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Effect of 2-hydroxychalcone on adiponectin level in type 2 diabetes induced experimentally in rats

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A R T I C L E   I N F O

A B S T R A C T

Type 2 diabetes mellitus (T2DM) is the most common type of diabetes, accounting for 90% of diabetic cases. It is characterized by chronic hyperglycemia which is caused by a combination of deficiency in insulin action and secretion. Adipose tissue regulates insulin sensitivity via the circulating adipocytokines, leptin, resistin and adiponectin. Hypoadiponectinemia contributes to the development of obesity and related disorders such as diabetes, hyperlipidemia and cardiovascular diseases. The present study aimed to evaluate the beneficial effect of flavonoid 2-hydroxychalcone in T2DM through its effect on peroxisome proliferator activated receptor gamma (PPAR-γ) and adiponectin. T2DM was induced in male Wistar rats using high fat diet and low dose of streptozotocin (STZ, 35 mg/kg, i.p.). The flavonoid 2-hydroxychalcone was administered by oral tubes. Levels of PPAR-γ in sub abdominal adipose tissue, serum adiponectin, serum tumor necrosis factor-α (TNF-α) and serum insulin levels were detected by ELISA. Moreover, malondialdehyde (MDA) and reduced glutathione (GSH) in sub abdominal adipose tissue, fasting serum glucose, serum triglycerides and serum total cholesterol levels were measured by colorimetric methods. Results showed that 2-hydroxychalcone attenuated changes induced by T2DM in rats. 2-Hydroxychalcone treatment increased PPAR-γ levels in adipose tissue, reduced oxidative stress, restored adiponectin levels and decreased high glucose levels in T2DM rats. In conclusion, 2-hydroxychalcone reduced hyperglycemia in T2DM by regulating adiponectin secretion. This effect involves PPAR-γ signaling pathway.

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Introduction

Type 2 diabetes is referred to as non-insulin-dependent diabetes or adult onset diabetes. It is the most common type of diabetes, representing 90–95% of all diabetic cases in high-income countries and may account for an even higher percentage in low- and middle income countries [1]. The hyperglycemia is caused by a combination of deficiency in insulin secretion and action, leading to reduced glucose uptake by peripheral tissues and increased gluconeogenesis by the liver. Untreated diabetes may progress to loss of β-cells function in the islets of Langerhans with eventual insulin deficiency. β-cells destruction is not immune-mediated and rarely progresses to a point where the patient became dependent on insulin for survival. Ketoacidosis is not common and is usually associated with a major intercurrent illness [2,3].

The management of diabetes is considered a global problem, a medical approach is not always sufficient for T2DM management and lifestyle modification should be considered. Thus, glycemic control is the basis for the treatment of type-2 diabetes. Existing antidiabetic agents are often associated with side effects including obesity, osteoporosis, sodium retention, hypoglycemia, and lactic acidosis [4,5]. To avoid such adverse side effects, there is a crucial need for new therapies for management and treatment of T2DM [6,7].

Adiponectin is an adipocytokine exclusively secreted by adipose tissue into the blood stream [8,9]. Plasma adiponectin level is negatively correlated with development of insulin resistance, T2DM and metabolic syndrome that are linked to obesity [10,11]. Indeed, plasma adiponectin levels were decreased in obesity. This reduction may play a causal role in the development of insulin resistance [12].

Transcription of adiponectin was tightly controlled by peroxisome proliferator-activated receptor gamma (PPAR-γ) [13]. PPAR-γ is highly expressed in adipocytes, where it plays an important role in glucose and lipid homeostasis, inflammation, and adipocyte differentiation [14]. A large body of evidence confirmed that PPAR-γ activation improves insulin sensitivity and enhances glucose disposal in adipose tissue and skeletal muscle [15].

Chalcones (originally isolated from natural plant sources) are considered as precursors of flavonoids. Chalcones are abundant in edible plants [16]. In addition, they can also be synthesized in laboratory [17]. Hydroxychalcones have been involved in various biological activities including antioxidant, anti-inflammatory, anti-cancer, anti hepatotoxic and antimalarial activities [18]. Interestingly, hydroxychalcone has been reported to mimic the effect of insulin by enhancing glucose uptake and phosphorylation of insulin receptor in adipocytes [19]. In addition, various synthetic chalcone derivatives have shown inhibitory activity against diabetic complications. Moreover, 2-hydroxy chalcone was reported as a potential dietary PPARγ ligand [20]. In the present study, we aimed to investigate the effect of 2-hydroxychalcone on adiponectin levels in T2DM induced experimentally in rats and the possible involvement of PPAR-γ.

Materials and methods

Animals: experimental protocols

Adult male Wistar rats (8 weeks old, weighing 160–180 g) were used for this study. Rats were housed in stainless steel rodent cages at room temperature (25 ± 2 °C) with 12 h dark/light cycle. The experimental protocol was approved by Research Ethics Committee, Faculty of Pharmacy, Mansoura University, Egypt. The animals were randomly divided into 3 groups (12 rats in each group): Normal control group, T2DM group and hydroxychalcone treated group. The rats (except the normal control group) were fed high fat diet (HFD) for 15 days to induce T2DM. HFD is composed of 58% fat, 25% protein and 17% carbohydrate, as a percentage of total kcal and libitum, respectively [21].

After 15 days, the rats in second and third groups were fasted for 12 h followed by a single intraperitoneal (i.p.) injection of 35 mg/kg STZ, (Sigma-Aldrich Co, St Louis, MO). The HFD was continued until the end of study. STZ was freshly dissolved in (0.1 M) citrate buffer (pH 4.5) and immediately injected into rats [22]. To overcome the hypoglycemia which follows STZ, during the first 24 h after their injection; diabetic rats were given 5% glucose solution to drink instead of tap water. Animals were monitored by periodic estimation of body weight and biochemical testing for blood glucose. Only animals with persistent blood glucose levels higher than 300 mg/dL for 7 days after STZ administration were considered diabetic and selected for further pharmacological studies [23]. One week after the STZ injection, the third group was treated by hydroxychalcone (Alfa Aesar, 26 parkridge Rd, USA) at a dose 25 mg/kg body weight daily by oral tube for 21 days. Hydroxychalcone was dissolved in dimethylsulfoxide (DMSO) – normal saline. The final concentration of DMSO in normal saline did not exceed 0.5%) [24]. The second (T2DM) group received solvent only. At the end of the study, after 24 h of the last dose of treatment, all rats were weighed, and then sacrificed.

Assessment of biochemical parameters

Fasting serum glucose, serum total lipid, serum triglycerides, serum total cholesterol, serum high density lipoprotein (HDL), serum low density lipoprotein (LDL), sub-abdominal adipose tissue malondialdehyde (MDA) and sub-abdominal adipose tissue reduced glutathione (GSH) concentrations were assayed using kits provided by Biodiagnostic Company (Giza, Egypt), according to the manufacturer's instructions.

Sub abdominal adipose tissue PPAR-γ, serum adiponectin, serum insulin, and serum tumor necrosis factor-α (TNF-α) levels were assessed using Enzyme-Linked Immunosorbent Assay (ELISA) kits provided from MyBioSource (San Diego, United States) according to the manufacturer's instructions.

Statistical analysis

The results were presented as means ± SEM. The statistical analyses were performed by one-way ANOVA followed by Turkey post hoc test.

Results

Effect of 2-hydroxychalcone treatment on body weight

As shown in (Fig. 1) Hydroxychalcone treatment caused a non-significant change in body weight compared to diabetic group. However, diabetic rats showed significant decrease in body weight by 25.25% compared to control group.

Effect of 2-hydroxychalcone treatment on sub abdominal adipose tissue weight

The sub abdominal adipose tissue weight of the diabetic rats was significantly decreased by 43.49% compared to that of the control rats. The diabetic rats treated with hydroxychalcone showed non-significant change in sub abdominal adipose tissue weight compared to diabetic group (Fig. 2).

Effect of 2-hydroxychalcone treatment on fasting serum glucose and insulin levels

Comparing to control group, levels of glucose and insulin in diabetic rats were significantly increased (4.48–2.05 fold
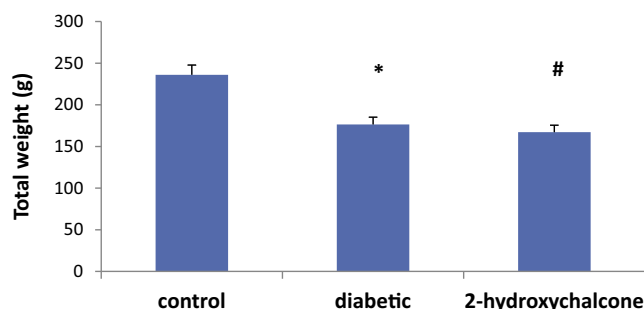

Fig. 1. Effect of 2-hydroxychalcone treatment on total body weight. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group $p < 0.01$. #significant compared to diabetic group $p < 0.05$.
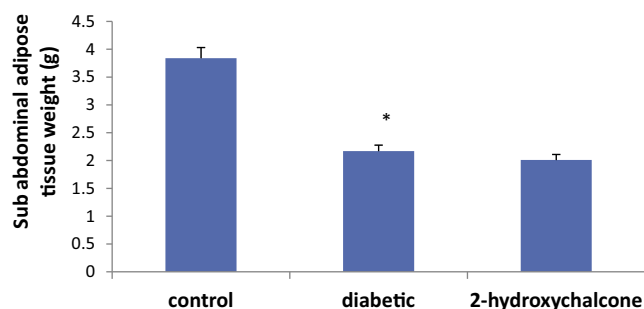

Fig. 2. Effect of 2-hydroxychalcone treatment on sub-abdominal adipose tissue weight. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group $p < 0.01$. #significant compared to diabetic group $p < 0.05$.
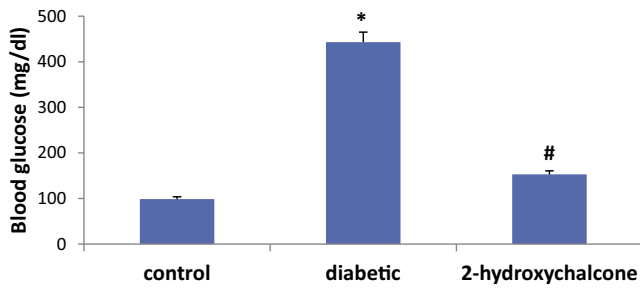
Fig. 3. Effect of 2-hydroxychalcone treatment on fasting blood glucose. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group p < 0.01. #significant compared to diabetic group p < 0.05.
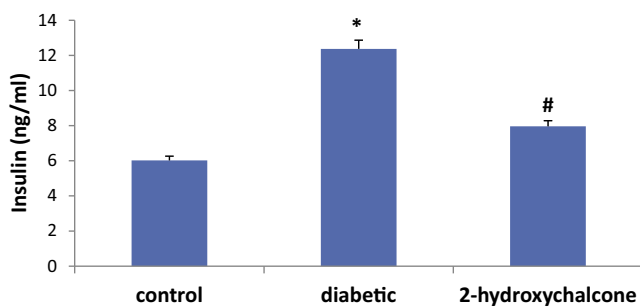

Fig. 4. Effect of 2-hydroxychalcone treatment on insulin levels. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group p < 0.01. #significant compared to diabetic group p < 0.05.

respectively). On the other hand, the diabetic rats treated with hydroxychalcone showed significantly decreased serum glucose and insulin levels (65.46%, 35.65% respectively) when compared to diabetic group (Figs. 3 and 4).

Effect of 2-hydroxychalcone treatment on serum lipid profile

As depicted in Table 1, the total cholesterol, triglyceride, total lipid, low density lipoprotein and very low density lipoprotein were significantly increased and high density lipoprotein was significantly decreased in the diabetic group when compared to control group. However, treatment with 2-hydroxychalcone significantly attenuated diabetes induced deleterious effect on lipid profile when compared to diabetic group.

Effect of 2-hydroxychalcone treatment on adiponectin and PPAR-γ levels

Serum adiponectin and sub abdominal adipose tissue PPAR-γ levels were significantly decreased in the diabetic group compared
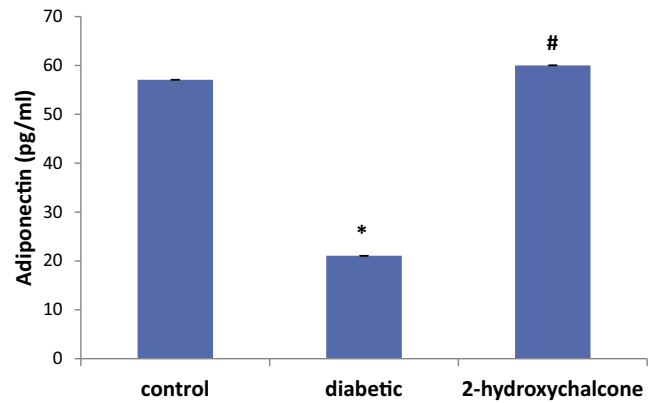

Fig. 5. Effect of 2-hydroxychalcone treatment on adiponectin levels. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group p < 0.01. #significant compared to diabetic group p < 0.05.
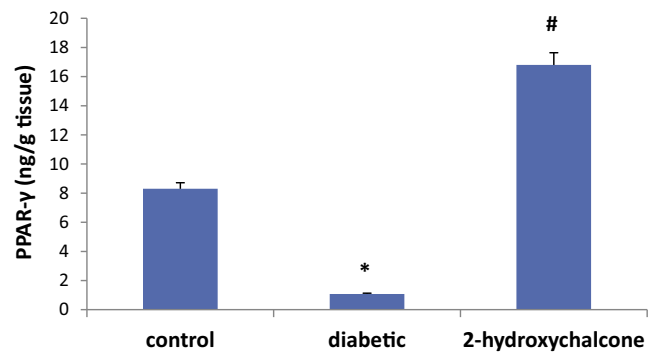

Fig. 6. Effect of 2-hydroxychalcone treatment on PPAR-γ levels in sub-abdominal adipose tissue. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group p < 0.01. #significant compared to diabetic group p < 0.05.

to control group (63.01% and 87.71%, respectively). 2-hydroxychalcone treatment significantly restored serum levels of adiponectin and PPAR-γ concentration (2.85 and 16.4 fold, respectively) when compared to diabetic group (Figs. 5 and 6). Negative correlation was observed between adiponectin and fasting glucose, insulin and total lipid. Moreover, positive correlation was observed between adiponectin and PPAR-γ as well as HDL-cholesterol levels. In addition, Negative correlation was observed between PPAR-γ and fasting glucose (Fig. 10).

Effect of 2-hydroxychalcone treatment on serum oxidative stress markers

Our results showed that serum MDA level was significantly increased (4.78 fold) but serum GSH level was markedly decreased

Table 1
Effect of 2-hydroxychalcone treatment on triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, VLDL-cholesterol and total lipids. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group p < 0.01. #significant compared to diabetic group p < 0.05.

Group	n	Triglyceride mg/d	Total cholesterol mg/d	HDL-cholesterol mg/dl	LDL-cholesterol mg/dl	VLDL-cholesterol mg/dl	Total lipids mg/dl
Control	12	102.2 ± 9.22	137 ± 4.6	65.4 ± 4	51 ± 5.85	20.4 ± 1.91	254 ± 16
Diabetic	12	366.4 ± 14.47*	238 ± 8.25	26.28 ± 7.3*	110.8 ± 4.9*	73.2 ± 2.85*	1344 ± 116*
2-Hydroxychalcone	12	169.2 ± 15.34#	172 ± 13.38	79.4 ± 7.3#	65 ± 4.9#	33.8 ± 2.95#	508 ± 49.7#

Fig. 7. Effect of 2-hydroxychalcone treatment on serum MDA levels. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group p < 0.01. #significant compared to diabetic group p < 0.05.
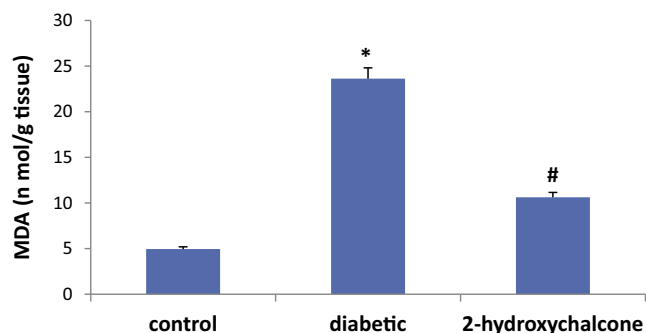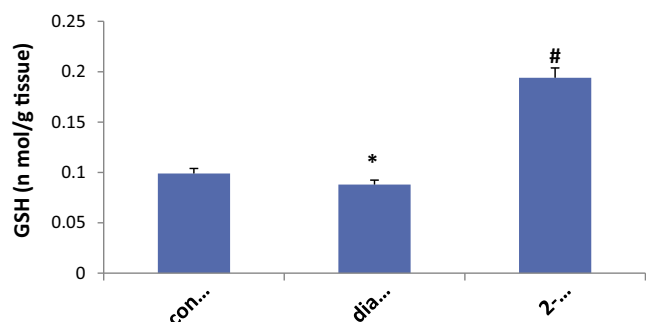

Fig. 8. Effect of 2-hydroxychalcone treatment on serum GSH levels. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group p < 0.01. #significant compared to diabetic group p < 0.05.

Fig. 9. Effect of 2-hydroxychalcone treatment on serum TNF-α level. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychalcone (25 mg/kg body weight daily by oral tube). n = 12, results are expressed as mean ± SE. *significant compared to control group p < 0.01. #significant compared to diabetic group p < 0.05.
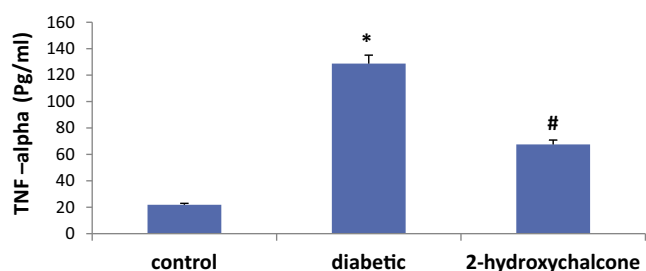
(31.3%) in diabetic group when compared to control group. However, 2-hydroxychalcone treatment reduced MDA by (55.04%) and increased GSH (2.2 fold) when compared to diabetic group (Figs. 7 and 8). Negative correlation was observed between adiponectin and MDA level. However, adiponectin level was positively correlated with GSH level (Fig. 10).

Effect of 2-hydroxychalcone treatment on serum TNF-α levels

Fig. 9 shows that serum TNF-α concentration was significantly increased (5.89 fold) in diabetic group when compared to control

group. However, the diabetic rats treated with 2-hydroxychalcone showed significant decrease in serum TNF-α (47.55%) when compared to diabetic group.

Discussion

This study used rat model of HFD feeding followed by low dose STZ as model for T2DM. Many researchers used the HFD-STZ model showed the significant loss in body weight after STZ injection. The body weight reduction in the STZ-treated rats can be explained by many reasons, including dehydration and excessive fats and proteins catabolism [25], which ultimately lead to muscle wasting [26]. On the other hand, treatment of diabetic rats with hydroxychalcone improved body weight, which could be explained by control of blood glucose levels by hydroxychalcone.

Many previous studies have been documented the relationship between diabetes mellitus and abnormalities in lipid metabolism [27,28]. Dyslipidemia in type 2 diabetic rats is associated with a significant decrease in HDL-C and a significant increase in LDL-C, total cholesterol, triglycerides and, VLDL-C [29,30]. Similarly, the results of our investigation revealed a significant dyslipidemia in diabetic rats when compared to control group. On the contrast, treatment with hydroxychalcone resulted in significant improvement of lipid profile when compared to diabetic untreated group, suggesting beneficial effect of 2-hydroxychalcone on T2DM-induced dyslipidemia.

Persistent high serum glucose is highly deleterious. It is a result of impaired insulin secretion and/or action [31–33]. Blood glucose level should be maintained in a normal range for an enhanced glucose-sensing pathway and sustained insulin output [34]. Firstly, persistent hyperglycemia leads to hyperinsulinemia, which seems likely to be an unsuccessful compensatory response of the islet β-cells. This is followed by decreased or absence of insulin release from β-cells. Indeed, the β-cell mass is reduced by 40%–60% in the patients with T2DM [35]. Therefore, T2DM is associated with insulin resistance, which could be explained by accumulated fat in different body cells that disturb their response to insulin, leading to insulin resistance, hyperinsulinemia, and increased blood glucose levels [36,37]. Insulin is a major anabolic hormone responsible for lipogenesis and inhibiting lipolysis [29,38]. So, Hyperinsulinemia is also correlated with metabolic lipid disorders in obesity as a result of decreased insulin biological activity. In consistent, our results showed increased blood glucose and insulin levels in T2DM rats, reflecting insulin resistance status. This resistance was significantly attenuated by 2-hydroxychalcone treatment.

Several studies have documented association between elevated MDA levels and the damage of β-cells in T2DM [39]. Convincing evidence has established a link between oxidative stress and insulin resistance. Increased free radical levels have deleterious effects on β cells, including decreased insulin secretion in response to glucose, impaired gene expression and cell death, leading ultimately to hyperglycemia and diabetes [40]. MDA is a reactive aldehyde and the major reactive electrophilic species known to elicit stress of toxic nature in cells and known to form covalent protein adducts which are referred to as advanced lipoxidation end products that are found to be analogous to advanced glycation end products [41]. It is often used to determine the oxidant/antioxidant balance in diabetic patients [42]. In this study, hydroxychalcone showed significant reduction of the elevated MDA level in diabetic rats.

GSH content were significantly decreased in T2DM diabetic rats when compared to non-diabetic rats [43]. In this study, the rats which treated with hydroxychalcone showed significant increase in GSH concentration when compared to untreated diabetic rats. Taken together, these results suggested which beneficial antioxidant properties of hydroxychalcone in T2DM. In addition to oxidative stress, inflammation is considered an important
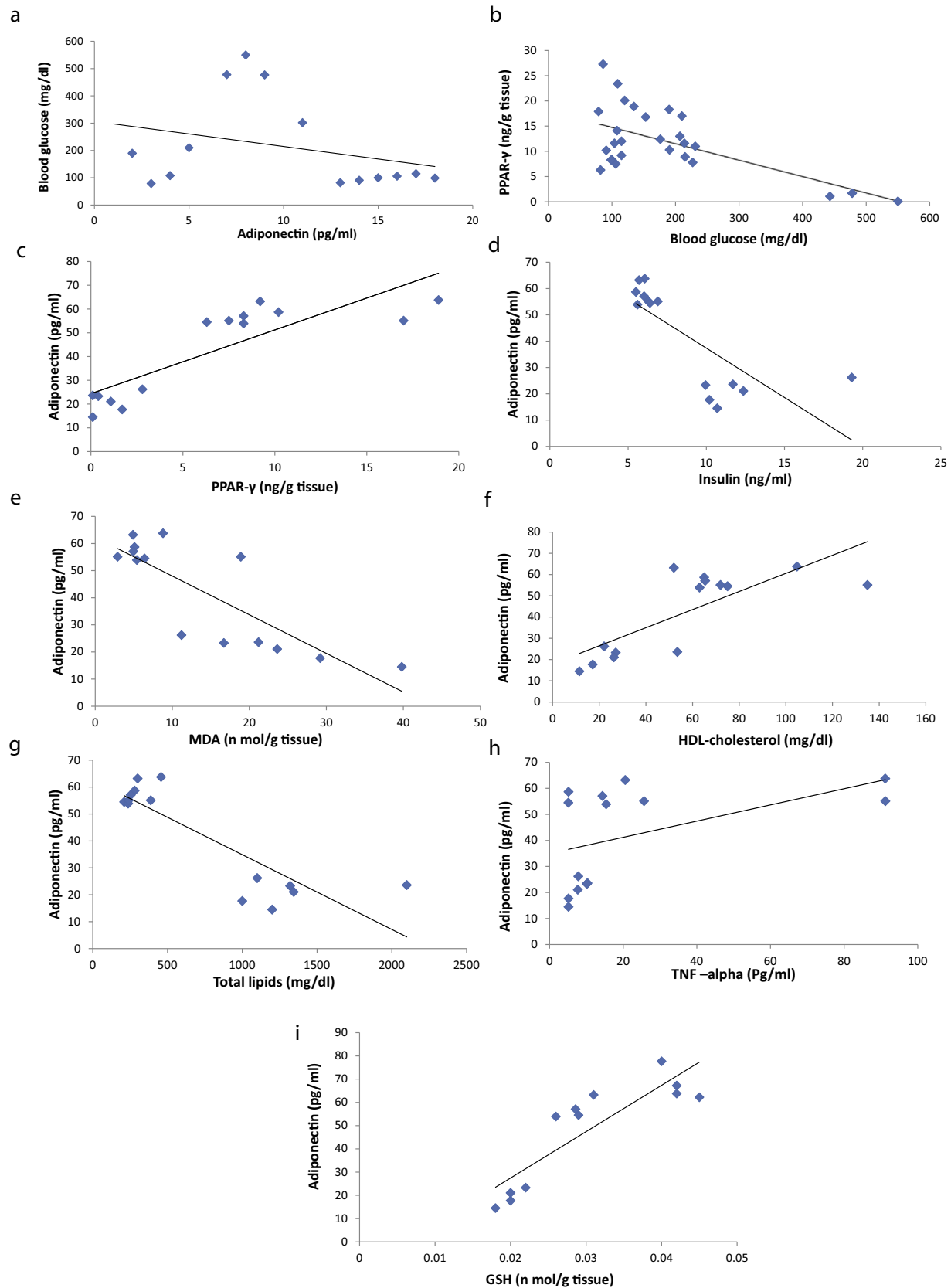
Fig. 10. Correlation studies. (A) Significant negative correlation between blood glucose and adiponectin (r = −0.3, p < 0.05). (B) Significant negative correlation between Sub abdominal adipose tissue concentration PPAR-γ concentration (ng/g tissue) and serum fasting blood glucose (mg/dl) (r = −61, p < 0.05). (C) Significant positive correlation between adiponectin and PPAR-γ (r = 0.847, p < 0.05). (D) Significant negative correlation between adiponectin and insulin (r = −0.765, p < 0.05). (E) Significant negative correlation between adiponectin and lipid peroxide(r = −0.82, p < 0.05). (F) Significant positive correlation between adiponectin and HDL-cholesterol (r = 0.77, p < 0.05). (G) Significant negative correlation between adiponectin and total lipids (r = −0.86, p < 0.05). (H) Significant negative correlation between adiponectin and TNF-α (r = −0.944, p < 0.05). (I) Significant positive correlation between adiponectin and GSH levels (r = 0.869, p < 0.05).
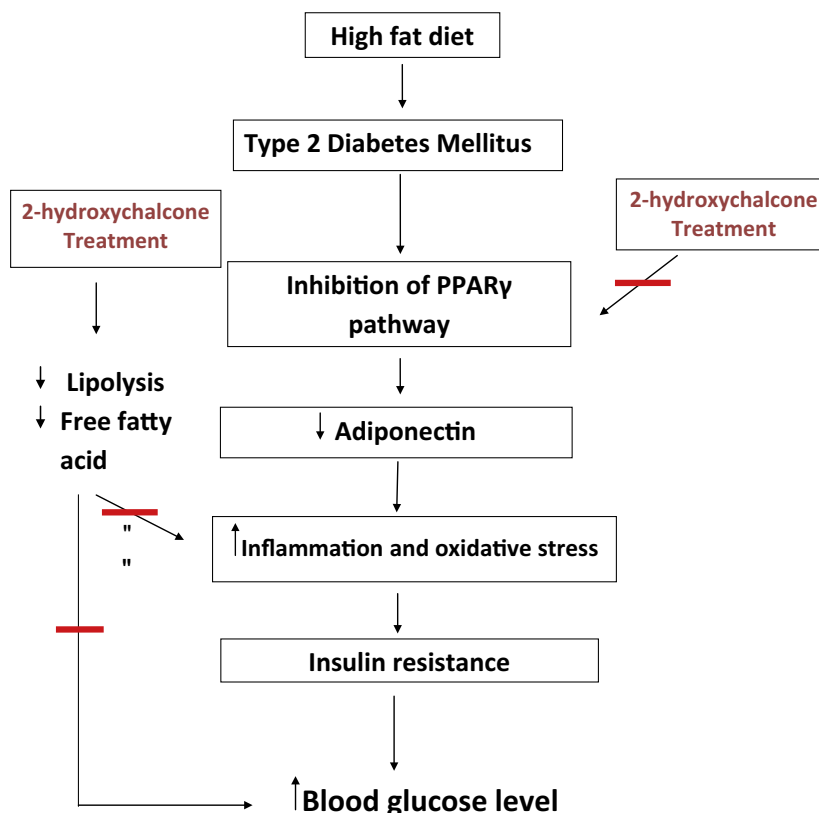
Fig. 11. Proposed mechanism of action for 2-hydroxychalcone in abrogating T2DM-induced changes in experimental rats.

pathogenic factor for the development of insulin resistance in T2DM. Oxidative stress and endoplasmic reticulum stress stimulate inflammatory signaling in T2DM. Circulating TNF-α levels are reported to be elevated in diabetic patients, as well as in STZ-induced diabetic rats [44], and this cytokine is implicated in apoptosis during diabetes [45]. Our results agreed with previous studies which showed that hydroxychalcone treatments significantly decreased T2DM-induced elevation of TNF-α level.

Adipose tissue is an important endocrine organ that plays a crucial role in pathophysiology of T2DM which secretes a number of biologically active adipokines such as adiponectin and TNF-α [46]. Adiponectin is adipokines secreted by adipose tissues [47]. In our study, adiponectin level showed a significant negative correlation with glucose level. These results agreed with previous study [48] which reported a negative correlation between adiponectin level and fasting glucose. Moreover, Insulin level showed in our results a significant negative correlation with adiponectin level. These results could be explained by insulin resistance status associated with T2DM, since adipose tissue itself serves as the site of triglyceride storage and free fatty acid/glycerol release in response to changing energy demands. Adipose tissue also participates in the regulation of energy homeostasis [49–51]. These activities are mediated via adipocytokines such as leptin and adiponectin. Indeed, adiponectin levels is known to correlate positively with insulin sensitivity [47].

Oxidative stress plays a critical role in obesity which associated with many conditions such as diabetes [52]. Some previous studies have shown an association between adiponectin and antioxidant markers [53,54]. There is a positive correlation between adiponectin and glutathione [55,56] and our results agreed with this. On the contrast, in our data, MDA showed a negative correlation with adiponectin level, which agreed with a pervious study [57]. These results could be explained by antioxidant, anti-inflammatory and anti-atherogenic properties of adiponectin [58].

Interestingly, Hydroxychalcone treatment controlled the hyperglycemic by increasing adiponectin levels which is regulated by PPAR-γ. The activation of PPAR-γ leads to increase insulin sensitivity, improve glucose metabolism and reduced inflammation [59].

In the present study, adiponectin showed a significant positive correlation with PPAR-γ, this could be explained by the regulated of adiponectin by PPAR-γ [60,61]. In the present study, decreased sub-abdominal adipose tissue PPAR-γ was observed in diabetic rats when compared to control group, which agreed with a previous study [62]. These adverse changes were attenuated by hydroxychalcone treatment. PPAR-γ activation in type 2 diabetic rats leads to improvement of insulin sensitivity [63]. Moreover, PPAR-γ in adipose tissue increases the glucose transporter and decreases levels of cytokines that induce insulin resistance in liver and muscle. In addition, PPAR-γ acts directly on multiple tissues to redistribute fatty acids away from muscle and liver and promote their storage in adipose tissue, resulting in improved glucose utilization in muscle and liver [64]. In this context, our results showed that 2-hydroxychalcone treatment increased PPAR-γ levels in sub-abdominal adipose tissue. This effect was associated with significant negative correlation with blood glucose and insulin level. These results suggested that 2-hydroxychalcone treatment resulted in PPAR-γ activation with subsequent improvement of insulin sensitivity.

Conclusion

The combination of HFD feeding followed by low dose STZ resulted in insulin resistance associated with hyperglycemia and reduced serum adiponectin concentration in rats. Treatment with 2-hydroxychalcone is able to activate PPAR-γ and to improve adiponectin level in diabetic rats resulting in antihyperglycemic effect (Fig. 11). These results suggested 2-hydroxychalcone as potential therapy for disorders associated with lipid and glucose metabolism.

Conflict of interest

All authors declare no potential conflict of interest including any financial, personal or other relationships with other people or organizations within that could inappropriately influence, or be perceived to influence, this work.

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