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**RESEARCH ARTICLE**

# Anti-Diabetic Effects of Curcumin-Magnesium Oxide Nanoparticles Conjugate in Type 2 Diabetic Rats

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**Abstract**

Diabetes is a disorder that impairs the ability of the body to process blood glucose. Diabetes is either due to the pancreas produces insufficient amount of insulin or the cells of the body do not react with the insulin produced. Type 2 diabetes (diabetes mellitus) is the most common type of diabetes and grows in prevalence worldwide. The aim of our study was to investigate the anti-diabetic impact with emphasis on hepatic lipid metabolism and spleen histopathology effect of curcumin-magnesium oxide nanoparticles conjugate (Cur-MgO NPs conjugate) in nicotinamide (NA)-streptozotocin (STZ) induced type 2 diabetic rats. This study included three groups: Group 1 (control group), Group 2 (STZ induced type 2 diabetic rats) and Group 3 (type 2 diabetic rats were orally administered Cur-MgO NPs conjugate (10 mg/Kg BW/day for 45 days)). The levels of plasma glucose, serum insulin, lipid profile and hepatic expression of lipogenic enzymes Malonyl-CoA decarboxylase (MCD), Peroxisome proliferator-activated receptor alpha (Ppar α) were measured. Moreover, histopathological examination of spleen was carried out. The assessment of Insulin Resistance (HOMA-IR), a significant reduction in serum insulin level and HOMA of β-cell function (HOMA β). Also, reduction in hepatic mRNA expression of MCD and Ppar-α and an altered lipid profile were noticed in diabetic group in comparison with the control group. Oral administration of Cur-MgO NPs conjugate restored glucose (102.73±2.16), TC (139.80±3.61) and LDL-c (87.56±3.72) to their physiological levels in the control group (108.29±2.45, 150.27±2.56 and 94.43±2.75 respectively). Histopathological examination of the spleen showed damage of lymphoid cells in type 2 diabetes (T2D), while in treated group showed moderate improvement in spleen tissue and cells are rescued from apoptosis. The outcome of present study revealed that Cur-MgO NP conjugate has potential ameliorative effect on the hematologic, immunologic and hepatic metabolic alterations in type 2 diabetic rats.

**Key words**: Type 2 diabetes, Nanoparticles, Curcumin and Magnesium.

## Introduction

Diabetes mellitus is considered a life threating disease owing to its complications. It is not a single disease; but it is a group of heterogeneous disorders as heart attack, stroke and peripheral vascular disease. Common symptoms include extreme hunger, increased thirst, frequent urination and fatigue [1]. Diabetes occurs either due to the pancreas produces insufficient amount of insulin or the cells of the body do not react with the produced insulin. The incidence of diabetes is increasing quickly worldwide [2]. Type 2 diabetes is considered a chronic metabolic disorder which is characterized by hyperglycemia, insulin resistance and loss of β-cell function developed gradually within the course of the disease. Type 2 diabetes represents about 90% of wholly diabetic cases. The global incidence of Type 2 diabetes is

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continuously increased, especially between the young [3]. It refers to adult-onset diabetes or non-insulin dependent diabetes mellitus. It is attended to target organ insulin resistance that restricts its responsiveness to both endogenous and exogenous insulin [4].

In the last years, researchers turned their attention to natural products and made many studies on this field for the management of this disease and its complications, which reach to epidemic levels all worldwide [5]. Curcumin is the major active constituent of turmeric, a natural product isolated from *curcuma longa* and well known with its pharmacological properties, as anti-inflammatory, antioxidant, antiviral, anti-infectious, antitumor effects as well as detoxifying and wound healing properties [6, 7]. Moreover, Curcumin could positively affect most of the leading features of diabetes, as hyperglycemia, hyperlipidemia, insulin resistance and islet apoptosis and necrosis [8]. Supplementation of curcumin decreases the markers of inflammation and increases the amount of endogenous antioxidants in the body [9]. Curcumin nanoparticles improved the physicochemical properties of curcumin, including reduction of the particle size, enhancement of the stability and solubility of curcumin in aqueous solution and formation of an amorphous state with hydrogen bonding, so result in increasing the drug release, Curcumin nanoparticles also can be used to reduce the dosage of curcumin and improve its bioavailability [10].

Magnesium is the fourth most abundant mineral present in the human body and the second intracellular cation in the living cells after potassium. There is a well-known linkage between magnesium deficiency and type 2 diabetes mellitus. The status of magnesium deficiency may be a secondary consequence of diabetes or may cause insulin resistance, altered glucose tolerance and then diabetes [11]. The main mechanism of magnesium depletion in type 2 diabetic patients is a lower magnesium intake and an increase in magnesium urinary excretion. Magnesium deficiency affects tyrosine kinase activity producing insulin resistance, so magnesium supplementations improve the enzyme activity [12]. Our purpose in this study was to explore the anti-diabetic influence of curcumin magnesium oxide nanoparticles conjugate (Cur-MgO NPs Conjugate) in type 2 diabetic rats via studying the hepatic metabolic and immunologic effects. Consequently, we investigated the hypothesis that Cur-MgO NPs Conjugate has ameliorative effect on hematologic, immunologic and hepatic metabolic parameters in rats induced by type 2 diabetes.

## Materials and methods

### *Animals*

Healthy 45 male albino rats weighing 160±20 gm were obtained from the animal house, Faculty of Veterinary Medicine, Zagazig University. The animals were housed in separate cages with provision of clean and fresh drinking water ad libitum. Rats were kept at constant environmental and nutritional conditions during the course of the experiment.

### *Chemicals and reagents*

All chemicals were purchased from Sigma-Aldrich (USA) unless stated otherwise. Cur-MgO NPs conjugate was synthesized from NanoTech Egypt for Photo-Electronics Communication Center (6$^{th}$ October, Giza, Egypt).

### *Experimental design and induction of type 2 diabetes in rats*

Rats were kept for 14 days for acclimatization; blood glucose was measured at day 15 by using digital glucometer (URight blood glucose meter TD-4251). Following overnight fasted (12 h), 30 randomly selected rats were injected with single dose of Nicotinamide (110 mg/kg BW) intraperitoneally (I/P) and then after 15 min, rats were injected freshly prepared STZ (65 mg/kg BW) dissolved in 0.1 M cold citrate buffer (pH 4.5) I/P [13]. Glucose solution (20%) was allowed to animals overnight to avoid hypoglycemia. Control group were I/P injected with the same volume of citrate buffer. After two weeks of STZ administration, blood glucose was measured. Only rats with glucose level more than 200 mg/dl were used in the study [14]. Rats were then allocated to one of three groups; Group 1 (G1): Control rats orally administered saline, Group 2 (G2): Type 2 diabetic rats orally administered saline and Group 3 (G3): type 2 diabetic rats orally administered Cur-MgO NPs conjugate (10 mg/kg BW/day for 45

days). Rats were examined weekly for fasting levels of serum glucose and insulin. All animal experiments were in accordance with the procedures approved by the Zagazig University Institutional Animal Care and Use Committee (IACUC) (ZU-IACUC/2/ F/204/2019).

***Sampling***

At the end of our study, rats were euthanized via cervical decapitation. Blood samples were collected with or without proper anticoagulant so that whole blood, serum and plasma were freshly subjected for the different biochemical assays. Fifty milligrams of liver tissue were collected, wrapped in aluminum foil immediately after euthanasia and placed in liquid nitrogen container and stored at -80°C until use for gene expression analysis (reference???). At necropsy, spleen was removed, rinsed with normal saline and then fixed at 10% buffered formalin for histopathology.

***Biochemical analysis***

Determination of serum glucose by oxidase method using Spectrum Diagnostics glucose kit [15]. Estimation of serum insulin level using Elisa rat insulin kits method [16].

Estimation of Insulin resistance index (HOMA-IR) and HOMA-β cell function**,** the equations of the original HOMA model are widely used and simplify to:

HOMA1-IR = (FPI × FPG)/22.5 for IR

HOMA1-B% = (20 × FPI)/(FPG − 3.5) for β-cell function

Where FPI is fasting plasma insulin concentration (mU/l) and FPG is fasting plasma glucose (mmol/l) [17].

The direct enzymatic colorimetric liquid method was used for determination of HDL-c [18]. LDL-C was calculated with the equation LDL= TC – HDL - (TG/5). Estimation of VLDL-c was carried out by Friedewald method [19]. Evaluation of Triacylglycerol (TAG) was done by GPO-PAP-enzymatic colorimetric method [20]. Cholesterol liquizyme CHOD-PAP enzymatic colorimetric method was used for determination of cholesterol [21]. Relevant kits were obtained from Egyptian Company for Biotechnology.

***Histopathological examination***

The samples (spleen) were collected and then fixed in 10% buffered neutral formalin to be processed to get 5 μm thick tissue in paraffin sections and then stained with Hematoxylin and Eosin (H&E) stain with the standard protocols for histopathological examination according to Suvarna and Layton [22].

***Relative quantitative RT-PCR analysis***

A detailed description of the protocols used has been previously reported in [23-25]. The real-time RT-PCR was accomplished in aMx3005P Real-Time PCR System (Agilent Stratagene, USA) using 5x HOT FIRE Pol EvaGreen qPCR Mix Plus (Solis BioDyne, Tartu, Estonia) following the manufacturer's guidelines using primers listed in Table1. The relative expression of each gene normalized to the housekeeping GAPDH was reported as fold change by $2^{-\Delta\Delta CT}$ relative to control [26].

**Table 1. The primers sequences of the investigated genes**

| | Forward primer (5′–3′) | Reverse primer (5′–3′) | Amplicon size | Accession No | **Reference** |
|---|---|---|---|---|---|
| MCD | CGGCACCTTCCTCATAAAGC | GGGTATAGGTGACAGGCTGGA | 88 | NM_053477.1 | [44] |
| PPAR-α | AGACACCCTCTCTCCAGCTTC | GAATCTTGCAGCTTCGATCAC | 230 | NM_013196 | [45] |
| GAPDH | GTGCCAGCCTCGTCTCATAG | CGTTGATGGCAACAATGTCCA | 122 | NM_017008.4 | [46] |

Malonyl-CoA decarboxylase (MCD), peroxisome proliferator–activated receptor (PPAR)–α and Glyceraldehyde 3-phosphate dehydrogenase (GAPDH)

***Statistical analysis***

Data were described as mean ±SEM. One-way ANOVA was applied to compare among means of the three groups for the different parameters. P-value < 0.05 was referred to statistically significant. With applying Duncan's multiple range test as Post hoc test

after significant ANOVA results to determine differences among groups. Data were analyzed by SPSS version 21.

## Results

### *Effect of oral administration of Cur-MgO Nps Conjugate on the glycemic index and HOMA in type 2 diabetic rats.*

Significant increase in the level of plasma glucose (mg/dl) was noticed in type 2 diabetic rats (314.27±18.57) compared to control group (108.29±2.45). This increase was normalized after administration of Cur-MgO NPs conjugate (102.73±2.16). A significant reduction in insulin level (ng/ml) was detected in type 2 diabetic rats (0.25±0.03) related to control group (0.35±0.01). This decrease was significantly increased after administration of Cur-MgO NPs conjugate (0.29±0.01). Significant rise in insulin resistance indicated by HOMA IR levels (0.20±0.01) and reduction in HOMA B (0.40±0.07) in type 2 diabetic rats related to control group (0.09±0.00 Vs 2.81±0.15, correspondingly). A significant reduction in HOMA IR levels (0.07±0.00) and an increase in HOMA B (2.73±0.19) after administration of Cur-MgO NPs conjugate (Table 2).

### *Effect of oral administration of Cur-MgO Nps Conjugate on the lipid profile in type 2 diabetic rats.*

The levels of TC (170.50±3.27 Vs 150.27±2.56), TAG (104.83±3.47 Vs 75.00±4.10), LDL-C (118.70±6.13 Vs 94.43±2.75) and VLDL-C (20.97±0.69 Vs 15.00±0.82) showed significant increase, while HDL-c levels (26.40±1.80 Vs 40.83±0.95) showed significant reduction in diabetic group versus control group. The increases in TC (139.80±3.61) and LDL-C level (87.56±3.72) were normalized in treated group in compare to diabetic group. No statistical significance was noticed in the levels of HDL-C (35.60±3.37), TAG (95.20±2.67) and VLDL-C (19.04±0.53) after treatment in comparison with diabetic group (Table 3).

**Table 2: Effect of oral administration of Cur-MgO NPs conjugate on fasting glucose level, plasma insulin, HOMA-IR and HOMA-B in NA-STZ induced diabetic rats.**

| Groups | Control | Diabetic Group | Treated group |
|---|---|---|---|
| **Glucose (mg/dl)** | $108.29\pm2.45^{b}$ | $314.27\pm18.57^{a}$ | $102.73\pm2.16^{b}$ |
| **INS (ng/ml)** | $0.35\pm0.01^{a}$ | $0.25\pm0.03^{b}$ | $0.29\pm0.01^{ab}$ |
| **HOMA-IR** | $0.09\pm0.00^{b}$ | $0.20\pm0.01^{a}$ | $0.07\pm0.00^{b}$ |
| **HOMA-β** | $2.81\pm0.15^{a}$ | $0.40\pm0.07^{d}$ | $2.73\pm0.19^{b}$ |

The mean values ± SEM are shown. $^{abc}$Means with different superscript are statistically different according to Duncan's multiple range test at $P < 0.05$. Insulin (INS), Homeostatic model assessment - insulin resistance (HOMA-IR), Homeostatic model assessment - β-cell function (HOMA-β).

**Table 3: Effect of oral administration of Cur-MgO NPs conjugate on lipid profile measurements (TC, TAG, LDL, HDL and VLDL) in STZ induced diabetic rats.**

| Groups | Control | Diabetic group | Treated group |
|---|---|---|---|
| TC | $150.27\pm2.56^{b}$ | $170.50\pm3.27^{a}$ | $139.80\pm3.61^{b}$ |
| TAG | $75.00\pm4.10^{b}$ | $104.83\pm3.47^{a}$ | $95.20\pm2.67^{ab}$ |
| HDL -C | $40.83\pm0.95^{a}$ | $26.40\pm1.80^{b}$ | $35.60\pm3.37^{ab}$ |
| LDL-C | $94.43\pm2.75^{b}$ | $118.70\pm6.13^{a}$ | $87.56\pm3.72^{b}$ |
| VLDL-C | $15.00\pm0.82^{b}$ | $20.97\pm0.69^{a}$ | $19.04\pm0.53^{a}$ |

The mean values ± SEM are shown. $^{abc}$Means with different superscript are statistically different according to Duncan's multiple range test at $P < 0.05$. Total cholesterol (TC), triacylglycerol (TAG), high-density lipoprotein (HDL-C), low-density lipoprotein cholesterol (LDLC) and very low-density lipoprotein cholesterol (VLDLC),

***Effect of oral administration of Cur-MgO Nps Conjugate on hepatic expression of MCD and Ppar-α in type 2 diabetic rats.***

Significant decrease in the hepatic mRNA expression of both Ppar α and MCD were noticed in type 2 diabetic rats paralleled to control group. This decrease was normalized after administration of Cur-MgO NPs conjugate (Figure 1).

***Effect of oral administration of Cur-MgO Nps Conjugate on the Splenic histopathology.***

In histopathological examination (Figure 2), splenic tissue showed normal histological picture (red and white pulps) in control group (Figure 2A). However, prominent lymphoid depletion and damage of lymphoid cells were noticed in diabetic group (Figure 2B). Regarding treated group, mild vascular congestion in spleen tissue was detected, lymphoid cells are rescued from apoptosis ((Figure 2C) in comparison to diabetic group.

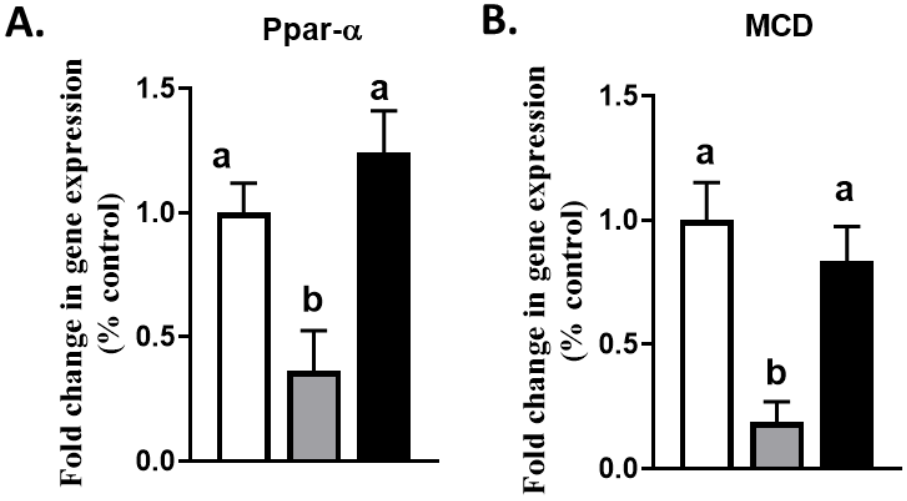


**Figure 1. Hepatic mRNA expression of (A) Ppar α and (B) MCD in control, diabetic and Cur-MgO NPs conjugate administered groups. Means with different superscripts were significantly different at P < 0.05.**

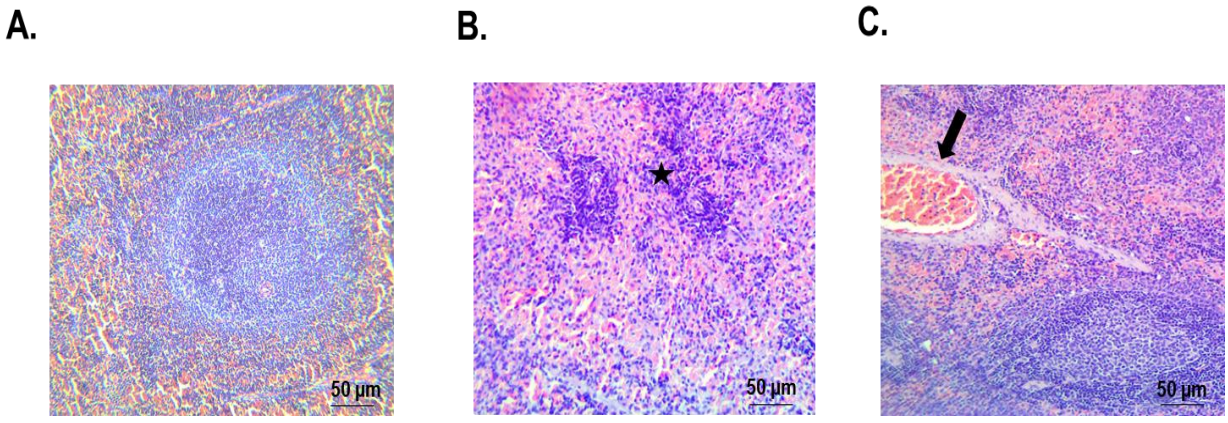


**Figure 2: Spleen sections from control, diabetic and Cur-MgO NPs conjugate administered groups. (A) Spleen of control rat showing normal histological picture (red and white pulps), H&E, x200, (B) Spleen of diabetic rat showing lymphoid depletion (star) (shrunken white pulps), H&E, x200 and (C) Spleen of Cur-MgO NPs conjugate administered rat with the conjugate showing moderate vascular congestion (arrow), H&E, x200.**

**Discussion**

Appropriate experimental models are needed for comprehensive studies on the hereditary, pathogenesis and complications of T2D and to find new strategies for the management of T2D [27]. Both STZ and NA administration have been used to induce T2DM. Streptozotocin is well-known to cause damage to the pancreatic B-cells according to the dose, while NA is given to rats to partially protect insulin-secreting cells against STZ [13, 28].

In this study, fasting blood glucose level after oral supplementation of Cur-MgO Nps conjugate was returned to the level of glucose in control. Studies recommended that nanocurcumin reduced FBG [29], this could be explained as curcumin inhibit the formation of inflammatory cytokines either directly or through inhibition of nuclear factor- kappa B (NF-κB) and PGE2, while activates AMPK and inhibits MAPK [30]. The studies which used magnesium supplements in diabetes have shown that magnesium have the ability to decrease blood glucose level in type 2 diabetic patients [31-33]. Mg is a necessary cofactor for enzymes shared in carbohydrate metabolism, especially in the phosphorylation of the tyrosine-kinase of the insulin receptor in addition to all other protein kinases in the insulin signaling, and all ATP and phosphate transfer-associated enzymes [34]. Also, Naghsh and Kazemi [35] recommended that nanomagnesium oxide can reverse insulin resistance in type 2 diabetes and decrease glucose level. The level of plasma insulin showed significant decrease in the diabetic group compared to control group, then after administration of Cur-MgO Nps conjugate showed significant increased. This occurred due to destruction of beta cells after injection of streptozotocin [36]. Curcumin inhibit advanced glycation end products (AGE) production by trapping an AGE precursor-methylglyoxal and increases the amount of endogenous antioxidants in the body [37]. Mechanistically, Cur was originated to increase superoxide dismutase, catalase and GSH. Cur could positively affect most of the leading features of diabetes, as hyperglycemia, hyperlipidemia, insulin resistance and islet apoptosis and necrosis [8].

Also the current study showed significant increase in insulin resistance indicated by HOMA IR levels in type 2 diabetic rats compared to control group. A significant reduction in HOMA IR levels after administration of Cur-MgO NPs conjugate. The result provided by Plasma Mg levels were found inversely correlated with the urinary Mg excretion rate and with fasting blood glucose values, suggesting that the tubular reabsorption of Mg is decreased in presence of hyperglycemia leads to Mg depletion [38] and insulin resistance due to inactivation of the tyrosine-kinase of the insulin receptor. After administration of the conjugate reverse insulin resistance in type 2 diabetes and decrease glucose level were recorded [35]. The results of HOMA β-cell function in type 2 diabetic rats showed significant reduction in comparison to control group due to destruction of beta cells after injection of streptozotocin [36]. A significant increase in HOMA β-cell function after administration of Cur-MgO NPs was noticed due to the anti-apoptotic effect of curcumin [39].

In the current study TC decreased in the treated group compared with type 2 diabetic group. Nanocurcumin supplementation could also significantly reduce TC level [29]. Serum cholesterol level in the placebo and treated groups were higher than the control group [35]. Contradictory to our results, [29] compared level of serum TAG before and after the treatment with nanocurcumin and significant reduction were found in nanocurcumin group. Qin *et al.* [40] showed significant decrease in serum TAG in patients with metabolic syndrome. Naghsh and Kazemi [35] also recommended that nanomagnesium oxide decreases TAG level in the treated group than the placebo group while, another study recommended no significant difference in serum TAG [41].

In line with our results, nanocurcumin supplementation decreased the level of LDL-C [29]. LDL-C level significantly decrease in patients with metabolic syndrome [40] in contrast with Panahi *et al.* [41] who showed no significant changes in LDL-C level. Also,

HDL-C level was not significantly changed with the nanocurcumin supplementation [29]. Also, in patients with metabolic syndrome HDL-C level were not improved [40]. Naghsh and Kazemi [35] found that HDL in the treated group showed higher level than placebo group with no difference with the control group. On the other hand, Yokota *et al.* [33] reported that magnesium supplementation did not show any significant changes in FBG and TC while HDL-C slightly increased and TAG level decreased but not significantly.

Regarding mRNA gene expression, significant reduction in mRNA level of PPARα and MCD in the diabetic group in comparison with control group, these decreases were normalized in the treated groups. This agree with the fact that the action of MCD reverse the action of ACC. As ACC catalyze acetyl CoA to malonyl CoA which is the building unit of new fatty acids. While, MCD is responsible for catalyze the conversion of malonyl-CoA to acetyl-CoA and carbon dioxide [42].

In our histopathological examination of spleen, control group showed clear and normal red and white pulps, while diabetic rat as expected showed lymphoid depletion (shrunken white pulps) and the treated rat with the conjugate showed moderate improvement. The spleen histopathological changes were illustrated as diabetes induced oxidative stress which leads to complications in the spleen as, in diabetes, increasing the level of blood glucose and the intracellular ROS decrease the cellular antioxidant enzymes activity. Also, GSH/GSSG ratio was subsequently resulted in white pulp depletion and damaging of the spleen. When rats were treated with curcumin, occur up regulation of inflammatory chemokines, cytokines, adhesion molecules and translocation of NFκB in the nucleus leading to inflammatory changes in the spleen of diabetic rats were decreased [43]. Yet, a mild degree of vascular congestion remains noticed following administration of Cur-MgO NPs as reported in our study. Curcumin could positively affect most of the leading features of diabetes, as hyperglycemia, hyperlipidemia, insulin resistance and islet apoptosis and necrosis [8].

## Conclusion

Curcumin could positively affect most of the leading features of diabetes, as hyperglycemia, hyperlipidemia and insulin resistance. Moreover, in this study we reported the potential role of Cur-MgO NPs conjugate in management of type 2 diabetes in rats.

## Conflict of interest

The authors declare no conflicts of interest, financial or otherwise.

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**الملخص العربي**

**التاثير العلاجي لمركب الكركم مع اكسيد المغنسيوم النانونيه في الفئران المصابه بالنوع الثاني من الاعتلال السكري**

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يمثل مرض السكرى اضطراب يضغف قدرة الجسم على معالجة نسبة الجلوكوز فى الدم. ويكون مرض السكرى اما بسبب عدم قدرة البنكرياس على انتاج ما يكفى من الانسولين او عدم استجابة خلايا الجسم للانسولين المنتج. ويعد مرض السكرى من النوع الثانى هو النوع الاكثر شيوعا فى جميع انحاء العالم. وكان الهدف من هذه الدراسة هو التحقق من التأثير المضاد للسكرى للمركب النانوى الذى يحتوى على الكركومين مع اكسيد الماغنسيوم على الفئران المصابة بمرض السكرى من النوع الثانى المستحث بالنيكوتيناميد والاستربتوزوتوسين.وقد اشتملت هذه الدراسة على ثلاث مجموعات: المجموعة الاولى (المجموعة الضابطة), والمجموعة الثانية (التى تحتوى على الفئران المصابة بمرض السكرى من النوع الثانى) و المجموعة الثالثة التى تحتوى على الفئران المصابة والتى اعطيت المركب النانوى محل الدراسة بجرعة 10 مليجرامات /كجم من الوزن / يوم لمدة 45 يوم عن طريق الفم). وقد تم قياس مستوى السكر و الانسولين فى الدم و صورة الدهون كما تم قياس التعبير الجيني للانزيمات مالونيل ثنائى الكاربوكسيل و مستقبلات الفا المنشط بالبيروكسيسوم الفا كما تم فحص انسجة من الطحال وكانت النتائج كالاتى:- ارتفاع معنوى فى نسبة الجلوكوز فى الدم وتحليل معامل مقاومة الخلايا للانسولين وانخفاض كبير فى مستوى الانسولين فى الدم وتحليل معامل مقاومة الخلايا بيتا وانخفاض فى التعبير الجيني للانزيمات مالونيل ثنائى الكاربوكسيل و مستقبلات الفا المنشط بالبيروكسيسوم ومستوي الدهون التى تم تغييرها فى مجموعة السكرى مقارنة مع المجموعة الحاكمة.وقد اعاد تناول المركب النانوى عن طريق الفم بعض العوامل الى مستوياتها الفسيولوجية بما فى ذلك الجلوكوز والكولستيرول الكلى و البروتين الدهنى المنخفض. كما اظهر الفحص النسيجى للطحال تلف الخلايا الليمفاوية للفئران المصابة بالسكرى من النوع الثانى, بينما وجد تحسنا معتدلا فى نسيج الطحال للمجموعة محل الدراسة كما انقذت الخلايا من الموت.ولذلك اثبتت هذه النتائج ان المركب النانوى الذى يحتوى على الكركومين مع اكسيد الماغنسيوم له تأثير محتمل لتحسين التغيرات الدموية والمناعية والايضية الكبدية للفئران المصابة بمرض السكرى من النوع الثانى.

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