Efficacy of a Novel water Soluble Curcumin Derivative versus Sildenafil Citrate in Mediating Erectile Function

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ABSTRACT

The present study was conducted to assess the efficacy of a novel curcumin derivative (NCD) versus sildenafil citrate in erectile signaling. The study was conducted on 10 control male rats and 50 diabetic male rats divided into the following groups:, diabetic, curcumin, NCD, sildenafil and NCD combined with sildenafil. Cavernous tissue gene expression levels of heme oxygenase-1 (HO-1), Nrf2, NF-β, and p38, enzyme activities of heme oxygenase (HO) and nitric oxide synthase (NOS), cGMP and intracavernosal pressure (ICP) were assessed. Results showed that 12 weeks after induction of diabetes, erectile dysfunction (ED) was confirmed by the significant decrease in ICP, a significant decrease in cGMP, NOS, HO enzyme activities, a significant decrease in HO-1 gene and a significant elevation of NF-β, p38 genes. Administration of all therapeutic interventions led to a significant elevation in ICP, cGMP levels, a significant increase in HO-1 and NOS enzymes, a significant increase in HO-1, and Nrf2 gene expression, and a significant decrease in NF-β, p38 gene expression. NCD or its combination with sildenafil showed significant superiority and more prolonged duration of action. In conclusion, NCD could enhance erectile function with more efficacy and more prolonged duration of action.

Key words: *erectile dysfunction, cGMP, HO-1, Nrf2, p38, NF-β, NOS, intra-cavernosal pressure.*

INTRODUCTION

Erectile response depends on nitric oxide (NO) generated by NO synthase (NOS) enzyme of the nerves and vascular endothelium in the cavernous tissue. A role similar to that of NOS/NO signaling was proved for carbon monoxide (CO) produced by heme oxygenase (HO) enzyme.[1,2] Interestingly, hydrogen sulfide (H_2S) a known vasodilator and smooth muscle relaxant was proved to be an inducer for HO-1 gene expression.[3, 4]

Moreover, Abdel aziz *et al.*[1,5] reported that the effect of sildenafil, verdenafil and tadalafil are partially mediated via upregulation of HO enzyme activity and cGMP and their effect is partially inhibited by HO inhibitor.

Curcumin induces de novo synthesis of phase II detoxifying genes including HO-1 gene.[6,7] Abdel Aziz *et al.*[8] proved that a water soluble derivative of curcumin could mediate erectile function via induction of HO-1 enzyme with upregulating cavernous tissue cGMP levels. The authors proved a synergism between sildenafil and curcumin, where curcumin potentiates the effect of sildenafil in rats. Several studies showed the involvement of Nrf2, AP-1 (via extracellular signal-regulated kinases; ERK), protein 38 mitogen-activated protein kinases; p38, and NF-Ƙβ in induction of HO-1 by dietary polyphenols including curcumin.[9-11] Xu *et al*.[12] stated that curcumin induces relaxation of isolated precontracted porcine coronary arteries and this effect is partially dependent on the action of NO, cGMP, and adrenergic β-receptor. Schini-Kerth et al.[13] stated that several polyphenols as curcumin are able to induce NO-mediated endothelium-dependent relaxations in several arteries through induction of endothelium-derived hyperpolarizing factor (EDHF)-mediated relaxations.

Clinical trials showed that the systemic bioavailability of orally administered curcumin is low.[14] Several water-soluble curcumin derivatives were prepared to achieve clinically efficient systemic bioavailability.

The present study was conducted to compare the molecular and physiological effects of a novel water-soluble curcumin protein conjugates (NCD) versus natural curcumin and sildenfail in experimental diabetic model of erectile dysfunction (ED).

MATERIALS & METHODS

The novel curcumin conjugate is registered as international patent protected by the rights of "The Patent Cooperation Treaty" under: (PCT/EG2010/000008, Published Patent Pending, WO 2011/100984) and is the personal property of its inventors.[15]

108 adult male white albino rats (Cux1: HEL1) of matched age and weight (180–200 g) were included in the study after the approval of the Institutional Animal Care and Use Committee (IACUC).

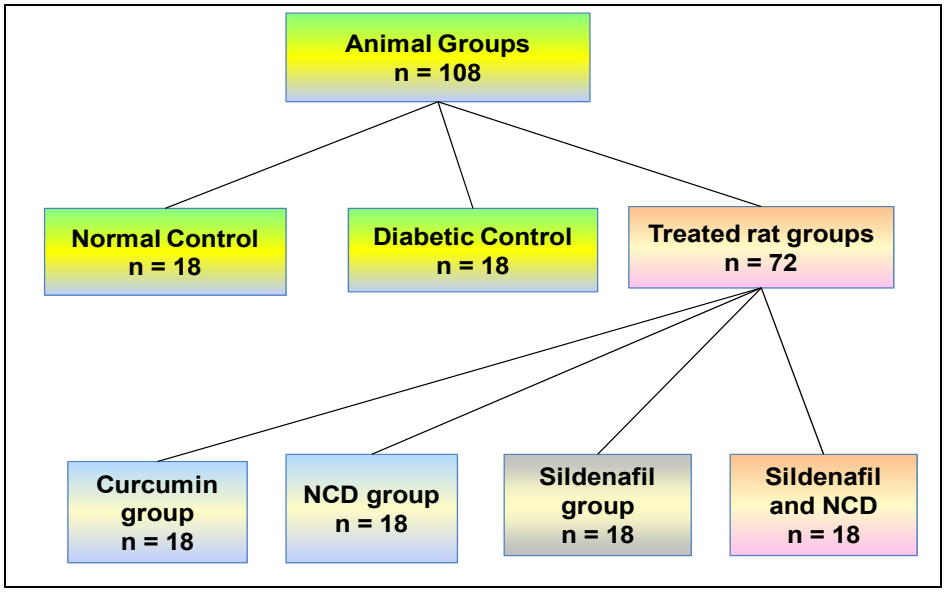
Experimental diabetes was induced by a single intraperitoneal injection of 65 mg/kg body weight of streptozotocin (STZ).[16] The treatment phase of the study lasted twelve weeks according to the findings reported by Li *et al*.[17] who stated that erectile dysfunction is established 12 weeks after diabetic induction in rats. Curcumin dose was chosen according to our previous studies.[1, 8]

Erectile dysfunction was proved by assessment of intracavernosal pressure (ICP) / mean arterial pressure (MAP) as a physiological index of erectile function**.** All drug interventions were initiated after 12 weeks of diabetes induction.

Animals involve 18 albino male rats served as control group and 90 STZ-induced diabetic rats that were equally divided into the following groups: untreated Diabetic control group, Curcumin group which received 10 mg/kg body weight (B.Wt.) oral dose of natural curcumin, NCD group which received 2 mg/kg B.Wt. single oral dose of NCD, Sildenafil group which received sildenafil citrate

dissolved in distilled water (4 mg/kg; equivalent to 50-mg dose in 70-kg adult man according to Paget's table of experimental studies), rat group that received NCD combined with sildenafil (NCD+sildenafil group).[18]

The following diagram illustrates all animal groups



Animal Groups:

Group (1): Normal Control
Group (2): Diabetic Control
Group (3): Treated rat groups divided into 4 subgroups:
Sub group (A): Treated pure curcumin
Sub group (B): Treated by NCD
Sub group (C): Treated by Sildenafil
Sub group (D): Treated by Sildenafil & NCD

Animals were euthanized after 1½ hr, 24 hr and 1 week following drug intervention regimens. The following parameters were assessed in the cavernous tissue: HO enzyme activity.[19] , NOS activity.[20], cGMP, intracavernosal pressure (ICP) as physiologic assessment of erectile function, and gene expression of HO-1, Nrf2, NFKB, and p38 gene by quantitative real time PCR.[19, 21]

HO Enzyme Activity Assay

CC (50 mg) homogenized samples were incubated with heme (50 mmol/L), rat liver cytosol (5mg/ mL), MgCl2 (2 mM/L), glucose-6-phosphate dehydrogenase (1U), glucose-6-phosphate (2 mM/L), and reduced nicotinamide adenine dinucleotide

phosphate (NADPH) (0.8 mM/L) in 0.5 mL of 0.1 M/L phosphate buffer saline (pH 7.4) for 60 minutes at 37°C. The reaction was stopped by putting the tubes on ice, and the reaction solution was extracted with chloroform. The rate of bilirubin formation was monitored at 464 nm and 520 nm by a spectrophotometer.[22]

ICP assessment

Measuring ICP changes elicited by electrical stimulation of the cavernous nerve (CN) was performed in rats according to the method previously described.[22] A frequency response curve was obtained where the maximum rise in ICP during nerve stimulation was measured and compared statistically to healthy control at each frequency.[21, 23]

RESULTS

Results showed that administration of either natural curcumin, NCD, sildenafil, or NCD&Sildenafil combination led to a significant elevation in HO-1 gene expression after 24 hr persisting up to 1 week (with natural curcumin, NCD, NCD combination with sildenafil) with more significant elevation with NCD administration in comparison to natural curcumin and sildenafil rat groups. Combined NCD with sildenafil showed significant enhancing effect when compared to sildenafil alone. **(Figure 1).**

Results showed that there was a marked decrease in HO enzyme activity in diabetic rat group. Administration of either natural curcumin, NCD, sildenafil, or sildenafil combined with NCD led to a significant elevation in the enzyme activity in comparison to diabetic group that persisted up to 24 hr with all of the above mentioned treatment protocols and up to 1 week with NCD and combined NCD + sildenafil. Combined NCD with sildenafil showed significant enhancing when compared to sildenafil alone **(Figure 2)**.

Results showed that there was a significant decrease in cGMP levels in the diabetic group. Administration of either curcumin, NCD or sildenafil or combinations of NCD with sildenafil led to a significant elevation of cGMP levels that persisted up to one week in comparison to the diabetic group. Administration of sildenafil alone led to a significant elevation of cGMP levels in comparison to the diabetic group that persisted for 1.5 hr **(Figure 3)**.

Results showed that there was a significant decrease in NOS enzyme activity levels in the diabetic group. There was a significant elevation in NOS activity levels in all treated rat groups that persisted up to one week in comparison to the untreated diabetic group (with curcumin, NCD, sildenafil, NCD combined with sildenafil). Administration of sildenafil or its combinations with NCD led to a significant elevation in NOS levels after 24 hr in comparison to NCD rat group **(Figure 4).**

Results showed that there was a significant decrease in ICP/MAP in the diabetic rat group. There was a significant progressive elevation in ICP/MAP that rises with increasing the frequency of electric current stimulation in all treated diabetic rat groups with all treatment regimens in comparison with untreated diabetic rat group. NCD showed superior effects in

comparison to curcumin at 0.3 and 0.5 Hz (**Figure 5)**.

Results showed that there was a significant elevation in NFϗ-β in the diabetic group. There was a significant decrease in NFϗ-β in all treated diabetic rat groups with all treatment regimens that persisted up to one week in comparison to untreated diabetic group except with sildenafil group where the effect persisted for 1.5hr **(Figure 6)**.

Results showed that there was a significant increase in p38 gene expression in the diabetic group. There was a significant decrease in p38 gene that persisted up to 24 hr in the diabetic rat groups treated with curcumin, NCD, NCD combinations with sildenafil in comparison to the untreated diabetic group **(Figure 7).**

Results showed that there was a significant increase in Nrf2 gene expression in diabetic rat groups treated with curcumin, NCD, combinations of NCD with Sildenafil in comparison to the untreated diabetic rat group and the control group **(Figure 8)**.

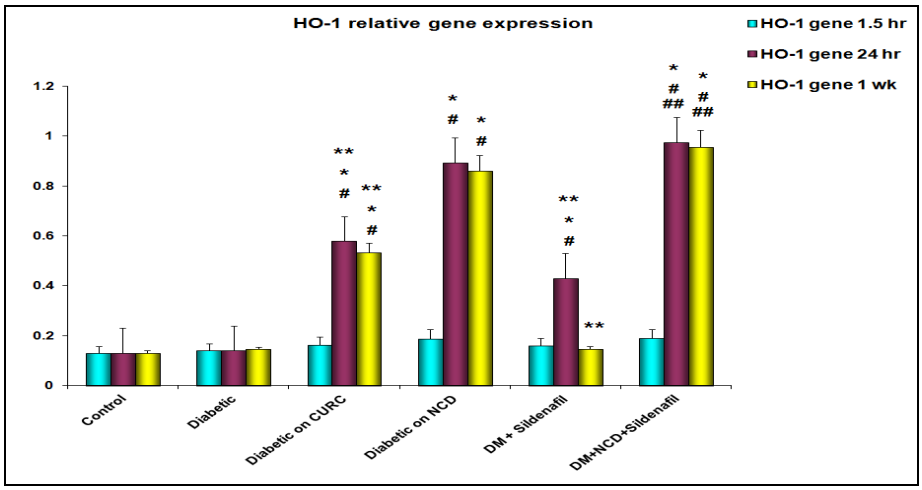


Figure 1. HO-1 relative gene expression in the studied rat groups expressed in Ct values relative to the housekeeping gene. * Comparison of each group versus control. # Comparison between each group versus diabetic group. ** Comparison between each group versus NCD group. ## Comparison between sildenafil treated rat group versus rat group received combinations of NCD with sildenafil.

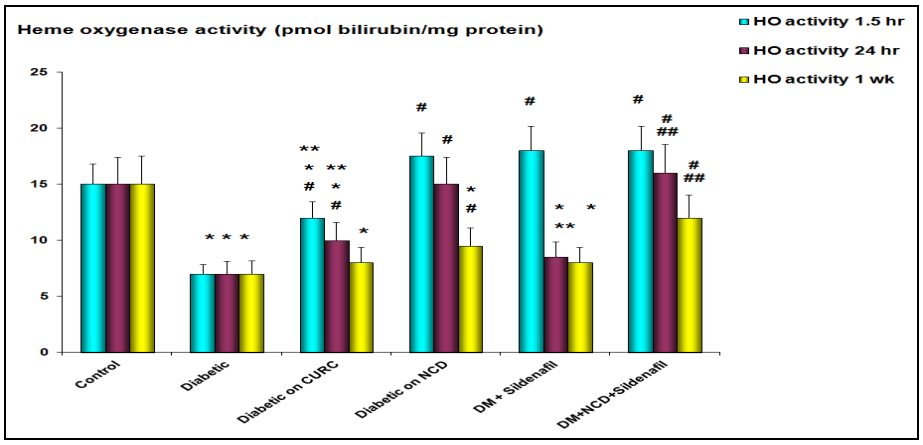


Figure 2. Heme oxygenase (HO) enzyme activity (pmol bilirubin/mg protein) in rat cavernous tissue. * Comparison of each group versus control. # Comparison between each group versus diabetic group. ** Comparison between each group versus NCD group. ## Comparison between sildenafil treated rat group versus rat group received combinations of NCD with sildenafil.

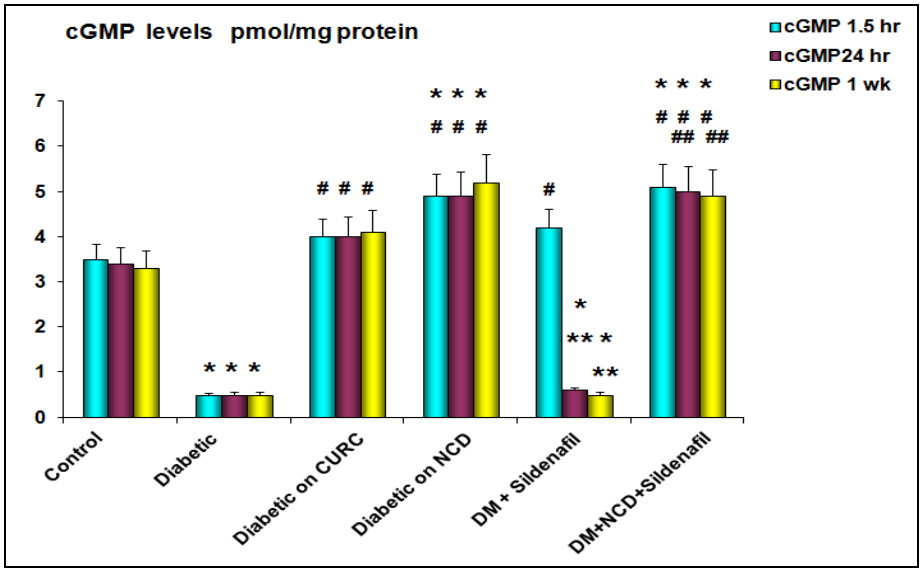


Figure 3. cGMP cavernous tissue levels (pmol/mg protein) in the studied rat groups. * Comparison of each group versus control. # Comparison between each group versus diabetic group. ** Comparison between each group versus NCD group. ## Comparison between sildenafil treated rat group versus rat group received combinations of NCD with sildenafil.

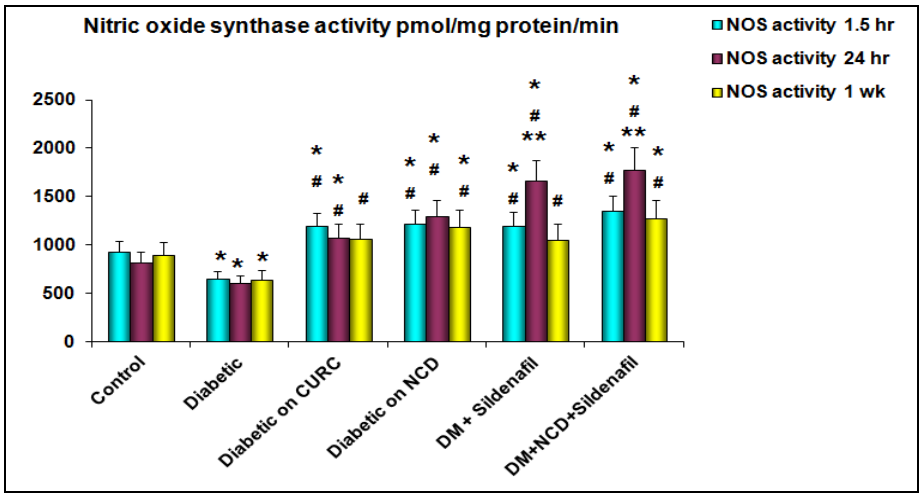


Figure 4. Nitric oxide synthase activity in the cavernous tissue (pmol/mg protein/ min) in the studied rat groups. * Comparison of each group versus control. # Comparison between each group versus diabetic group. ** Comparison between each group versus NCD group. ## Comparison between sildenafil treated rat group versus rat group received combinations of NCD with sildenafil.

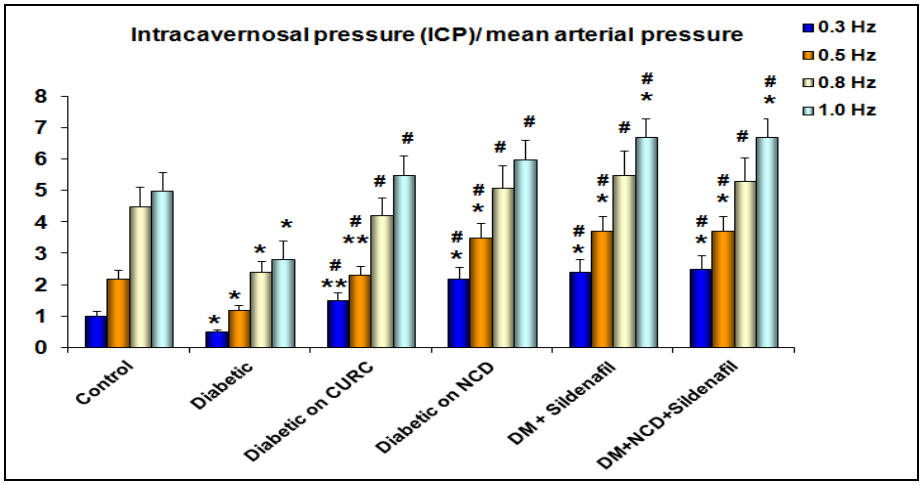


Figure 5. Intracavernosal pressure/mean arterial pressure (ICP/MAP) in response to 0.3, 0.5, 0.8, 1.0 Hertz. * Comparison of each group versus control. # Comparison between each group versus diabetic group. ** Comparison between each group versus NCD group. ## Comparison between sildenafil treated rat group versus rat group received combinations of NCD with sildenafil.

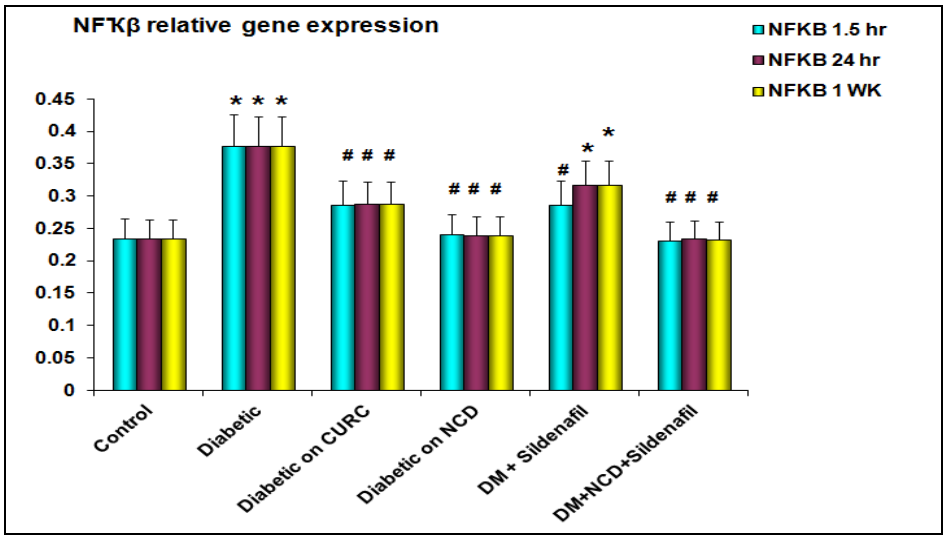


Figure 6. NFƘ-β relative gene expression in the studied rat groups expressed in Ct values relative to the housekeeping gene. * Comparison of each group versus control. # Comparison between each group versus diabetic group. ** Comparison between each group versus NCD group. ## Comparison between sildenafil treated rat group versus rat group received combinations of NCD with sildenafil.

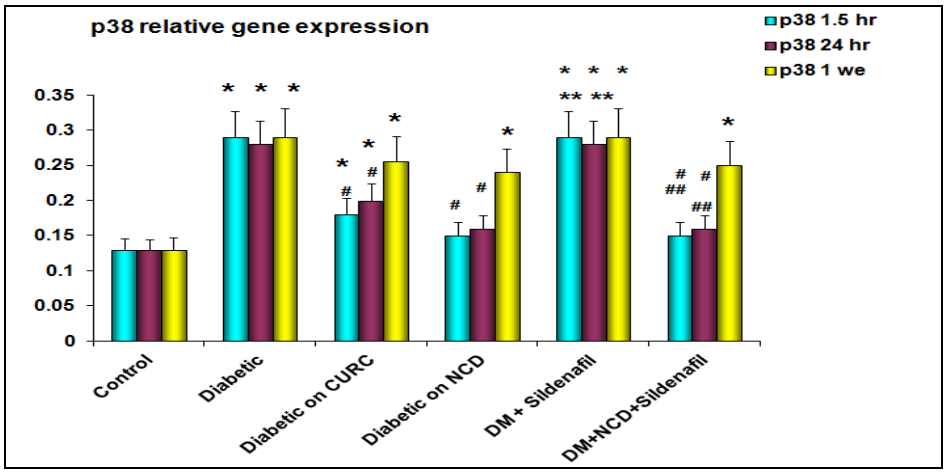


Figure 7. p38 relative gene expression in the studied rat groups expressed in Ct values relative to the housekeeping gene. * Comparison of each group versus control. # Comparison between each group versus diabetic group. ** Comparison between each group versus NCD group. ## Comparison between sildenafil treated rat group versus rat group received combinations of NCD with sildenafil.

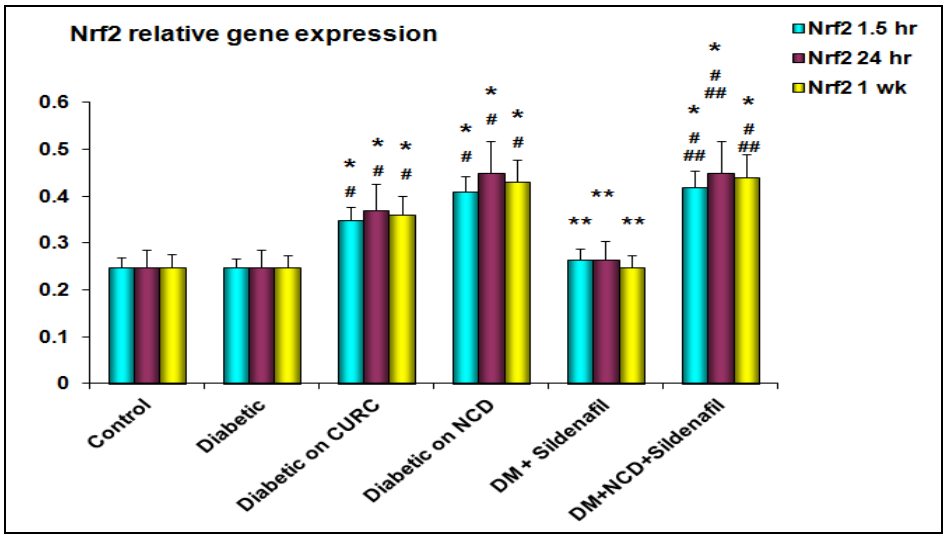


Figure 8. Nrf2 relative gene expression in the studied rat groups expressed in Ct values relative to the housekeeping gene. * Comparison of each group versus control. # Comparison between each group versus diabetic group. ** Comparison between each group versus NCD group. ## Comparison between sildenafil treated rat group versus rat group received combinations of NCD with sildenafil.

DISCUSSION

Results showed that administration of all drug regimen interventions led to a significant increase in ICP/MAP as compared to the diabetic group.

Endothelial dysfunction is the main aetiologic factor of vasculogenic erectile dysfunction (ED).[24] In diabetes hyperglycemia affects endothelial functions by synthesis of growth factors and vasoactive agents.[25] Hyperglycemia activate protein kinase-C (PKC) that induces phosphorylation of p115RhoGEF , a guanine nucleotide exchange factor for Rho GTPase.[26-28] Active RhoA is implicated in arginase induction leading to decrease in nitric oxide (NO) bioavailability.[29-31] Furthermore, activated PKC leads to sustained increases in the production of superoxide anion ($O_2^{\bullet}$) that activates NF-Ƙβ and affecting the expression of endothelial NOS (eNOS).[30]

Results of the present study also revealed that there were significant decreases in cavernous tissue cGMP, NOS and heme oxygenase enzymatic activities in diabetic rats as compared to control rats. These results coincided with previous studies.[31-33] Administration of either curcumin, NCD, sildenafil or Sildenafil combined with NCD led to significant elevations in cGMP levels, NOS and HO-1 cavernous tissue enzyme levels with significantly higher sustained effect in favor of NCD.

Rungseesantivanon *et al*.[34] stated that curcumin supplementation could improve diabetes-induced endothelial dysfunction via decrease in vascular superoxide production and PKC inhibition. A clinical study by Usharani *et al*.[35] showed that curcumin administration significantly reduced the levels of malondialdehyde, endothelin (ET-1), interleukin-6 (IL-6) and TNF-α in type 2 diabetes patients. Ahmad *et al*.,[36] and Ryter *et al*.[37] reported that HO protects NO through scavenging of reactive oxygen species (ROS), preventing the formation of peroxynitrite and subsequent degradation of NO. Ahmad *et al*.,[36] stated that overexpression of HO-1 may mediate an increase in eNOS and a decrease in iNOS, with restoration of vascular responses in diabetic rats. Curcumin as an inducer of HO-1 could indirectly potentiate eNOS effects on vascular endothelium. Shamloul.[38] and Ryter et al.,[37] stated that CO like NO, acts as a vasorelaxant. HO-1-derived CO has a positive effect on both sGC and cGMP levels in vascular endothelial cells. [39]

In the present study, gene expression profile of NFϏβ and p38 were significantly increased in STZ-induced diabetic rat. Administration of either natural curcumin or NCD led to a significant lowering effect on their gene expression with more significant superior effects with NCD. Nrf2 gene expression was unchanged in STZ-induced diabetic rats, whereas its levels were significantly elevated with curcumin and NCD. Aggarwal *et al*.[39] stated that curcumin suppresses NFϏβ and activates Nrf2 cell-signaling pathways.

In conclusion, NCD could enhance erectile function in a diabetic model via up-regulation of cavernous tissue levels of HO-1 gene and cGMP. NCD is superior to curcumin with more prolonged duration of action.

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تاثير العقاقير المثبطة للفوسفوداي استيراز مقارنة بالكوركومين النقى والمشتق الذائب فى الماءفى اداء عملية الانتصاب لدى الفئران البيضاء

اجريت دراسة مقارنة بين مركب الكوركومين النقى ومشتق الكوركومين المذاب فى الماء ومركب الفوسفوداى استيراز المثبط وقد اجريت هذة الدراسة على 108 من ذكور الفئران البضاء التى يتراوح وزنها بين ١٨٠ جم الى ٢٠٠ جم تم تقسيمها الى 6 مجموعات كل مجموعة مكونة من 18 فئران كالاتى:

١- مجموعة ضابطة غير مصاب

باقى الفئران تم حقنها بواسطة مادة استربتوزوتوسن المدمرة لخلايا البنكرياس وذلك من خلال الغشاء البروتونى لتحويلها الى فئران مصابة بالسكر وتم تاكيد ذلك بعمل متابعة السكر فى الدم بواسطة قياس السكر الصائم وكذلك الهيموجلوبين السكرى وعلى هذا الاساس تم استكمال المجموعات التى تم معالجتها باستخدام مركبات مختلفة عن طريق تجريع بالفم كالاتى ...

٢- مجموعة مصابة بالداء السكرى فقط

٣- مجموعة مصابة بالداء السكرى ومعالجة بواسطة الكوركومين النقى.

٤- مجموعة مصابة بالداء السكرى ومعالجة بواسطة مشتق الكوركومين.

٥- مجموعة مصابة بالداء السكرى ومعالجة بواسطة السلدنافيل (فياجرا) .

٦- مجموعة مصابة بالداء السكرى ومعالجة بواسطة السلدنافيل (فياجرا) مع مشتق الكوركومين

تم بعد ذلك ذبح الفئران على ثلاث فترات مختلفة واخذ عينتان من كل فار واحدة من الدم والثانية من النسيجالاسفنجى المكون للعضو الذكرى :

١- بعد ساعة واحدة من التجريع بالفم .

٢- بعد ٢٤ ساعة من التجريع بالفم .

٣- بعد اسبوع واحد من التجريع بالفم .

لقد اوضحت النتائج ان المجموعة المصابة بالداء السكرى احدثت انخفاض واضح للضغط داخل النسيجالاسفنجى وهو دلالة على ضعف الانتصاب،كذلك انخفاض فى معدل النيتريك اوكسيد المخلق، الهيم اوكسيجنيز (اتش أو وان) المنشط وظهور نقص فى السيكليك ام بى وزيادة فى تركيز تى ان الفا.

بمقارنة النتائج فى الحالات المعالجة تبين لنا ان مشتق الكوركومين كان لة تاثير واضح فى تحسين الحالات المصابة بالداء السكرى مقارنة بالمواد الاخرى .