WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES
SJIF Impact Factor 7.421
Volume 7, Issue 10, 325-343 Research Article ISSN 2278 – 4357

# BIOCHEMICAL STUDY ON THE REGENERATIVE EFFECT OF CHROMIUM PICOLINATE ON EXPERIMENTALLY INDUCED DIABETES

**Yakout A. El Senosi*[1], Omayma, A. R. Abou Zaid[2], Afaf Desouky A. Elmaged[3], Mohamed A. M. Ali[4*]**

[1,2,3,4]Department of Biochemistry, Faculty of Vet., Medicine Benha University, Egypt.

Article Received on
03 August 2018,
Revised on 24 August 2018,
Accepted on 13 Sept. 2018,
DOI: 10.20959/wjpps201810-12444

***Corresponding Author**
**Yakout A. El Senosi**
Department of Biochemistry, Faculty of Vet., Medicine Benha University, Egypt.

In the present study, the potential therapeutic effect of Chromium picolinate administration diabetic rats was evaluated. Thirty male albino rats were divided into three equal groups of 10 rats each. Group I :( Control group): received no drugs. Group II :( Diabetic rats group): rats received a single dose of Streptozotocin (STZ) (50- mg/kg-b.wt i.p). Group III :( Diabetic rats + Chromium picolinate treated group): rats are treated with + Chromium picolinate 8.8 mg /kg body weight /day, orally) for 21 days after diabetes induction. Blood samples and pancreatic tissue were collected at the 22th day from the onset of + Chromium picolinate administration. The obtained results showed that, STZ-induced diabetic rats exhibited a significant increase in serum glucose, triacylglycerols, total cholesterol, LDL-cholesterol, malondialdehyde (MDA), advanced glycation end products (AGEs) and glycated hemoglobin (HbA1c) with marked decrease in HDL-cholesterol, insulin levels, Catalase (CAT), glutathione peroxidase (GSH-px), superoxide dismutase (SOD). Treatment with chromium picolinate was able to mitigate diabetic abnormalities through decreasing serum glucose, triacylglycerols, total cholesterol, LDL-cholesterol, malondialdehyde (MDA), advanced glycation end products (AGEs) and glycated hemoglobin (HbA1c) and increasing HDL-cholesterol, insulin levels, Catalase (CAT), glutathione peroxidase (GSH-px) and superoxide dismutase (SOD), These results suggest that chromium picolinate are effective in increasing insulin sensitivity and secretion in diabetic rats and improving other biochemical blood parameters.

**KEYWORDS**: chromium picolinate; STZ; Diabetes; lipid profil; Antioxidant enzymes; AGEs and HBA1c.

## INTRODUCTION

Diabetes mellitus (DM) is a serious disease in which the body cannot control the amount of sugar in circulation due to either a deficiency of insulin secretion or a decreased sensitivity of the tissues to insulin. There are two main types of diabetes as follows: Type 1 and Type 2 **(Vigneri et al., 2009).** Both types can cause serious health complications, including kidney failure, heart disease, blurred vision, ketoacidosis, peripheral neuropathy, itchiness, fatigue, and even coma (**Stolar, 2010).** An insulin deficiency leads to elevations of cholesterol, phospholipids, and free fatty acids **(Yadav et al., 2004).** Therefore, it is important that an ideal DM therapy should not only involve maintaining blood glucose levels but also involve the regulation of the lipid profile.

Diabetes Mellitus was a leading cause of most renal diseases and the cause of heart attacks leading to blindness and nontraumatic amputations **(Chan et al., 2016)**. Diabetes is the most serious disease with multiple complications and mortality and responsible for at least 10% of total health care disbursement in the world **(King et al., 1998).**

Diabetes mellitus was a serious metabolic disease that tendency to diseases and multiple-organ impairment **(De la Monte et al., 2014).** The lacks of β-cells in the pancreas were the main cause of pathophysiological markers in the progress of both two types of diabetes either 1 or 2 **(Harper et al., 2016).** Therefore, the great therapeutic goal is to achieve the remarkable production and generation of pancreatic islets that would consequently ameliorate diabetes and reduced its complications (**Ibrahim et al., 2016)**.

To treat DM, several antidiabetic drugs are used. However, these drugs are not without side effects and pose an economic burden to the patient. Therefore, scientists have turned to natural remedies, including Chromium (Cr).

Chromium is a transitional element that is ubiquitous in nature, occurring in air, water, soil and biological materials, over a range of concentrations. Chromium picolinate, derived from chromium (III) and picolinic acid is a chemical compound available as a nutritional supplement to prevent or treat chromium deficiency. Several studies have reported beneficial effects of chromium on glucose tolerance and or lipid metabolism. Chromium dietary spplements use is especially popular among patients with Type 2 Diabetes Mellitus (T2DM) or those attempting to lose weight **(Shapiro and Gong, 2002).** It has been reported **(Martin**

**et al, 2006)** that Chromium picolinate supplementation in subjects with (T2DM) who are taking sulfonylurea agents, show significant improvement in insulin sensitivity and glucose control as well as significant attenuated body weight gain and visceral fat accumulation.

Chromium (Cr) in the trivalent oxidation state is a trace mineral necessary for livestock animals in some conditions. This trace element functions as a cofactor for regulating the metabolism of carbohydrates, lipids and proteins via insulin function in humans and animals **(Krzysik et al., 2011)**. Cr deficiency in healthy humans and animals is unlikely to develop and dietary Cr supplement is usually unnecessary **(Trumbo et al., 2001).** However, under stress conditions, chromium supplementation can alleviate the negative effects of heat stress on animal health and performance **(Anderson, 1994; Sahin et al., 2002).** In the recent studies **(McNamara & Valdez, 2005; Moeini et al., 2011)**, the effects of organic and inorganic sources of Cr on immune response, performance, reproduction parameters and health in animals under heat stress or non-stress conditions were examined.

## MATERIALS AND METHODS

### *Experimental animals*

Thirty 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, Benha University. Rats Animals were housed in separate metal cages, exposed to good ventilation, humidity and to a 12 hr light/dark cycle. Fresh and clean drinking water was supplied ad-libtium. Constant supplies of standard pellet diet, fresh and clean drinking water were supplied ad-libitum.The animals were left for 15 days for acclimatization prior to the beginning of the experiment, and kept at constant environmental and nutritional conditions throughout the period of the experiment.

### Chemicals used

### Chromium

Chromium picolinate is reddish-pink color with Chemical Formula **(C18H12CrN3O6)** Chromium picolinate tablets were purchased from was purchased from Oxford laboratory Reagent Company.

**Preparation** of The Chromium picolinate was dissolved in normal saline (NS; 0.9% NaCl) or drinking-water (**Doddigarla et al., 2016)**.

***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).**

***Experimental design***

Thirty male albino rats were divided into three equal groups of 10 rats each. Group I: (Control group): received no drugs. Group II :( Diabetic rats group): rats received a single dose of Streptozotocin (STZ) (50- mg/kg-b.wt i.p). Group III :( Diabetic rats + Chromium picolinate treated group): rats are treated with + Chromium picolinate 8.8 mg /kg body weight /day, orally) for 21 days after diabetes induction. Treating started 5 days after diabetes induction.

***Sampling***

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

**1 - Blood sampling**

Approximately 9 mL blood gathered into two tubes from each rat, EDTA was added to one sample to obtained whole blood, and serum were separated by centrifugation at 3000 r. p. m for 30 minutes the clean, clear-serum was separated by Pasteur pipette and received in dry sterile sample tubes, processed directly for glucose determination, then kept in a deep freeze at - 20°C until used for subsequent biochemical analysis. **(Sanford, 1954).**All sera were analyzed for glucose, Insulin, lipid profile, HBA1c,

***Tissue samples***

Pancreases were washed with ice-cold saline solution (0.9 % NaCl), weighed and stored at -80 ºC for the biochemical analyses.

**(GSH-Px, Catalase, SOD, MDA and AGEs)**

**Tissue preparation**

The tissues were homogenized with 0.1 M phosphate buffer saline at pH 7.4, to give a final concentration of 20 % w/v for the biochemical assays.

***Biochemical analysis***

Serum glucose was determined enzymatically according to the method described by **Trinder (1969).** Serum insulin was determined with the method described by (**Mattews *et al.*, 1985)**. Plasma triacylglycerols, cholesterol, HDL, LDL was determined enzymatically according to the method of **Young, (2001), Young, (2001), Warnick *et al.*, (1983)** and **Okada et al.,(1998)** respectively using diagnostic kit by Spin React Company, Egypt**.** Rat Advanced Glycation End Products (AGEs) **by (ELISA Kit Catalog Number. MBS700464).** Rat HbA1c (Glycosylated Hemoglobin/Hemoglobin A1c) **by ELISA Kit Catalog No: MBS2509196 (96T) 6th Edition, revised in June, 2015**. Serum lipid peroxidation (L-MDA) was calorimetrically determined according to the method adapted by **Esterbauer *et al.*, (1982).** Glutathione (GSH) was calorimetrically determined according to the method adapted by **Eyer et al., (1986)** using cayman chemical kit,USA. Erythrocyte superoxide dismutase activity was determined according to the method described by **Misra and Fridovich (1972).** Catalase activities were determined according to the method described by **(Sinha, 1972).**

**Statistical analysis**

All values were expressed as mean ± standard error (SE). All statistical analyses were performed using SPSS (version 19). Statistical differences among the experimental groups were assessed by ANOVA. Duncan's test was used as a follow-up test and significance was defined at $p<0.05$.

**RESULTS**

***Effect of treatment with Chromium picolinate on some serum and pancreas tissue parameters in STZ-induced diabetic rats***

The obtained results in table (1,2 and 3) revealed that, a significant increase in serum glucose, triglycerides, total cholesterol, LDL-cholesterol, malondialdehyde (MDA), advanced glycation end products (AGEs) and glycated hemoglobin (HbA1c) with marked decrease in HDL-cholesterol, insulin levels, Catalase (CAT), glutathione peroxidase (GSH-px), superoxide dismutase (SOD). Treatment with chromium picolinate was able to mitigate diabetic abnormalities through decreasing serum glucose, triglycerides, total cholesterol, LDL-cholesterol, malondialdehyde (MDA), advanced glycation end products (AGEs) and

glycated hemoglobin (HbA1c) and increasing HDL-cholesterol, insulin levels, Catalase (CAT), glutathione peroxidase (GSH-px) and superoxide dismutase (SOD), These results suggest that chromium picolinate are effective in increasing insulin sensitivity and secretion in diabetic rats and improving other biochemical blood parameters.

**Table (1): Effect of chromium picolinate (Cr.pic) on the serum level of glucose, insulin, Hb1AC and AGE in STZ-induced diabetic rats (Mean±SE).**

| Group | Glucose (mg/dL) | Insulin (mg/dL) | Hb1AC (ng/ml) | AGE (µg/ml) |
|---|---|---|---|---|
| Control (normal) | 83.2±1.59$^{c}$ | 4.98±0.14$^{a}$ | 12.20±0.23$^{c}$ | 31.2±0.64$^{c}$ |
| STZ | 357.0±5.38$^{a}$ | 1.02±0.04$^{c}$ | 24.49±0.44$^{a}$ | 108.7±2.73$^{a}$ |
| STZ + (Cr.pic) | 159.2±2.92$^{b}$ | 1.84±0.06$^{b}$ | 19.73±0.18$^{b}$ | 74.0±2.08$^{b}$ |

**a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.**

**Table (2): Effect of chromium picolinate (Cr.pic) on lipid profile of serum in STZ-induced diabetic rats (Mean±SE).**

| Group | Triglycerides (mg/DL) | Total cholesterol (mg/dL) | HDL-cholesterol (mg/dL) | LDL-cholesterol (mg/dl) |
|---|---|---|---|---|
| Control (normal) | 140.80±2.27$^{c}$ | 105.40±0.75$^{c}$ | 53.40±1.44$^{a}$ | 23.84±1.49$^{c}$ |
| STZ | 226.20±2.15$^{a}$ | 194.20±2.46$^{a}$ | 42.20±0.86$^{c}$ | 106.76±2.86$^{a}$ |
| STZ + (Cr.pic) | 181.00±0.89$^{b}$ | 128.60±3.08$^{b}$ | 49.40±0.93$^{b}$ | 43.00±2.34$^{b}$ |

**a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.**

**Table (3): Effect of chromium picolinate (Cr.pic) on MDA, CAT, GSH, and SOD in STZ-induced diabetic rats (Mean±SE).**

| Group | MDA (nM/g tissue) | CAT (IU/g tissue) | GSH-px (IU/g tissue) | SOD (IU/g tissue) |
|---|---|---|---|---|
| Control (normal) | 34.12±0.38$^{c}$ | 7.10±0.29$^{a}$ | 25.07±0.36$^{a}$ | 12.30±0.56$^{a}$ |
| STZ | 73.53±0.78$^{a}$ | 1.25±0.13$^{c}$ | 8.08±0.32$^{c}$ | 3.13±0.28$^{c}$ |
| STZ + (Cr.pic) | 59.24±1.03$^{b}$ | 2.78±0.20$^{c}$ | 12.48±0.52$^{b}$ | 6.30±0.39$^{b}$ |

**a, b & c: There is no significant difference (P>0.05) between any two means, within the same column have the same superscript letter.**

## DISCUSSION

In this study, rats treated with STZ showed a significant increase in glucose concentration and decreased in insulin level compared to control group. These results are nearly similar to those reported by **Doddigarla et al., (2016)** who reported that, STZ-induced diabetic rats

showed a significant increase in blood glucose level and decreased in insulin level in (diabetic) group compared with control group after 3 weeks (P< 0.05).

**Also, Huang et al., 2014** who reported that, STZ-induced diabetic rats showed a significant increase in blood glucose level and decreased in serum insulin in (diabetic) group compared with control group after 3 weeks (P< 0.05).

As a result of the STZ action, $\beta$-cells undergo destruction by necrosis. After CrPic supplement, the inflammatory cells infiltration was reduced or appeared and the function of $\beta$-cells was recovered. The results provided evidence for the ability of CrPic in regulating the levels of, insulin. T2DM frequently results from progressive failure of pancreatic $\beta$- cell function in the presence of chronic insulin resistance **(Buchanan et al., 2002)** Some previous studies have reported that CrPic supplementation could increase insulin sensitivity in subjects with type 2 diabetes (**Martin et al., 2006)**.

Administration of Chromium picolinate in STZ-induced diabetic rats resulted in a significant decrease in serum glucose level and a significant decreased in serum insulin concentrations. These results are nearly similar to those of **Doddigarla et al., (2016)** who showed that chromium picolinate improves the metabolic status in diabetic conditions and **Khulan et al., (2015)** chromium picolinate treatment can induce hypoglycemia in rats with STZ-induced diabetes **(Mahesh *et al.*, 2004).** In diabetes, Chromium has been shown the possibility to improve glucose levels and related variables in subjects with glucose intolerance and type 1, type 2, gestational and steroid induced diabetes **(Anderson 2000)**. The main mechanism of Cr in glucose control has been explained by its improvement of insulin sensitivity **(Vincent, 1999)**.

Mechanism by which chromium decreases serum glucose level is that Cr might enhance insulin receptor binding **(Vincent 2000),** increase the number of insulin receptors **(Cefalu and Hu 2004)** and insulin receptor phosphorylation **(Wang *et al*. 2005),** resulting in the reduction of insulin resistance **(Morris *et al*. 1993, 2000)** Those results, along with clinical data, suggest that Cr might be beneficial in treating type2 diabetes.

Our results revealed a significant (P≤0.05) increase in the pancreas level of advanced glycation end products (AGEs) and HbA1c in STZ-induced diabetic rats (STZ) as compared to untreated control group (Normal) These results are nearly similar to those of (**Refat et al.,**

**2016)** who reported that, STZ-induced diabetic rats showed a significant (P≤0.05) increase in the pancreas level of advanced glycation end products **(AGEs)** and HbA1c in STZ-induced diabetic rats (STZ) as compared to untreated control group (Normal) after 3 weeks (P< 0.05).

Also, **Huang et al., 2014** reported that, In the diabetic group streptozotocin-injected dramatically increased in the pancreas level of advanced glycation end products **(AGEs)** and HbA1c in STZ-induced diabetic rats (STZ) as compared to untreated control group (Normal) Moreover, Glycation is a non-enzymatic reaction between sugars and a free amino group of proteins resulting in advanced glycation end-products (AGEs) (**Li et al., 2010)**. Protein glycation and AGEs are accompanied by increased free radical activity that leads to the biomolecular damage in diabetes (**Sen et al., 2005)**. AGEs generate oxygen free radicals that may potentiate the development of atherosclerosis (**Bernheim et al., 2001)**.

Moreover, AGEs can produce oxygen free radicals through an indirect process, by inducing the release of cytokines through interaction of AGEs with their cellular receptors (**Grillo and Colombatto, 2008)**. Because of widespread occurrence of AGEs and the oxidative stress derived from them in a variety of diseases and diabetes complications, it has a great deal of interest to identify and develop AGE inhibitor that can suppress AGE formation (**Reddy and Beyaz, 2006)**. Numerous AGE inhibitors have been developed, such as amino guanidine the most well-known AGE inhibitor.

Administration of Chromium picolinate in STZ-induced diabetic rats resulted in a significant decrease advanced glycation end products **(AGEs)** and HbA1c. These results are nearly similar to those of **Cefalu et al., (2010); Brownley et al., (2013)** reported that, focused on effects of CrPic in diabetes showed an improvement of evaluated parameters. Decreases were observed in plasma glucose, fasting blood glucose (FBG), advanced glycation end products (AGES), glycated hemoglobin (HbAc1), and glucose area under the curve (AUC), while an increase in insulin sensitivity level was observed, demonstrating a recovery of function for hepatic β cells. A reduction in macroangiopathy was also observed after CrPic supplementation.

Also, Suksomboo and colleagues **(Suksomboon et al., 2014)** found an important reduction of HbA1c and advanced glycation end products (AGES), with CrPic that was similar to reductions exerted by antidiabetic agents. Thus, insulin stimulation and increase of glucose

cellular uptake were promoted by CrPic supplementation, contributing to an improvement in glucose control and insulin sensitivity in diabetic subjects **(Suksomboon et al., 2014).**

In our study, the average of hemoglobin decreased in diabetic status and diabetic group treated. It is important to refer that Cr+3 is prevent a significant increment in HbA1c in diabetic rats. There are increasing the level of total hemoglobin and reduced glycated hemoglobin in diabetic group due to improvement of glycaemic control using Cr. These data were good agreement with Crinò *et al*., 2004, studies **(Crinò, et al., 2004).** After 4 weeks post administration of STZ and other treatments, the diabetic group induced a considerable increase in HbA1c with respect to a normal control group accompanied by diabetic groups treated with Cr+3 % in comparison with the control rats.

The obtained data showed significant increase in serum cholesterol, triglycerides, low-density lipoprotein (LDL) and significant decrease in high-density lipoprotein (HDL) in STZ-induced diabetic rats when compared with normal control animal groups.

These results are nearly similar to those of **Doddigarla et al., 2016** who reported that, hypercholesterolemia is common in diabetes. The pronounced increase in cholesterol levels in diabetic rats come in agreement with results reported previously by **Huang et al., 2014** who observed that, the untreated diabetic rats had the increased levels of triglycerides, cholesterol, HDL and LDL, as compared with the healthy control rat. Also**, Wankasi et al., 2014)** reported that, there was pronounced increase in triglycerides, cholesterol, HDL and LDL, in diabetic rats as compared with the healthy control rat. Dyslipidemia observed in experimental diabetes (high TG and low HDL levels) are attributed mainly to the decreased activity of lipoprotein lipase which is an insulin sensitive enzyme demonstrates significant alteration in diabetics **(Tsutsitmi *et al.*, 2001).**

**Thirunavukkarasu *et al.*, (2004)** reported that, STZ-induced diabetes has increases in serum TG, LDL-C, and triglycerides as well as decreases HDL-C concentrations. The mechanism is possibly due to reduction in lipoprotein lipase activity secondary to reduced plasma insulin levels. Cholesteryl ester transfer protein, which is important in regulating lipoprotein lipid composition increased in DM condition and may contributed to dyslipidemia **(Wasan *et al.*, 1998).**

Administration of Chromium picolinate in STZ-induced diabetic rats resulted in a significant

amelioration in serum total cholesterol and triglycerides and significant increase in HDL compared to STZ group. These results go in hand with **(Mahesh *et al.*, 2004)** who reported that, the mechanism by which Chromium picolinate this situation is probably its hypocholesterolemic influence, antioxidant nature, and free-radical scavenging property. The obtained results showed a significant decrease in serum cholesterol and triacylglycerols in addition to significan decrease in HDL concentrations in diabetic rats treated with chromium nanoparticles. These results are nearly similar to those of **Mahdi, (1996)** who reported that, trivalent chromium has been identified as an essential nutrient element for lipid metabolism, and chromium deficiency is associated with diabetes and dyslipidemia disease **(Mahdi, 1996) Besong *et al.*, (2001)** found lower levels of TG and cholesterol after chromium supplementation. The mechanism by which chromium decreases hyperlipidemia is its ability to improve insulin sensitivity and thereby probably contributes to the reduction of triglyceride hydrolysis in adipocytes.

Other mechanism by which chromium decreases hyperlipidemia is that it may directly affect insulin receptor and increase its tyrosine kinase activity. Chromium may exhibit its insulin-sensitizing effect also by reducing the content and activity of the tyrosine phosphatase and by stimulating the translocation of GLUT4 glucose transporter to the plasma membrane associated with decreased plasma membrane cholesterol **(Chen *et al.*, 2006).**

Lipid profile was assessed by Seif and colleagues **(Seif, 2015)** in hypercholesterolemic rats that were fed a hyperlipidic diet. A decrease in platelet hyperaggregability and risk of cardiovascular disease was observed when CrPic supplementation was used, and an improvement in lipid profile was also detected. Similarly, Cefalu and colleagues **(Cefalu et al., 2010; Seif, 2015)** demonstrated a decrease in myocellular and intrahepatic lipid levels in groups that received CrPic supplementation.

In this way, CrPic appears to possess a property for lowering the risk of cardiovascular diseases, due to an enhancement in mitochondrial β-oxidation of free fatty acids (FFA), and may indirectly contribute to minimizing esterified cholesterol, which is responsible for the formation of atherosclerotic plaque **(Refaie et al., 2009; Seif, 2015)**.

The recorded data demonstrated a significant increase in MDA concentration in STZ-induced diabetic rats when compared with control group. These results are nearly similar to those reported by **Kailash, (2000)** who showed that, the diabetic rats had higher serum MDA

than the normal rats. However increased lipid peroxidation has been observed in STZ-induced diabetes in rats and in patients with diabetes. This could be due to increased levels of reactive oxygen species (ROS)**.**

Also, **Doddigarla et al., (2016)** who showed that, the diabetic rats had higher serum MDA than the normal rats however increased lipid peroxidation has been observed in STZ-induced diabetes in rats and in patients with diabetes**.**

The increase in MDA could be due to increased production of ROS from macrophages through a mechanism stated by **Kailash, (2000)** that reactive oxygen species (ROS) has a role in the pathogenesis of diabetes mellitus and pancreatic islet β-cell destruction as a consequence of immune/inflammatory cell-mediated processes in rodents**.**

Decrease in MDA infers less ROS attack on lipids, which further improves insulin resistance. Discussed action is seen in the histology of liver as we observed relatively normal structure after administration of CrPic for three weeks **Doddigarla et al., (2016).**

Oxidative stress associated with overproduction of reactive oxygen species plays an important role in the development of diabetic complications, including diabetic nephropathy (**Akude et al., 2011)**.

Another mechanism indicates the ability of chromium to reduce MDA is their activation of adiponectin secretion where adiponectin protects against damage induced by oxidative stress and lipid peroxidation. The level of adiponectin was found to be significantly correlated with the MDA levels **(Morihiro *et al.*, 2013).**

The recorded data demonstrated a significant decrease in tissue GSH-px, CAT and SOD concentration of STZ- induced diabetic rats when compared with control group. These results came in agreement with those reported by **Huang et al., 2014** also, **Doddigarla et al., 2016** who found an inverse correlation between blood glucose levels and tissue GSH, CAT and SOD

GSH-px, CAT and SOD are antioxidant known to protect lipids against oxidation by scavenging free radicals. In diabetes, GSH, CAT and SOD are significantly decreased, giving evidence of consumption of this molecule to fight oxidative stress **(Davi et al., 2005).**

There is a significant association between acute blood glucose, GSH, CAT and SOD in patients with type 2 diabetes. Fluctuations in blood glucose induce oxidative stress and metabolic disarrangements that may be risk factors for chronic complications. A decrease in the efficacy of the antioxidant response may be a warning signal of metabolic defense **(Chia *et al*., 2012).**

**Wu *et al*., (2004)** reported that, GSH, CAT and SOD is an abundant antioxidant within the blood and decreases both in type 1 and 2 diabetic patients.

Diabetes produces disturbances of lipid profiles, especially an increased susceptibility to lipid peroxidation **(Fatmah et al., 2012).** An enhanced oxidative stress has been observed in diabetic patients by increased free radical production, lipid peroxidation and diminished antioxidant status **(Palmieri and Sblendorio, 2007)**. During oxidative stress, endogenous mechanisms, enzymes and antioxidant molecules are deployed to destroy reactive oxygen species and reduce the harmful effect of oxidants. In normal conditions, these mechanisms are sufficient to counteract free radical production, but in diabetes, they are overwhelmed due to an increased oxidative stress **(Tewthanom et al., 2008).**

On the other hand, chromium has a potential effect in regulating oxidative stress in diabetic subjects by upregulating GSH in elevated oxidative stress subjects **(Rains and Jain 2011).**

**Sundaram et al., 2013** performed a study using diabetic rats which found an antioxidant activity of CrPic. The results showed increases in glutathione (GSH), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) levels, as well as no enzymatic plasma antioxidants. Moreover, decreases in lipid peroxidation were found, as evaluated by malondialdehyde (MDA) concentrations.

Likewise, Refaie and colleagues **(Refaie et al., 2009)** demonstrated an antioxidant role of CrPic supplementation through a decrease in hepatic and cerebral MDA concentrations, similar to hepatic and cerebral SOD, GPx and CAT activity in diabetic rats **(Sundaram et al., 2013).** These findings indicate a preventive capacity of CrPic for oxidative damage induced by hyperglycemia, which is corroborated by both Al-Rasheed and colleagues **(Al-Rasheed et al., 2013)** and Sahin and colleagues **(Sahin et al., 2013)** who demonstrated a reduction in blood and kidney MDA concentration and increases in GSH, SOD, GPx and CAT activity in myocardium, respectively.

Moreover, this improvement in oxidative stress has been related to decreases in tumor necrosis factor alpha (TNF-α) levels and nuclear factor-κB (NF-kB) inhibition **(Al-Rasheed et al., 2013; Sundaram et al., 2013; Sahin et al., 2013).**

Oxidative stress is one of the most dangerous effects on the cellular activities and thus, according to our results Cr+3 greatly scavenged free radical molecules and thus decreased MDA level and also increased the enzymatic capacities of SOD and GSH and thus improving liver function activities and thus enhancing the conversion of blood glucose into glycogen and thus decreasing blood glucose level which reflect the solution for diabetes mellitus complications.

Our results are completely agreed with Bhuvaneshwari *et al*., (**Bhuvaneshwari et al., 2013)** who refereed that hyperglycemia was associated with increase in oxidative stress in liver, increasing lipid peroxidation and decreasing glutathione limits. Chromium is a main nutrient which required glucose and lipid metabolism (**Anderson, 1998)**. Accordance with our results, in diabetic animals the usage of Cr+3 through four weeks able to retrieve normal blood glucose limits. These data were agreement with Abdourahman and Edwards (**Abdourahman and Edwards, 2008)**.

## CONCLUSION

In conclusion, the present study demonstrated that chromium picolinate (Crpic) administration provided an effective treatment against insulin resistance in STZ-induced diabetic rats, since chromium picolinate (Crpic) were able to ameliorate serum biochemical parameters and increase insulin secretion in STZ-induced diabetic rats.

This study has demonstrated the antidiabetic and anti-inflammatory effect of chromium picolinate (Crpic) on diabetic animal models of male rats.

## REFERENCES

1. Vigneri, P.; Frasca, F.; Sciacca, L.; Pandini, G. and Vigneri, R. “Diabetes and cancer,” *Endocrine-Related Cancer*, 2009; 16(4): 1103–1123.
2. Stolar, M. “Glycemic control and complications in type 2 diabetes mellitus,” American Journal of Medicine, 2010; 123(3): S3–S11.
3. Yadav, U. C. S.; Moorthy, K. and. Baquer, N. Z. “Affects of sodium-orthovanadate and Trigonella foenum-graecum seeds on hepatic and renal lipoenic enzymes and lipid profile during alloxan diabetes," Journal of Biosciences, 2004; 29(1): 81-91.

4. Chan, S.-Y.; Ou, S.-M.; Chen, Y.-T. and Shih, C.-J. Int. J. Cardiology, 2016; 218: 170.
5. King, H.; Aubert, R.E.and Herman, W.H. Diabetes Care, 1998; 21: 1414.
6. De la Monte, S.M. Endocrinology and Metabolism Clinics of North America, 2014; 43(1): 245.
7. Harper, E. H.; Forde, C.; Davenport, K.D.; Rochfort, D. and Smith, P.M. Cummins, Vascular Pharmacology, 2016; 82: 30.
8. Ibrahim, M.A.; Habila, J.D.; Koorbanally, N.A.; Md. S. and Islam, J.: Ethnopharmacology, 2016; 183: 103.
9. Shapiro K., and Gong W. C. Natural products used for diabetes. J. Am. Pharm. Assoc, 2002; 42: 217–226.
10. Martin J., Wang Q. Z., Zhang H. X., Wachtel D., Volaufova J., Matthews E. D., Cefalu, T.W. Attenuates Body Weight Gain and Increases Insulin Sensitivity in Subjects with Type 2 Diabetes. Diabetes Care, 2006; 29(8): 1826–1832.
11. Krzysik M., Grajeta H., Prescha A., Weber R. Effect of cellulose, pectin and chromium (III) on lipid and carbohydrate metabolism in rats. Journal of Trace Element and Medical Biology, 2011; 25: 97–102.
12. Trumbo P., Yates A.A., Schlickek S., Poos M. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, molybdenum, nickel, silicon, vanadium, and zinc. Journal of American Dietary Association, 2001; 101: 294–301.
13. Anderson R.A. Stress effects on chromium nutrition of humans and farm animals. In: Lyons TP, Jacques KA (eds) Biotechnology in Feed Industry. University Press, Nottingham, 1994; 267–274.
14. Sahin, K., Sahin, N., & Kucuk, O. Effects of dietary chromium picolinate supplementation on serum and tissue mineral contents of laying Japanese quails. Journal of Trace Element Experiment and Medicine, 2002; 15: 163-169.
15. McNamara J.P., and Valdez F. Adipose tissue metabolism and production responses to calcium propionate and chromium propionate. Journal of Dairy Science, 2005; 88: 498–507.
16. Moeini, M.M., Akram Bahrami, Shahab Ghazi, Mohammad Reza Targhibi. The Effect of Different Levels of Organic and Inorganic Chromium Supplementation on Production Performance, Carcass Traits and Some Blood Parameters of Broiler Chicken Under Heat Stress Condition. Biological Trace Element Research, 2011; 144: 715–724.

17. Doddigarla Z, Ahmad J, Parwez I. Effect of chromium picolinate and melatonin either in single or in a combination in high carbohydrate diet-fed male Wistar rats. BioFactors, 2016; 42: 106-114.
18. Ramanathan, M.; Jaiswal, A.K. and Bhattacharya, S.K. Superoxide dismutase, catalase jand glutahiones peroxidase activities in the brain of streptozotocin induced diabetic rats. Indian. J.Exp. Biol., 1999; 37: 182-183.
19. Sanford, H.S. Science, 1954; 119: 100.
20. Trinder, P. An. Clin. Biochem, 1969; 6: 24.
21. Mattews, D.R.; Hosker, J.P. and Naylor, B.A. Homeostasis model assessment: insulin resistance and beta cell function from fasting plasma glucose and insulin concentration in man. Diabetologia, 1985; 28: 412-9.
22. Young, D.S. Effects of disease on clinical Lab Tests, 4 $^{th}$Ed community college, 2001.
23. Warnick, G.R.; Benderson, V. and Albers, N. Selected Methods Clin Chem, 1983; 10: 91-99.
24. Okada M. et al. Low-density lipoprotein cholesterol can be chemically measured J. Lab. Clin. Mad., 1998; 132: 195-201.
25. Esterbauer, H.; Poli, G. and Slater, T.F. Separation and characterization of the aldehyde products of ADP/$Fe^{2+}$ (stimulated lipid peroxidation in rat liver microsomes. Biochem. J., 1982; 208: 129-140.
26. Eyer, P. and Podhradsky, D. Evaluation of the micromethod for determination of glutathione using enzymatic cycling and Ellman's reagent. *Anal. Biochem*, 1986; 153: 57-66.
27. Misra, H.P. and Fridovich, I. The role of super oxide anion in the the auto oxidation of epinephrine and simple super oxide dismutase. J. Boil. Chem., 1972; 247: 3170-3175.
28. Sinha, A.K. (1972): Colorimetric assay of catalase, Analytical biochemistry 47: 389.
29. Mousavi, S.M.; Imani, S.; Haghighi, S.; Mousavi, S.E.; Karimi, A. Effect of Iranian Honey bee (*Apis mellifera*) Venom on Blood Glucose and Insulin in Diabetic Rats. J Arthropod-Borne Dis., 2012; 6(2): 136–143.
30. Huang, S.; Peng, W.; Jiang, X.; Shao, K.; Xia, L.; Tang, Y. and Qiu, J. (2014): The Effect of Chromium Picolinate Supplementation on the Pancreas and Macroangiopathy in Type II Diabetes Mellitus Rats, Article ID 717219: 8.
31. Buchanan, T. A. Xiang, A. H.; Peters, R. K. et al., "Preservation of pancreatic *β*-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women," *Diabetes*, 2002; 51(9): 2796–2803.

32. Khulan TS, Ambaga M, Chimedragcha CH: Effect of Honey Bee Venom (*Apis mellifera*) on Hyperglycemia and Hyperlipidemia in Alloxan Induced Diabetic Rabbits. J Diabetes Metab, 2015; 6: 507.
33. Mahesh, T.; Balasubashini, M.M. and Menon, V.P. Photo-irradiated curcumin supplementation in streptozotocin-induced diabetic rats: effect on lipid peroxidation. Therapies, 2004; 59: 639–44.
34. Anderson, R.A. Chromium in the prevention and control of diabetes. Diabetes & Metabolism, 2000; 26(1): 22–27.
35. Vincent, J.B. Mechanisms of chromium action: low molecular weight chromium binding substance. Journal of the American College of Nutrition, 1999; 18(1): 6–12.
36. Cefalu, W.T. and Hu, F.B. Role of chromium in human health and in diabetes. Diabetes Care, 2004; 27(11): 2741–2751.
37. Wang, H.; Kruszewski, A. and Brautigan, D.L. Cellular chromium enhances activation of insulin receptor kinase. Biochemistry, 2005; 44(22): 8167–8175.
38. Morris, B.W.; Gray, T.A. and MacNeil, S. Glucose-dependent uptake of chromium in human and rat insulin-sensitive tissues. Clinical Science, 1993; 84(4): 477–482.
39. Refat, M.S.; El-Megharbel, S.M.; Hussien, M.A.; Hamza, R.Z.; Al-Omar, M.A.; Naglah, A.M.; Afifi, W.M.; Kobeasy, M.I. (2016): Spectroscopic, structural characterizations and antioxidant capacity of the chromium (III) niacinamide compound as a diabetes mellitus drug model.
40. Li, H. Zheng, X. Wang, H. Zhang, Y. Xin, H. Chen, X. XLF-III-43, a novel coumar in aspirin compound, prevents diabetic nephropathy in rats via inhibiting advanced glycation end products, Eur. J. Pharmacol, 2010; 627: 340–347.
41. Sen, S. Kar, M. Roy, A. Chakraborti, A.S. Effect of nonenzymatic glycation on functional and structural properties of hemoglobin, Biophys. Chem., 2005; 113: 289–298.
42. Bernheim J., Rashid G., Gavrieli R., Korzets Z., Wolach B., In vitro effect of advanced glycation end-products on human polymorphonuclear superoxide production, Eur. J. Clin. Invest, 2001; 31: 1064–1069.
43. Grillo, M.A. and Colombatto, S. Advanced glycation end-products (AGEs): involvement in aging and in neurodegenerative diseases, Amino Acids, 2008; 35: 29–36.
44. Reddy, V.P. and Beyaz, A. Inhibitors of the Maillard reaction and AGE breakers as therapeutics for multiple diseases, Drug Discov. Today, 2006; 11: 646–654.
45. Cefalu W.T; Rood J.; Pinsonat P.; Qin J.; Sereda O.; Levitan L; Anderson R.A.; Zhang X.H.; Martin J.M.; Martin C.K.; Wang Z.Q.; and Newcomer B., "Characterization of the

metabolic and physiologic response to chromium supplementation in subjects with type 2 diabetes mellitus", *Metabolism-Clinical and Experimental*, 2010; 59(5): 755-762.

46. Brownley K.A.; Von Holle A.; Hamer R.M.; La via M. and Bulik C.M.; "A double-blind, randomized pilot trial of chromium picolinate for binge eating disorder: Results of the Binge Eating and Chromium (BEACh) Study", *Journal of Psychosomatic Research.*, 2013; 75(1): 36-42.
47. Suksomboon N.; Poolsup N.; and Yuwanakorn A.; "Systematic review and meta-analysis of the efficacy and safety of chromium supplementation in diabetes*", Journal of Clinical Pharmacy and Therapeutics*, 2014; 39(3): 22-30.
48. Crinò, A.; Schiaffini, R.; Manfrini, S.; Mesturino, C.; Visalli, G. Beretta Anguissola, G. B.; Suraci, C.; Pitocco, D.; Spera, S. Corbi, S.; Matteoli, M.C.; Patera, I.P.; Bitti, M.L.M. ; Bizzarri, C. ; Pozzilli, P. Eur. J. Endocrinol, 2004; 150: 719.
49. Wankasi, M.M.; George, G.S.; Nwankwo, N. Studies on Chromium Picolinate Pre Treated Albino Rats Given High Concentrations of Glucose D. *Journal of Food and Nutrition Sciences*, 2014; 2(2): 43-46.
50. Tsutsumi, K.; Hagi, A.; andInoue, Y. The relationship between plasma high density lipoprotein cholesterol levels and cholesteryl ester transfer protein activity in six species of healthy experimental animals. Biological and Pharmaceutical Bulletin, 2001; 24: 579–581.
51. Wasan, K.M.; Ng, S.P.; Wong, W. and Rodrigues, B.B. Streptozotocin-and alloxan - induced diabetes modifies total plasma and lipoprotein lipid concentration and composition without altering cholesteryl ester transfer activity. Pharmacol. Toxicol, 1998; 83: 169-175.
52. Mahdi G.S. Chromium deficiency might contribute to insulin resistance, type 2 diabetes, dyslipidemia and atherosclerosis. Diabetic Medicine, 1996; 13(4): 389–390.
53. Besong, S.; Jackson J.A.; Trammell, D.S. and Akay, V. Influence of supplemental chromium on concentrations of liver triglyceride, blood metabolites and rumen VFA profile in steers fed moderately high fat diet. J Dairy Sci., 2001; 84: 1679–85.
54. Chen G.L.; Liu P.; Pattar G.; Tackett L.; Bhonagiri P.; Strawbridge A.B.; and Elmendorf J.S., "Chromium activates glucose transporter 4 trafficking and enhances insulin-stimulated glucose transport in 3T3-L1 adipocytes via a cholesterol-dependent mechanism", *Molecular Endocrinology*, 2006; 20(4): 857-870.

55. Seif A.A. "Chromium picolinate inhibits cholesterol-induced stimulation of platelet aggregation in hypercholesterolemic rats", *Irish Journal of Medical Science*, 2015; 184(2): 291-296.
56. Refaie F.M.; Esmat A.Y.; Mohamed A.F.; and Nour W.H.A., "Effect of chromium supplementation on the diabetes induced-oxidative stress in liver and brain of adult rats", *Biometals*, 2009; 22(6): 1075-1087.
57. Kailash, P. Oxidative stress as a mechanism of diabetes in diabetic BB prone rats: Effect of secoisolariciresinol diglucoside.Molecular and Cellular Biochemistry, 2000; 209: 89–96.
58. Akude E, Zherebitskaya E, Chowdhury SK, et al. Diminished superoxide generation is associated with respiratory chain dysfunction and changes in the mitochondrial proteome of sensory neurons from diabetic rats, Diabetes, 2011; 60: 288–297.
59. Morihiro, M.; Ritsu, T.; Kotaro, K.; Takatsugu, S.; Haruyuki, K.; Orie, N.; Hirohiko, N. and Toshiharu, K. Impact of dyslipidemic components of metabolic syndrome, adiponectin levels, and anti-diabetes medications on malondialdehyde-modified low-density lipoprotein levels in statin-treated diabetes patients with coronary artery disease. Diabetology & Metabolic Syndrome, 2013; 5: 77.
60. Davi, G.; Falco, A. and Patrono, C. Lipid peroxidation in diabetes mellitus. Antioxid Redox Signal, 2005; 7: 256–68.
61. Chia-Jen, T.; Ching-Jung, H.; Shih-Chen, T.; Ming-Chun, K. and Feng-Chih, S. Acute blood glucose fluctuations can decrease blood glutathione and adiponectin levels in patients with type 2 diabetes.diabetes research and clinical practice, 2012; 98: 257–263.
62. Wu LL, Chiou CC, Chang PY, Wu JT. Urinary 8-OHdG: a marker of oxidative stress to DNA and a risk factor for cancer, atherosclerosis and diabetics. Clin Chim Acta, 2004; 339: 1–9.
63. Fatmah, A.; Siti, B.; and Zariyantey, A. The Role of Oxidative Stress and Antioxidants in Diabetic Complications. Sultan Qaboos Univ Med J., 2012; 12(1): 5–18.
64. Palmieri, B. and Sblendorio, V. Oxidative stress tests: overview onreliability and use. European Review for Medical and Pharmacological Sciences, 2007; 11: 309-342.
65. Tewthanom, K.; Janwityanuchit, S.; Totemchockchyakarn, K. and Panomvana, D. Correlation of lipid peroxidation and glutatione levels with severity of systemiclupus erythematosus: A pilot study from single center. J Pharm Pharmaceut Sci., 2008; 11(3): 34.

66. Rains, J.L. and Jain, S.K. Oxidative stress, insulin signaling, and diabetes. Free Radic Biol Med., 2011; 50: 567–575.
67. Sundaram B.; Aggarwal A.; and Sandhir R. "Chromium picolinate attenuates hyperglycemia-induced oxidative stress in streptozotocin-induced diabetic rats", *Journal of Trace Elements in Medicine and Biology*, 2013; 27(2): 117-121.
68. Al-Rasheed N.M.; Attia H.A.; Mohamed R.A; Al-Rasheed N.M.; and Al-Amin M.; "Preventive Effects of Selenium Yeast, Chromium Picolinate, Zinc Sulfate and their Combination on Oxidative Stress, Inflammation, Impaired Angiogenesis and Atherogenesis in Myocardial Infarction in Rats", *Journal of Pharmacy and Pharmaceutical Sciences*, 2013; 16(5): 848-867.
69. Sahin, K.; Tuzcu, M.; Orhan C. et al., "Anti-diabetic activity of chromium picolinate and biotin in rats with type 2 diabetes induced by high-fat diet and streptozotocin," *British Journal of Nutrition*, 2013; 110(2): 197–205.
70. Bhuvaneshwari, S. Aanchal, A. Rajat, S. J. Trace Elements Med. Biology, 2013; 27: 117.