[Egyptian Journal of Basic and Applied Sciences 4 (2017) 1–8](http://dx.doi.org/10.1016/j.ejbas.2016.12.002)



Contents lists available at [ScienceDirect](http://www.sciencedirect.com/science/journal/2314808X)

Egyptian Journal of Basic and Applied Sciences

journal homepage: [www.elsevier.com/locate/ejbas](http://www.elsevier.com/locate/ejbas)

Full Length Article

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



# Laila Ahmed Eissa [a](#_bookmark0),[⇑](#_bookmark2), Nehal Mohsen Elsherbiny [a](#_bookmark0),[b](#_bookmark1), Abdalkareem Omar Maghmomeh [a](#_bookmark0)

a *Department of Biochemistry, Faculty of Pharmacy, University of Mansoura, Mansoura 35516, Egypt*

b *Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Tabuk, Tabuk 71491, Saudi Arabia*

## a r t i c l e i n f o

*Article history:*

Received 19 September 2016

Received in revised form 15 December 2016 Accepted 23 December 2016

Available online 5 January 2017

*Keywords:*

Type 2 diabetes mellitus Insulin resistance Adiponectin

PPAR-c

2-Hydroxychalcone

## 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 adipocytoki- nes, 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 per-

oxisome proliferator activated receptor gamma (PPAR-c) 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-c in sub abdominal adipose tissue, serum adiponectin, serum tumor necrosis factor-a (TNF-a) 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-c 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-c signaling pathway.

© 2017 Mansoura University. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Type 2 diabetes is referred to as non-insulin-dependent dia- betes or adult onset diabetes. It is the most common type of dia- betes, 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]](#_bookmark12). The hyperglycemia is caused by a combination of deficiency in insulin secretion and action, leading to reduced glucose uptake by peripheral tissues and increased glu- coneogenesis by the liver. Untreated diabetes may progress to loss of b-cells function in the islets of Langerhans with eventual insulin deficiency. b-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]](#_bookmark12).

The management of diabetes is considered a global problem, a medical approach is not always sufficient for T2DM management

\* Corresponding author.

*E-mail address:* [lailaeissa2002@yahoo.com](mailto:lailaeissa2002@yahoo.com) (L.A. Eissa).

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]](#_bookmark12). To avoid such adverse side effects, there is a crucial need for new therapies for management and treatment of T2DM [[6,7]](#_bookmark12).

Adiponectin is an adipocytokine exclusively secreted by adipose tissue into the blood stream [[8,9]](#_bookmark13). Plasma adiponectin level is neg- atively correlated with development of insulin resistance, T2DM and metabolic syndrome that are linked to obesity [[10,11]](#_bookmark14). Indeed, plasma adiponectin levels were decreased in obesity. This reduc- tion may play a causal role in the development of insulin resistance [[12]](#_bookmark18).

Transcription of adiponectin was tightly controlled by peroxi- some proliferator-activated receptor gamma (PPAR-c) [[13]](#_bookmark22). PPAR- c is highly expressed in adipocytes, where it plays an important role in glucose and lipid homeostasis, inflammation, and adipocyte

differentiation [[14]](#_bookmark24). A large body of evidence confirmed that PPAR- c activation improves insulin sensitivity and enhances glucose dis- posal in adipose tissue and skeletal muscle [[15]](#_bookmark27).

<http://dx.doi.org/10.1016/j.ejbas.2016.12.002>

2314-808X/© 2017 Mansoura University. Production and hosting by Elsevier B.V.

This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Chalcones (originally isolated from natural plant sources) are considered as precursors of flavonoids. Chalcones are abundant in edible plants [[16]](#_bookmark30). In addition, they can also be synthesized in laboratory [[17]](#_bookmark31). Hydroxychalcones have been involved in various biological activities including antioxidant, anti-inflammatory, anti- cancer, anti hepatotoxic and antimalarial activities [[18]](#_bookmark33). Interest- ingly, hydroxychalcone has been reported to mimic the effect of insulin by enhancing glucose uptake and phosphorylation of insu- lin receptor in adipocytes [[19]](#_bookmark34). In addition, various synthetic chal- cone derivatives have shown inhibitory activity against diabetic complications. Moreover, 2-hydroxy chalcone was reported as a

potential dietary PPARc ligand [[20]](#_bookmark35). 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-c.

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 Commit- tee, Faculty of Pharmacy, Mansoura University, Egypt. The animals were randomly divided into 3 groups (12 rats in each group): Nor- mal 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]](#_bookmark38).

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 con- tinued until the end of study. STZ was freshly dissolved in (0.1 M) citrate buffer (pH 4.5) and immediately injected into rats [[22]](#_bookmark39). To overcome the hypoglycemia which follows STZ, during the first 24 h after their injection; diabetic rats were given 5% glucose solu- tion to drink instead of tap water. Animals were monitored by peri- odic 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 consid- ered diabetic and selected for further pharmacological studies [[23]](#_bookmark41). 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. Hydroxychal- cone was dissolved in dimethylsulfoxide (DMSO) – normal saline. The final concentration of DMSO in normal saline did not exceed 0.5%) [[24]](#_bookmark42). 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-c, serum adiponectin,

serum insulin, and serum tumor necrosis factor-a (TNF-a) levels were assessed using Enzyme-Linked Immunosorbent Assay (ELISA) kits provided from MyBioSource (San Diego, United States) accord- ing to the manufacturer’s instructions.

*Statistical analysis*

The results were presented as means ± SEM. The statistical anal- yses 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](#_bookmark3)) 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 con- trol rats. The diabetic rats treated with hydroxychalcone showed non-significant change in sub abdominal adipose tissue weight compared to diabetic group ([Fig. 2](#_bookmark4)).

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

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

300

**\***

**#**

250

**Total weight (g)**

200

150

100

50

0

### control diabetic 2-hydroxychalcone

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-hydroxy- chalcone (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.

4.5

\*

**Sub abdominal adipose tissue weight (g)**

4

3.5

3

2.5

2

1.5

1

0.5

0

#### control diabetic 2-hydroxychalcone

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.

500

**Blood glucose (mg/dl)**

400

300

200

100

0

70

60

**\***

**#**

**#**

**\***

**Adiponectin (pg/ml)**

50

40

30

### control diabetic 2-hydroxychalcone 20

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.

**\***

**#**

10

0

### control diabetic 2-hydroxychalcone

14

12

**Insulin (ng/ml)**

10

8

6

4

2

0

### control diabetic 2-hydroxychalcone

Fig. 5. Effect of 2-hydroxychalcone treatment on adiponectin levels. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxy- chalcone (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.

20

**#**

**\***

18

16

**PPAR-γ (ng/g tissue)**

14

12

10

8

6

Fig. 4. Effect of 2-hydroxychalcone treatment on insulin levels. After induction of T2DM, rats were treated with solvent (DMSO – normal saline) or 2-hydroxychal- cone (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.

4

2

0

### control diabetic 2-hydroxychalcone

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](#_bookmark5)).

*Effect of 2-hydroxychalcone treatment on serum lipid profile*

As depicted in [Table 1](#_bookmark7), the total cholesterol, triglyceride, total lipid, low density lipoprotein and very low density lipoprotein were significantly increased and high density lipoprotein was sig- nificantly decreased in the diabetic group when compared to con- trol 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-c levels*

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

Fig. 6. Effect of 2-hydroxychalcone treatment on PPAR-c 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-c concentration (2.85 and 16.4 fold,

respectively) when compared to diabetic group ([Figs. 5 and 6](#_bookmark6)). Negative correlation was observed between adiponectin and fast- ing glucose, insulin and total lipid. Moreover, positive correlation

was observed between adiponectin and PPAR-c as well as HDL-

cholesterol levels. In addition, Negative correlation was observed between PPAR-c and fasting glucose ([Fig. 10](#_bookmark10)).

*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# |

30

**\***

**#**

25

**MDA (n mol/g tissue)**

20

15

10

5

0

### control diabetic 2-hydroxychalcone

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-hydroxy- chalcone (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.

0.25

**#**

**\***

**GSH (n mol/g tissue)**

0.2

0.15

0.1

0.05

0

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-hydroxy- chalcone (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.

160

**\***

**#**

**TNF –alpha (Pg/ml)**

140

120

100

80

60

40

20

0

#### control diabetic 2-hydroxychalcone

Fig. 9. Effect of 2-hydroxychalcone treatment on serum TNF-a 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. How- ever, 2-hydroxychalcone treatment reduced MDA by (55.04%) and increased GSH (2.2 fold) when compared to diabetic group ([Figs. 7 and 8](#_bookmark8)). Negative correlation was observed between adipo- nectin and MDA level. However, adiponectin level was positively correlated with GSH level ([Fig. 10](#_bookmark10)).

*Effect of 2-hydroxychalcone treatment on serum TNF-a levels*

[Fig. 9](#_bookmark9) shows that serum TNF-a 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-a (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 pro- teins catabolism [[25]](#_bookmark43), which ultimately lead to muscle wasting [[26]](#_bookmark15). On the other hand, treatment of diabetic rats with hydroxy- chalcone improved body weight, which could be explained by con- trol of blood glucose levels by hydroxychalcone.

Many previous studies have been documented the relationship between diabetes mellitus and abnormalities in lipid metabolism [[27,28]](#_bookmark15). 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]](#_bookmark15). 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 improve- ment 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]](#_bookmark15). Blood glucose level should be maintained in a normal range for an enhanced glucose-sensing pathway and sustained insulin output [[34]](#_bookmark15). Firstly, persistent hyperglycemia leads to hyperinsulinemia, which seems likely to be an unsuccessful compensatory response of the islet b- cells. This is followed by decreased or absence of insulin release from b-cells. Indeed, the b-cell mass is reduced by 40%–60% in the patients with T2DM [[35]](#_bookmark15). 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]](#_bookmark15). Insulin is a major anabolic hormone respon- sible for lipogenesis and inhibiting lipolysis [[29,38]](#_bookmark15). So, Hyperinsu- linemia 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 signif- icantly attenuated by 2-hydroxychalcone treatment.

Several studies have documented association between elevated MDA levels and the damage of b-cells in T2DM [[39]](#_bookmark16). Convincing evidence has established a link between oxidative stress and insu- lin resistance. Increased free radical levels have deleterious effects on b cells, including decreased insulin secretion in response to glu- cose, impaired gene expression and cell death, leading ultimately to hyperglycemia and diabetes [[40]](#_bookmark17). 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]](#_bookmark19). It is often used to determine the oxidant/antioxidant balance in diabetic patients [[42]](#_bookmark20). 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]](#_bookmark21). 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 anti- oxidant properties of hydroxychalcone in T2DM. In addition to oxidative stress, inflammation is considered an important

# a b

600

500

**Blood glucose (mg/dl)**

**PPAR-γ (ng/g tissue)**

400

300

200

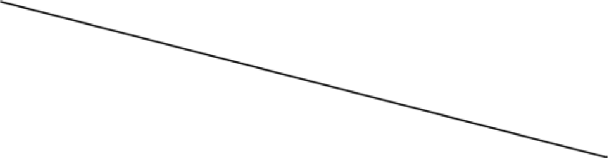
100

0

0 5 10 15 20

30

25



20

15

10

5

0

0 100 200 300 400 500 600

c 80

70

**Adiponectin (pg/ml)**

60

50

40

30

20

10

0

# e

70

60

**Adiponectin (pg/ml)**

50

40

30

20

10

0

**Adiponectin (pg/ml)** d

0 5 10 15 20

**PPAR-γ (ng/g tissue)**

# f

**Blood glucose (mg/dl)**

70

60

**Adiponectin (pg/ml)**

50

40

30

20

10

0

0 5 10 15 20 25

**Insulin (ng/ml)**

80



70

**Adiponectin (pg/ml)**

60

50

40

30

20

10

0

0 10 20 30 40 50

g **MDA (n mol/g tissue)**

h

70



60

**Adiponectin (pg/ml)**

**Adiponectin (pg/ml)**

50

40

30

20

10

0

0 500 1000 1500 2000 2500

**Total lipids (mg/dl)**

0 20 40 60 80 100 120 140 160

**HDL-cholesterol (mg/dl)**

70



60

50

40

30

20

10

0

0 20 40 60 80 100

**TNF –alpha (Pg/ml)**

i 90

80

**Adiponectin (pg/ml)**

70

60

50

40

30

20

10

0

0 0.01 0.02 0.03 0.04 0.05

**GSH (n mol/g tissue)**

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-c concentration (ng/g tissue) and serum fasting blood glucose (mg/dl) (r = —61, p < 0.05). (C) Significant positive correlation between adiponectin and PPAR-c (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-a (r = —0.944, p < 0.05). (I) Significant positive correlation between adiponectin and GSH levels (r = 0.869, p < 0.05).

**High fat diet**

**Type 2 Diabetes Mellitus**

**Adiponectin**

**Inflammation and oxidative stress**

**Blood glucose level**

**Lipolysis Free fatty acid**

"

"

**Insulin resistance**

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 stimu- late inflammatory signaling in T2DM. Circulating TNF-a levels

"

**Inhibition of PPARγ pathway**

**2-hydroxychalcone Treatment**

**2-hydroxychalcone Treatment**

are reported to be elevated in diabetic patients, as well as in STZ- induced diabetic rats [[44]](#_bookmark23), and this cytokine is implicated in apop- tosis during diabetes [[45]](#_bookmark25). Our results agreed with previous studies which showed that hydroxychalcone treatments significantly

decreased T2DM-induced elevation of TNF-a level.

Adipose tissue is an important endocrine organ that plays a cru- cial role in pathophysiology of T2DM which secretes a number of biologically active adipokines such as adiponectin and TNF-a

[[46]](#_bookmark26). Adiponectin is adipokines secreted by adipose tissues [[47]](#_bookmark28). In our study, adiponectin level showed a significant negative corre- lation with glucose level. These results agreed with previous study

[[48]](#_bookmark29) 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 asso- ciated 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]](#_bookmark32). These activities are mediated via adipocytokines such as leptin and adiponectin. Indeed, adiponectin levels is known to correlate positively with insulin sensitivity [[47]](#_bookmark28).

Oxidative stress plays a critical role in obesity which associated with many conditions such as diabetes [[52]](#_bookmark36). Some previous studies have shown an association between adiponectin and antioxidant markers [[53,54]](#_bookmark37). There is a positive correlation between adiponec- tin and glutathione [[55,56]](#_bookmark40) and our results agreed with this. On the contrast, in our data, MDA showed a negative correlation with adi- ponectin level, which agreed with a pervious study [[57]](#_bookmark44). These results could be explained by antioxidant, anti-inflammatory and anti-atherogenic properties of adiponectin [[58]](#_bookmark45).

Interestingly, Hydroxychalcone treatment controlled the hyper- glycemic by increasing adiponectin levels which is regulated by PPAR-c. The activation of PPAR-c leads to increase insulin sensitiv-

ity, improve glucose metabolism and reduced inflammation [[59]](#_bookmark46).

In the present study, adiponectin showed a significant positive correlation with PPAR-c, this could be explained by the regulated of adiponectin by PPAR-c [[60,61]](#_bookmark46). In the present study, decreased

sub-abdominal adipose tissue PPAR-c was observed in diabetic rats when compared to control group, which agreed with a previous study

[[62]](#_bookmark47). These adverse changes were attenuated by hydroxychalcone treatment. PPAR-c activation in type 2 diabetic rats leads to improve- ment of insulin sensitivity [[63]](#_bookmark47). Moreover, PPAR-c in adipose tissue increases the glucose transporter and decreases levels of cytokines

that induce insulin resistance in liver and muscle. In addition, PPAR-c acts directly on multiple tissues to redistribute fatty acids away from muscle and liver and promote their storage in adipose tis-

sue, resulting in improved glucose utilization in muscle and liver [[64]](#_bookmark47). In this context, our results showed that 2-hydroxychalcone treat- ment increased PPAR-c 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-c activation with sub- sequent 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-c and to improve adipo-

nectin level in diabetic rats resulting in antihyperglycemic effect ([Fig. 11](#_bookmark11)). 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.

References

1. [International Diabetes Federation (IDF). IDF diabetes atlas. 6th ed. Brussels,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0005) [Belgium: International Diabetes Federation; 2013](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0005).
2. [Skamagas M, Breen TL, LeRoith D. Update on diabetes mellitus:](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0010) [prevention, treatment, and association with oral diseases. Oral Dis 2008;](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0010) [14(2):105–14](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0010).
3. [Maraschin JF. Classification of diabetes. In: Diabetes: an old disease, a new](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0015) [insight. New York: Springer; 2012. p. 12–9](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0015).
4. [Hamza N, Berke B, Cheze C, Agli AN, Robinson P, Gin H, Moore N. Prevention of](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0020) [type 2 diabetes induced by high fat diet in the C57BL/6J mouse by two](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0020) [medicinal plants used in traditional treatment of diabetes in the east of](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0020) [Algeria. J Ethnopharmacol 2010;128:513–8](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0020).
5. [Kobayashi M, Iwata M, Haruta T. Clinical evaluation of pioglitazone. Nippon](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0025) [Rinsho 2000;58:395–400](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0025).
6. [Ryu JK, Lee T, Kim DJ, Park IS, Yoon SM, Lee HS, Song SU, Suh JK. Free radical-](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0030) [scavenging activity of Korean red ginseng for erectile dysfunction in non-](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0030) [insulin-dependent diabetes mellitus rats. Urology 2005;65:611–5](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0030).
7. [Gupta S, Sharma SB, Bansal SK, Prabhu KM. Antihyperglycemic and](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0035) [hypolipidemic activity of aqueous extract of *Cassia auriculata* L. leaves in](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0035) [experimental diabetes. J Ethnopharmacol 2009;123:499–503](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0035).
8. [Scheen AJ. Pathophysiology of type 2 diabetes. Acta Clin Belg 2003;58](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0040) [(6):335–41](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0040).
9. [Hotta K, Funahashi T, Arita Y, Takahashi M, Matuda M, et al. Plasma](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0045) [concentration of a novel, adipose-specific protein, adiponectin, in type 2](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0045) [diabetic patients. J Clinic Endocrinol Metab 2001;86:1930–5](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0045).
10. [Renaldi O, Pramono B, Sinorita H, Purnomo LB, Asdie RH, et al.](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0050) [Hypoadiponectinemia: a risk factor for metabolic syndrome. Acta Med](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0050) [Indones 2009;41(1):20–4](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0050).
11. [Diez JJ, Iglesias P. The role of the novel adipocyte-derived hormone](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0055) [adiponectin in human disease. Eur J Endocrinol 2003;148(3):293–300](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0055).
12. [Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, et al. Proteolytic](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0060) [cleavage product of 30-kDa adipocyte complement-related protein increases](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0060) [fatty acid oxidation in muscle and causes weight loss in mice. Proc Natl Acad](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0060) [Sci USA 2001;98(4):2005–10](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0060).
13. [Sharabi Y, Oron-Herman M, Kamari Y, Avni I, Peleg E, Shabtay Z, et al. Effect of](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0065) [PPAR-gamma agonist on adiponectin levels in the metabolic syndrome:](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0065) [lessons from the high fructose fed rat model. Am J Hypertens 2007;20](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0065) [(2):206–10](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0065).
14. [Yamamoto Y, Hirose H, Miyashita K, Nishikai K, Saito I, Taniyama M, et al. PPAR](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0070) [gamma 2 gene Pro12Ala polymorphism may influence serum level of an](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0070) [adipocytederived protein, adiponectin, in the Japanese population.](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0070) [Metabolism 2002;51(11):1407–9](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0070).
15. [Lakota K, Wei J, Carns M, Hinchcliff M, Lee J, Whitfield ML, et al. Levels of](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0075) [adiponectin, a marker for PPAR-gamma activity, correlate with skin fibrosis in](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0075) [systemic sclerosis: potential utility as biomarker? Arthritis Res There 2012;14](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0075) [(3):102](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0075).
16. [Alam S, Mostahar S. Studies of antimicrobial activity of two synthetic, 2,4,6,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0080) [trioxygenated flavones. J Appl Sci 2005](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0080).
17. [Alan L, Miller ND. Antioxidant flavonoids: Structure, function and clinical](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0085) [usage. Altern Med Rev 1996;1(2):103–11](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0085).
18. [Lim SS, Jung SH, Ji J, Shin KH, Keum SRJ. Synthesis of flavonoids and their](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0090) [effects on aldose reductase and sorbitol accumulation in streptozotocin-](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0090) [induced diabetic rat tissues. Pharm Pharmacol 2001;53(5):653–68](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0090).
19. [Jarvill-Taylor KJ, Anderson RA, Graves DJ. A hydroxychalcone derived from](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0095) [cinnamon functions as a mimetic for insulin in 3T3-L1 adipocytes. J Am Coll](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0095) [Nutr 2001;20(4):327–36](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0095).
20. [Jung Sang Hoon, Park Soo Young, Kim-Pak Youngmi, Lee Hong Kyu, Park Kyong](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0105) [Soo, Shin Kuk Hyun, Ohuchi Kazuo, Shin Hyun-Kyung, Keum Sam-Rok, Lim](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0105) [Soon Sung. Synthesis and PPAR-gamma ligand-binding activity of the new](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0105)

[series of 2](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0105)0 [-hydroxychalcone and thiazolidinedione derivatives. Chem. Pharm.](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0105)

[Bull. 2006;54(3):368–70](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0105).

1. [Reed MJ, Meszaros K, Entes LJ, Claypool MD, Pinkett JG, Gadbois TM, et al. A](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0110) [new rat model of type 2 diabetes: the fat-fed. Metabolism 2000;49](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0110) [(11):1390–4](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0110).
2. [Srinivasan K, Viswanad B, Asrat L, Kaul CL, Ramarao P. Combination of high-fat](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0115) [diet-fed and low-dose streptozotocin-treated rat: a model for type 2 diabetes](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0115) [and pharmacological screening. Pharmacol Res 2005;52:313–20](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0115).
3. [Zhang F, Ye C, Li G, Ding W, Zhou W, Zhu H, et al. The rat model of type 2](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0120) [diabetes mellitus and its glycometabolism characters. Exp Anim](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0120) [2003;52:401–7](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0120).
4. [Jayanthi M, Jegatheesan K, Vidhya R, Kanagavalli U. Hypoglycemic effect of 2-](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0125) [hydroxychalcone on high fructose fed diabetic rat. IJPSR 2012;3(2):600–4](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0125).
5. [Hakim ZS, Patel BK, Goyal RK. Effects of chronic ramipril treatment in](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0130) [streptozotocin induced diabetic rats. Indian J Physiol Pharmacol](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0130) [1997;41:353–60](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0130).
6. [Rajkumar L, Srinivasan N, Balasubramanian K, Govindarajulu P. Increased](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0135) [degradation of dermal collagen in diabetic rats. Indian J Exp Biol](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0135) [1991;29:1081–3](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0135).
7. [Singh DP, Kondepudi KK, Bishoni M, Chopra K. Altered monoamine](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0140) [metabolism in high fat diet induced neuropsychiatric changes in rats. Jobes](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0140) [Weight Loss Ther 2014;4(4):234–9](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0140).
8. [Kumar A, Singh V. Atherogenic dyslipidemia and diabetes mellitus what’s new](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0145) [in the management arena? Vasc Health Risk Manage 2010;6:665–9](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0145).
9. [Vaverkova. Dyslipoproteinemia and diabetes mellitus. Vnitr Lek](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0150) [2000;46:532–8](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0150).
10. [Taskinen. Controlling lipid levels in diabetes. Acta Diabetol 2002;2:29–34](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0155).
11. [Poitout V, Robertson RP. Glucolipotoxicity: fuel excess and beta-cell](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0160) [dysfunction. Endocr Rev 2008;29(3):351–66](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0160).
12. [Del Prato S. Role of glucotoxicity and lipotoxicity in the pathophysiology of](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0165) [Type 2 diabetes mellitus and emerging treatment strategies. Diabet Med](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0165) [2009;26(12):1185–92](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0165).
13. [Cernea S, Dobreanu M. Diabetes and beta cell function: from mechanisms to](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0170) [evaluation and clinical implications. Biochem Med 2013;23(3):266–80](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0170).
14. [Wang Q, Jin T. The role of insulin signaling in the development of beta-cell](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0175) [dysfunction and diabetes. Islets 2009;1(2):95–101](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0175).
15. [Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA, Butler PC. Beta-cell](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0180) [deficit and increased beta-cell apoptosis in humans with type 2 diabetes.](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0180) [Diabetes 2003;52(1):102–10](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0180).
16. [Leahy JL, Hirsch IB, Peterson KA, Schneider D. Targeting beta-cell function early](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0185) [in the course of therapy for type 2 diabetes mellitus. J Clin Endocrinol Metab](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0185) [2010;95(9):4206–16](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0185).
17. [Widjaja A, Stratton IM, Horn R, Holman RR, Turner R, Brabant G. Plasma leptin,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0190) [obesity and plasma insulin in type 2 diabetic subjects. J Clin Endocrinol Metab](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0190) [1997;82(2):654–7](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0190).
18. [Kopecky J, Flachs P, Bardova K, Brauner P, Prazak T, Sponarova J. Modulation of](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0195) [lipid metabolism by energy status of adipocytes implications for insulin](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0195) [sensitivity. Ann N Y Acad Sci 2002;967:88–101](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0195).
19. [Okutan H, Ozcelik N, Ramazan Yilmaz H, Uz E. Effects of caffeic acid phenethyl](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0200) [ester on lipid peroxidation and antioxidant enzymes in diabetic rat heart. Clin](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0200) [Biochem 2005;38(2):191–6](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0200).
20. [Park K, Gross M, Lee DH, Holvoet P, Himes JH, Shikany JM, et al. Oxidative](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0205) [stress and insulin resistance: the coronary artery risk development in young](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0205) [adults study. Diabetes Care 2009;32(7):1302–7](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0205).
21. [Farmer EE, Davoine C. Reactive electrophile species. Curr Opin Plant Biol](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0210) [2007;10(4):380–6](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0210).
22. [Pasaoglu H, Sancak B, Bukan N. Lipid peroxidation and resistance to oxidation](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0215) [in patients with type 2 diabetes mellitus. Tohoku J Exp Med 2004;203](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0215) [(3):211–8](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0215).
23. [Biswas M, Chan JY. Role of Nrf1 in antioxidant response element-mediated](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0220) [gene Huiression and beyond. Toxicol Appl Pharm 2010;244(1):16–20](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0220).
24. [Chen G, Goeddel DV. TNF-R1 signaling: a beautiful pathway. Science 2002;296](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0225) [(5573):1634–5](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0225).
25. [Chiarelli F, Di Marzio D. Peroxisome proliferator-activated receptor-gamma](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0230) [agonists and diabetes: current evidence and future perspectives. Vasc Health](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0230) [Risk Manage 2008;4(2):297–304](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0230).
26. [Scheen AJ. Pathophysiology of type 2 diabetes. Acta Clin Belg 2003;58](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0235) [(6):335–41](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0235).
27. [Morigny P, Houssier M, Mouisel E, Langin D. Adipocyte lipolysis and insulin](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0240) [resistance. Biochimie 2016;125:259–66](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0240).
28. [Vandana S, Megha K, Amita Y, Anju. Role of leptin and adiponectin in](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0245) [gestational diabetes mellitus: a study in a North Indian tertiary care hospital.](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0245) [Internet J Med Update 2015;10(1):11–4](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0245).
29. [Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0250) [et al. Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. Nat](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0250) [Med 2002;8(7):731–7](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0250).
30. [Yatagaia T, Nagasaka S, Taniguchib A, Fukushimac M, Nakamuraa T, et al.](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0255) [Hypoadiponectinemia is associated with visceral fat accumulation and insulin](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0255) [resistance in Japanese men with type 2 diabetes mellitus. Metabolism 2003;52](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0255) [(10):1274–8](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0255).
31. [Spiegelman BM, Flier JS. Adipogenesis and obesity: rounding out the big](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0260) [picture. Cell 1996;87(3):377–89](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0260).
32. [Furukawa S, Fujita T, Shimabukuro M, et al. Increased oxidative stress in](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0265) [obesity and its impact on metabolic syndrome. J Clin Invest 2004;114](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0265) [(12):1752–61](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0265).
33. [Nakanishi S, Yamane K, Kamei N, Nojima H, Okubo M, Kohno NA. Protective](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0270) [effect of adiponectin against oxidative stress in Japanese Americans: the](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0270) [association between adiponectin or leptin and urinary isoprostane.](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0270) [Metabolism 2005;54(2):194–9](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0270).
34. [Kaur S, Zilmer K, Kairane C, Kals M, Zilmer M. Clear differences in adiponectin](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0275) [level and glutathione redox status revealed in obese and normal-weight](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0275) [patients with psoriasis. Br J Dermatol 2008;159(6):1364–7](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0275).
35. [Shin MJ, Lee JH, Jang Y, et al. Insulin resistance, adipokines, and oxidative stress](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0280) [in nondiabetic, hypercholesterolemic patients: leptin as an 8-epi-](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0280) [prostaglandin F2alpha determinant. Metabolism 2006;55(7):918–22](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0280).
36. [Hui X, Lam KS, Vanhoutte PM, Xu A. Adiponectin and cardiovascular health: an](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0285) [update. Br J Pharmacol 2012;165(3):574–90](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0285).
37. [Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, et al. Weight reduction](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0290) [increases plasma levels of an adipose-derived anti-inflammatory protein,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0290) [adiponectin. J Clin Endocrinol Metab 2001;86(8):3815–9](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0290).
38. [Satoh J, Yagihashi S, Toyota T. The possible role of tumor necrosis factor- alpha](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0295) [in diabetic polyneuropathy. Exp Diabesity Res 2003;4(2):65–71](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0295).
39. [Kuhad A, Chopra K. Attenuation of diabetic nephropathy by tocotrienol:](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0300) [involvement of NF-kB signaling pathway. Life Sci 2009;84(9–10):](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0300) [296–301](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0300).
40. [Foryst-Ludwig A, Hartge M, Clemenz M, Sprang C, Hess K, Marx N, Unger T,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0305) [Kintscher U. PPAR gamma activation attenuates T-lymphocyte-dependent](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0305) [inflammation of adipose tissue and development of insulin resistance in obese](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0305) [mice. Cardiovasc Diabetol 2010;9:64](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0305).
41. [Guo N, Woeller CF, Feldon SE, Phipps RP. Peroxisome proliferatoractivated](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0310) [receptor gamma ligands inhibit transforming growth factor-beta-induced,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0310) [hyaluronan-dependent, T cell adhesion to orbital fibroblasts. J Biol Chem](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0310) [2011;286(21):18856–67](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0310).
42. [Dong X, Swaminathan S, Bachman LA, Croatt AJ, Nath KA, Doran AC, Meller N,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0315) [Cutchins A, Deliri H, Slayton RP, Oldham SN, Kim JB, Keller SR, McNamara CA.](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0315) [The helix-loop-helix factors Id3 and E47 are novel regulators of adiponectin.](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0315) [Circ Res 2008;103(6):624–34](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0315).
43. [Wen-wen, Li-yong Zhong, Xiao-rong Li, Guang Li, Zhao-xia Liu, Jin feng Hu,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0320)

[Nai-hong Chen. Hyperglycemia induces the variations of 11b-hydroxysteroid](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0320) [dehydrogenase type 1 and peroxisome proliferator-activated receptor-c](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0320) [expression in hippocampus and hypothalamus of diabetic rats. Exp Diabetes](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0320)

[Res 2012;107:130](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0320).

1. [Rosen ED, Spiegelman BM. PPAR c a nuclear regulator of metabolism,](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0325) [differentiation, and cell growth. J Biol Chem 2001;276(41):37731–4](http://refhub.elsevier.com/S2314-808X(16)30053-7/h0325).