diabetic rats group): received a single dose of Streptozotocin (STZ) (50-mg/kg i.p) and was used for diabetes mellitus induction. Group IV:(Diabetic rats + Curcumin + Chromium treated group): treated with curcumin combined with chromium for 21 days after diabetes induction. Blood samples and adipose tissue were collected at the 22$^{th}$ day from the onset of curcumin and chromium administration. The obtained results showed that, STZ-induced diabetes causing a significant increase in serum glucose, total cholesterol, triglyceride, L-MDA, and IL-6 and a significant decrease in adiponectin secretion, GSH level and PPAR-γ expression. Curcumin combined with chromium was able to mitigate diabetes induced by STZ through decreasing serum glucose, total cholesterol, triglyceride, L-MDA, and IL-6 and increasing adiponectin secretion, GSH level and PPAR-γ expression. These results suggest that, curcumin and chromium combination may be effective in increasing insulin sensitivity in diabetic rats by increasing adiponectin secretion and exhibiting anti-inflammatory, antioxidant effects.

**Keywords:** Curcumin; Chromium; STZ; Diabetes mellitus; Adiponectin; Antioxidant enzymes; Peroxisome proliferator-activated receptor gamma (PPAR-γ).

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## 1. INTRODUCTION

Diabetes mellitus is a hyperglycemic disorder that affects the brain, kidney, heart, liver, and other organs. Inflammation has been shown to play a major role in development of type II diabetes *(Pillarisetti and Saxena, 2004)*. Diabetes is a syndrome, which characterized by hyperglycemia, lipoprotein abnormalities and raises the proportion of basic metabolism and a defect in enzymes of high oxidative stress resulting from damage to beta cells in the pancreas *(Sharma et al., 2010)*. Diabetes is a serious chronic disease worldwide and is caused by defects in insulin production, insulin secretion and insulin signals *(Skayler, 2007)*. Insulin resistance is a major risk factor for the development of type 2 diabetes *(Kahn and Flier, 2000)*. The development of inflammation and oxidative stress in adipose

tissue leads to insulin resistance *(Furukawa et al., 2004).* Adiponectin, an adipocyte-secreted cytokine, plays a role in the development of insulin resistance and subsequent type 2 diabetes. Lower adiponectin levels are more closely related to the degree of insulin resistance and hyperinsulinemia than to the degree of adiposity and glucose intolerance.

Adiponectin levels decrease in type 2 diabetic patients and are negatively correlated with postprandial glucose levels *(Wang et al., 2011). Sun et al (2010)* also found that via mitochondrial superoxide overproduction, intermittent hyperglycemia decreases adiponectin production in adipocytes. Therefore, aside from being a marker of insulin resistance, adiponectin may relate to superoxide defense. Presently, there are few studies available that have investigated whether acute or chronic oscillations in blood glucose alter serum levels of antioxidants and adiponectin *(Darmaun et al., 2012).* Many naturally occurring dietary polyphenols possess antioxidant and anti-inflammatory properties *(Alappat and Awad, 2010).*

Curcumin is the most active component of turmeric contains chemical constituents known as the curcuminoids, composed of curcumin (curcumin I), demethoxycurcumin (curcumin II) and bisdemethoxycurcumin (curcumin III). Commercial curcumin contains curcumin I (~77%), curcumin II (~17%) and curcumin III (~3%) as its major components *(Aggarwal et al., 2007)*

Curcumin is the substance that gives the spice turmeric, which is extensively used in Indian cuisine as a component of curry powder, its yellow color. Curcumin is extracted from the roots of the Curcuma longa plant (Turmeric). It is believed that curcumin is a potent antioxidant and anti-inflammatory agent. Practitioners of traditional Indian medicine believe that curcumin powder is beneficial against many diseases including biliary disorders, anorexia, coughs, diabetes, hepatic disorders, rheumatism, sinusitis, cancer, and Alzheimer disease *(Aggarwal et al., 2003).* Chromium, like many transition elements, is essential to animals and humans at low concentrations, but it is toxic to many systems at higher concentrations *(Baruthio 1992).* We have decided to use trivalent chromium because recently it has been postulated that this element may act as an antioxidant and diminish oxidative stress *(Goldhaber et al., 2003).* Moreover, it has been reported that Cr (III) has a very large safety range and that there have been no documented sings of Cr toxicity in any of the nutritional studies at levels up to 1 mg per day *(Anderson 1997).*

Accordingly, the purpose of the present study was to investigate the effect of Curcumin and Chromium combination on adiponectin secretion, insulin resistance and other metabolic parameters in STZ-induced diabetic rats.

## 2. MATERIALS AND METHODS

### *2.1. Experimental animals:*

Fourty white male Albino rats of 10-14 weeks old and weighting 160-200 gm were used in the experimental investigation of this study. The rats were obtained from the Laboratory Animals Research Center, Faculty of Veterinary Medicine, and Benha University. Rats were housed in separated wire mesh cages and kept at constant environmental and nutritional conditions throughout the period of experiment. The animals were fed on constant ration and fresh, clean drinking water was supplied *ad-libitum*. The animals were left 14 days for acclimatization before the beginning of the experiment.

### *2.2. Drugs used:*

Curcumin is an orange yellow powder, with the molecular formula $C_{21}H_{20}O_6$, molecular weight 368.39 and soluble in ethanol and Dimethylsulfoxide (DMSO**).** Curcumin

(purity ~99%) was manufactured by Fluka Co. for chemicals and purchased from Elgoumhouria Co. for Trading Chemicals Medicines and Medical Appliances, Egypt. Chromium chloride Hexahydrate ($CrCl_3.6H_2O$) was purchased from Sigma and dissolved in dimethyl sulfoxide (DMSO).

*2.3. Diabetes induction:*

Rats were fasted for 18 hrs and allowed free access of water. The experimental induction of diabetes in male rats was induced by a single intraperetinoel (i.p) injection of 50 mg/kg body weight of Streptozotocin (STZ) freshly dissolved in citrate buffer, pH 4.5. A week later, STZ-treated rats were fasted for 12 h and blood samples were collected from the tail vein for glucose determination. Only those rats in diabetic group with blood glucose level higher than 250mg/dl were considered diabetic *(Ramanathan et al., 1999).*

*2.4. Experimental design:*

Rats were randomly divided into four main equal groups, 10 rats each, placed in individual cages and classified as follow: -

Group 1: Control group: received no drugs, served as control non-treated for all experimental groups.
Group 2: Curcumin +Chromium group served as non-diabetic group treated with Curcumin (100 mg/kg. b.wt/day) combined with Chromium (1 mg/kg. b.wt /day) orally for 21 days.
Group 3: STZ group: served as STZ-induced diabetic rats group and received a single intraperetinoel (i.p) injection of 50 mg/kg body weight.
Group 4: STZ + Curcumin + Chromium group: Served as STZ-induced diabetic rats group treated with Curcumin (100 mg/kg. b.wt/day) combined with Chromium (1 mg/kg. b.wt /day) dissolved in distilled water and administrated orally for 21 days.

*2.5. Sampling:*

Blood samples and tissue specimens (adipose tissue) were collected at the end of experiment (on 22th day) from all experimental groups.

*2.5.1. Blood samples:*

Blood samples for serum separation were collected at the end of each experimental period and after overnight fasting in dry, clean, and screw capped tubes and serum were separated by centrifugation at 2500 r.p.m for 15 minutes .The clean, clear serum was separated by automatic pipette and received in dry sterile samples tube and kept in a deep freeze at -20 °C until used for subsequent biochemical analysis .All sera were analyzed for glucose, lipid profile, GSH, MDA, Adiponectin, and IL-6.

*2.5.2. Tissue samples (Adipose tissue):*

At the end of the experiment, rats of each group were sacrificed by cervical decapitation. The abdomen was opened and adipose tissue specimen was quickly removed and suspended in lysing buffer for evaluating gene expression of PPAR gamma by Relative Quantification PCR. The primers used were: for PPAR-γ Forward 5′ GCG GAG ATC TCC AGT GAT ATC 3′and Reverse 5′ TCA GCG ACT GGG ACT TTT CT 3′; for β-actin gene Forward primer: 5′CCAGGCTGGATTGCAGTT3′ and Reverse primer: 5′GATCACGAGGTCAGGAGATG3′.

*2.6. Biochemical analysis:*

Serum glucose was enzymatically determined according method described by *Trinder (1969).* Lipid profile was measured according to *Allain et al., (1974).*

Serum adiponectin measured by Rat Total Adiponectin ELISA kit (Quantikine® ELISA, Cat.No RRP300). Serum GSH, L-MDA activity were analyzed according to the

*Beutler et al., (1963);* and *Mesbah et al., (2004),* respectively. Relative Quantification of real time-PCR of PPAR-γ gene expression in adipose tissue performed according to method described by *Afonina et al., (1997).*

*2.7. Statistical analysis:*

The obtained data were statistically analyzed by one-way analysis of variance (ANOVA) followed by the Duncan multiple test. All analyses were performed using the statistical package for social science (SPSS, 13.0 software, 2009). Values of $P<0.05$ were considered to be significant.

## 3. RESULTS

*3.1. Effect of treatment with Curcumin combined with Chromium on some blood serum parameters of STZ-induced diabetic rats.*

The obtained results in table (1) revealed that, a significant increase in blood serum glucose, triglycerides, cholesterol and MDA levels and a significant decrease in adiponectin and GSH levels were observed in STZ induced diabetic rats. Treatment with Curcumin and chromium combination in STZ-induced diabetic rats resulted in significant decrease in serum glucose, triglycerides, cholesterol and MDA levels and a significant increase in adiponectin and GSH levels.

*3.2. Effect of treatment with Curcumin combined with Chromium on PPAR-γ gene expression of adipose tissue in STZ-induced diabetic rats.*

Real-time quantitative polymerase chain reaction (qPCR) results showed a decrease in PPAR-γ gene expression in adipose tissue in STZ-induced diabetic rats. But the group treated with curcumin and chromium combination showed an increase in PPAR-γ gene expression in adipose tissue.

Table (1): Effect of treatment with curcumin and chromium combination on some serum and tissue parameters in STZ-induced diabetic rats.

| Treatment period | | | | |
|---|---|---|---|---|
| Experimental Groups / Parameters | Normal Control | Cur +Chrom | STZ | STZ + Cur + Chrom |
| Glucose (mg /dl) | 110 ± 3.8 $^{b}$ | 105.8 ± 4.7 $^{b}$ | 509.4 ±14.3 $^{a\,b}$ | 133.8 ± 4.8 $^{a\,b}$ |
| Triglyceride (mg /dl) | 50.4 ±2.2 $^{b}$ | 52.0 ±1.9 $^{b}$ | 86.0 ±3.4 $^{a\,b}$ | 48.7 ±1.8 $^{b}$ |
| Cholesterol (mg /dl) | 131.3 ± 1.4 $^{b}$ | 130.8 ± 2.2 $^{b}$ | 201.4 ± 1.3 $^{a\,b}$ | 142.0 ± 2.7 $^{a\,b}$ |
| HDL (mg /dl) | 52.3 ± 0.8 $^{b}$ | 49.7 ± 2.1 $^{b}$ | 23.6 ± 1.4 $^{a\,b}$ | 47.4 ± 2.5 $^{a\,b}$ |
| Adiponectin (ng/ml) | 12.3 ± 0.2 $^{b}$ | 12.5 ± 0.1 $^{b}$ | 2.0 ± 0.1 $^{a\,b}$ | 12.0 ± 0.4 $^{b}$ |
| GSH (nM/mg protein) | 45.1 ± 1.2 $^{b}$ | 47.5 ± 0.7 $^{b}$ | 24.7 ± 1.2 $^{a\,b}$ | 43.7 ± 1.6 $^{b}$ |
| MDA (mM/mg Protein) | 1.3 ± 0.1 $^{b}$ | 1.4 ± 0.1 $^{b}$ | 12.6 ± 0.6 $^{a\,b}$ | 2.7 ± 0.2 $^{a\,b}$ |
| PPAR-Y (Relative Quantification) | 1.4 ± 0.1 $^{a\,b}$ | 1.5 ± 0.1 $^{b}$ | 0.2 ± 0.0 $^{a\,b}$ | 1.0 ± 0.0 $^{a\,b}$ |
| IL-6 (µg/ml) | 31.8 ± 1.5 $^{b}$ | 28.4 ± 0.5 $^{b}$ | 100.0 ± 1.3 $^{a\,b}$ | 53.1 ± 2.5 $^{a\,b}$ |

Data are presented as (Mean ± S.E).
S.E = Standard error.
Mean values with different superscript letters in the same column are significantly different at ($P<0.05$).

## 4. DISCUSSION

Insulin resistance is a major risk factor for the development of type 2 diabetes *(Kahn and Flier, 2000).* Adiponectin has emerged as an important adipocytokine, which improves insulin sensitivity and might represent a novel pharmacological target for the treatment of insulin resistance and type 2 diabetes *(Hu et al., 1996).*The recorded data in (table 1) demonstrated that, a significant increase in serum glucose level and a significant decrease in serum adiponectin level in Streptozotocin-induced diabetic rats all over the period of experiment. The increase in serum glucose level in STZ-induced diabetic rats is nearly similar to those reported by *Sayed et al. (2006)* who observed that, STZ-induced diabetic rats showed approximately five-fold increase in blood glucose levels after STZ administration. *Dias et al., (2005)* reported that the plasma glucose concentration was significantly increased in diabetic rats. The decrease in adiponectin level in STZ-induced diabetic rats is nearly similar to those reported by *Hotta et al. (2000)* who reported that adiponectin levels decreased in type 2 diabetes. The development of inflammation and oxidative stress in adipose tissue leads to insulin resistance *(Furukawa et al., 2004).* Administration of curcumin and chromium combination in STZ-induced diabetic rats resulted in a significant decrease in serum glucose level and increase in serum adiponectin level. These results are nearly similar to those reported by *Mukhopadhyay et al. (2002)* who reported that reduction of the infiltration of macrophages into adipose tissue may be explained by the effect of curcumin on adiponectin. Other study revealed that chromium might increase the number of insulin receptors, enhance receptor binding, potentiate insulin action, and improve insulin resistance *(Anderson et al., 1987).* The obtained data presented in (table 1) revealed that, a significant increase in cholesterol and triglyceride in STZ-induced diabetic rats all over the period of experiment when compared with normal control animal group. These results are nearly similar to those reported by *Black et al., (1993)* who observed that triglyceride and cholesterol concentrations were significantly elevated in STZ-induced diabetic rats. Blood lipid concentrations increased but HDL decreased with decrease in adiponectin concentration. Administration of Curcumin-Chromium combination in STZ-induced diabetic rats resulted in a significant decrease in serum total cholesterol and triglycerides and significant increase in HDL. These data go in hand with *(Mahesh et al., 2004)* who reported that, the mechanism by which curcumin improves this situation are probably its hypocholesterolemic influence, antioxidant nature, and free-radical scavenging property. Trivalent chromium has been identified as an essential nutrient element for normal glucose and lipid metabolism, and chromium deficiency is associated with diabetes and dyslipidemia *(Mahdi 1996).* Oral chromium chloride treatment led to improvements in blood glucose and lipid profiles in type 2 diabetics *(Abraham et al. 1992).* The recorded data in (table 1) demonstrated that a significant increase in malondialdehyde (MDA) and a significant decrease in serum reduced glutathione (GSH). These results are nearly similar to those reported by *Wu et al (2004)* who reported that glutathione is an abundant antioxidant and decreases both in type 1 and 2 diabetic patients. It is capable of detoxifying oxygen radicals to prevent cellular damage and oxidative stress. In addition, oxidation of lipids may form lipid radical species that damage other cellular macromolecules. For example, lipid peroxides like malondialdehyde (MDA) *(Berlett and Stadtman, 1997).* Accumulated evidence suggests that adipose tissue

oxidative stress plays central and causal roles in the pathogenesis of metabolic syndrome *(Baynes and Thorpe, 1999).* Administration of Curcumin combined with Chromium in STZ-induced diabetic rats resulted in a significant increase in GSH and a significant decrease in MDA concentration. These results support study that showed that generation of superoxide radicals by high glucose levels in a cell-free system was inhibited in the presence of curcumin *(Sushil et al., 2005)*. Both curcumin and its metabolite tetrahydrocurcumin (THC) have been shown to decrease blood glucose levels, increase plasma insulin levels, and modulate hepatic key enzyme levels in STZ-induced diabetic rats *(Murugan and Pari, 2005)* through modulation of oxidative stress *(Murugan and Pari, 2006)* and reduction in lipids and lipid peroxidation *(Murugan and Pari, 2006).* There have been several reports showing that Cr inhibits the secretion of pro-inflammatory cytokines and reduces oxidative stress in monocytes, not in pancreatic β cells, exposed to high glucose and standard oxidants like $H_2O_2$ *(Jain and Kannan 2001).* There have been several reports showing that Cr and reduces oxidative stress in monocytes exposed to high glucose and standard oxidants like $H_2O_2$ *(Jain and Kannan 2001).* Recent studies disclosed that chromium could improve the cellular antioxidant capacity and, thus, its supplementation is an effective treatment strategy to minimize increased oxidative stress in type 2 diabetic patients Restoration of chromium deficiency with type 2 DM may counteract the deleterious effects of oxidative stress and may help prevent complications associated with diabetes *(Cheng et al., 2004).* The obtained data in (table 1) showed significant decreased expression of Peroxisome proliferator-activated receptor gamma (PPAR-γ) which evaluated by relative quantification real time quantitative PCR (RT-qPCR). The results showed also a significant increase in IL-6.these results go in hand with those reported by *Rotter et al. (2002)* who has demonstrated that adipocytes secrete various proteins, called adipocytokines, which influence insulin sensitivity profoundly thereby providing a possible molecular link between increased adiposity and reduced sensitivity of target tissues to insulin. Thus, it has been shown that IL-6 and tumor necrosis factor (TNF) decrease insulin sensitivity in vivo and in vitro *(Hotamisligil, 2000).* IL-6 was originally described as a proinflammatory cytokine, which is produced in a variety of tissues including adipocytes, activated leucocytes, and endothelial cells *(Mohamed et al., 1997).* Recently, several studies have shown that IL-6 plasma levels are significantly upregulated in states of insulin resistance such as diabetes mellitus, as well as obesity, and IL-6 plasma concentrations at baseline independently predict future risk of developing type 2 diabetes mellitus *(Pickup et al., 1997).* Administration of curcumin and chromium combination significantly increased PPAR-γ gene expression and decreased IL-6 level as shown in (table 1). There have been several reports confirmed these results showing that Cr inhibits the secretion of pro-inflammatory cytokines (i.e., IL-6) and reduces oxidative stress in monocytes exposed to high glucose and standard oxidants like H2O2 *(Jain et al. 2004, 2007).* Previous studies have also shown that curcumin activates PPAR-γ *(Xu et al., 2003).* Curcumin suppresses, IL-6 and this documented the anti-inflammatory activities of curcumin in adipose tissue suggest that curcumin is a potential dietary polyphenolic source to effectively control adipose tissue expansion and inflammation *(Gonzales et al 2008).* Previous studies have reported that several adipocytokines are regulated by pharmacological drugs that activate peroxisome proliferator-activated receptors (PPAR-γ) *(Zhao and Wu, 2004)* and that may give a mechanism by which adiponectin

secretion increased by increasing the expression of PPAR-γ as reported by *Chinetti et al., (2004).*

In conclusion, the present study demonstrated that curcumin and chromium administration provided an effective treatment against insulin resistance in STZ-induced diabetic rats, since curcumin and chromium were able to ameliorate serum biochemical parameters and increase adiponectin secretion. We recommended that, administration of diet rich in the curcumin and chromium is very important for protection against hyperglycemia and hyperlipidemia.

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**التاثير البيوكيميائي لمادتي الكركمين والكروميم علي افراز الاديبونيكتين وعمليات الايض في الفئران المحدث فيها البول السكري تجريبيا بالاستربتوزوتوسين.**

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[2] قسم الميكروبيولوجي هيئة الطاقة الذرية

## الملخص العربي

في هذه الدراسة تم تقييم التأثر العلاجي المحتمل للكركمين والكروميم على التغيرات في مستوي الاديبونيكتين ، الجلوكوز ، والكوليسترول ، والدهون الثلاثية، ،والمالون ثنائي الالدهيد و الجلوتاثيون (GSH)، الانترلوكين ٦ ، مكاثر البيروكسمات جاما PPAR γ في الجرذان المصابة بداء البول السكري تجريبيا بواسطة بالاستربتوزوتوسين (STZ). هذا وقد استخدم لهذه الدراسة أربعون من ذكور الجرذان البيضاء اعمارهم تتراوح م ١٠ إلى ١٤ اسبوع واوزانهم من ١٦٠ الي ٢٠٠ جرام وتم تقسيمهم الي اربع مجموعات متساوية اشتملت كل مجموعة علي عدد عشرة فئران تم توزيعهم كالتالي: المجموعة الاولي :( الضابطة): لم تتلقي اي ادوية واستخدمت كمجموعة ضابطة للمجموعات الأخرى. مجموعة الثانية:( الفئران الغير مصابة تم حقنها بالكركمين والكروميوم). المجموعة الثالثة :( المحدث فيها مرض السكري): تلقت جرعة واحدة من الاستربتوزوتوسين (STZ) (50 ملغم / كغم من وزن الحيوان) لإحداث مرض السكر بها. المجموعة الرابعة :( الجرذان المصابة بداء السكري والمعالجة بالكركمين والكروميم) : يتم حقن الفئران المصابة بمرض السكري بالكركومين والكروميم عن طريق الفم لمدة 21 يوما بعد إحداث السكري. تم جمع عينات الدم والأنسجة الدهنية في اليوم 22 من بداية العلاج بالكركومين والكروميم. أظهرت النتائج المتحصل عليها أن، الاستريبتوزوتسين يسبب زيادة في نسب الجلوكوز في الدم، الكولسترول الكلي، الدهون الثلاثية، ,والمالون ثنائي الالديهايد ، والانترلوكين 6 وانخفاض ملحوظ في إفراز اديبونيكتين، ومستوى الجليوتاثيون والتعبير الجيني لمستقبلات مكاثر البيروكسيمات جاما – PPAR γ. كما ان النتائج اظهرت ان المجموعة الرابعة والتي تم العلاج فيها باستخدام الكركمين والكروميم خفض نسب الجلوكوز في مصل الدم، الكولسترول الكلي، الدهون الثلاثية، والمالون ثنائي الالديهيد، والانترلوكين ٦ وزيادة إفراز اديبونيكتين، ومستوى الجلوتاثيون المختزل والتعبير الجيني لمستقبلات البيروكسيمات جاما. هذه النتائج تشير إلى أن الكركمين والكروم معا قد يكون لهم دور فعال في زيادة حساسية الانسولين في الفئران المصابة بالسكري عن طريق زيادة إفراز اديبونيكتين وايضا بدورهم كمضادات للالتهاب والاكسدة المضادة للالتهابات.

**(مجلة بنها للعلوم الطبية البيطرية: عدد 27(2) ،396–404: ديسمبر 2014)**