

Xanthene Attenuates High-Fat Diet-Induced Hyperlipidemia in Rats via Modulation of the Ang II/Ang-(1–7) Balance, Adiponectin, and Nrf2 Signaling

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ABSTRACT

Background: Hyperlipidemia induced by a high-fat diet (HFD) is associated with metabolic disturbances, hepatic injury, oxidative stress, and activation of the renin–angiotensin system.

Aim: This study evaluated the protective effects of xanthene in comparison with rosuvastatin and telmisartan in an experimental model of HFD-induced hyperlipidemia.

Methods: Forty adult male Wistar albino rats were randomly allocated into five groups: control, HFD, HFD plus rosuvastatin (10 mg/kg/day), HFD plus telmisartan (8 mg/kg/day), and HFD plus xanthene (2 mg/kg/day).

Results: The HFD significantly increased triglycerides, low density lipoprotein-cholesterol (LDL-C), fasting glucose, AST, ALT, ALP, and angiotensin II, while decreasing High density lipoprotein (HDL)-cholesterol, ACE 1-7, adiponectin, and Nrf2 expression ($p < 0.05$). Rosuvastatin, telmisartan, and xanthene significantly ameliorated most abnormalities, pathological changes in adipose tissue. Xanthene showed the greatest improvements in triglycerides, fasting glucose, and liver enzymes, while also favorably affecting LDL-C, angiotensin II, ACE 1-7, adiponectin, and Nrf2. Telmisartan significantly increased body weight ($p < 0.05$).

Conclusion: The present study showed that the HFD induced significant metabolic, hepatic and oxidative disturbances. Rosuvastatin, telmisartan, and xanthene improved most of these abnormalities, with xanthene showing particularly favorable effects on triglycerides, fasting glucose, liver enzymes, Nrf2, angiotensin II, ACE 1-7, and adiponectin. Overall, xanthene demonstrated broad protective effects and, in several parameters, efficacy comparable or superior to standard treatments.

Keywords: Xanthene; Hyperlipidemia; High-fat diet; Nrf2

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INTRODUCTION

Hyperlipidemia is characterized by elevated serum levels of cholesterol, triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) (1).

Hyperlipidemia exerts widespread effects on multiple organ systems through mechanisms involving lipid accumulation, oxidative stress, endothelial dysfunction, and chronic inflammation. In the cardiovascular system, it accelerates atherosclerosis, hypertension, and coronary artery disease (2).

In the liver, excessive lipid deposition contributes to hepatic steatosis, non-alcoholic fatty liver disease (NAFLD), and progression toward steatohepatitis and fibrosis (3,4).

In the pancreas, lipotoxicity impairs β -cell function, aggravating insulin resistance and increasing the risk of type 2 diabetes (5).

Angiotensin-converting enzyme 2 (ACE2) is a counter-regulatory enzyme within the renin–angiotensin system (RAS) that degrades Ang II to angiotensin-(1–7), thereby exerting vasodilatory, anti-inflammatory, and anti-fibrotic effects (7). Thus, ACE2 activity provides vascular protection and helps prevent hyperlipidemia and atherosclerosis. Conversely, depletion of ACE2 and

overproduction of Ang II exacerbate vascular dysfunction, promoting hyperlipidemia and its related complications (8). Adiponectin is an adipocyte-derived hormone that plays an important role in lipid and glucose metabolism and cardiovascular homeostasis. Its levels are generally reduced in obesity and high-fat diet (HFD)-induced metabolic disturbances, contributing to insulin resistance, dyslipidemia, inflammation, and cardiovascular dysfunction. Therefore, modulation of adiponectin may provide a protective effect against HFD-induced metabolic abnormalities (9).

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a key regulator of cellular antioxidant defense. activation of Nrf2 enhances the expression of antioxidant and cytoprotective genes, thereby limiting oxidative stress. Impaired Nrf2 signaling has been implicated in obesity, dyslipidemia, and HFD-induced metabolic and cardiovascular complications (10).

Despite the established involvement of the renin–angiotensin system, adiponectin, and Nrf2 in metabolic and cardiovascular dysfunction, the potential role of xanthene in modulating these pathways in HFD-induced hyperlipidemia remains unclear. Thus, further investigation

is warranted to elucidate whether xanthene exerts its protective effects through modulation of the Ang II/Ang-(1–7) balance, adiponectin, and Nrf2 signaling.

MATERIALS AND METHODS

Study design and experimental animals

This experimental controlled animal study was conducted using 40 healthy adult male albino rats weighing 150–170 g. Animals were obtained from the Animal House, Faculty of Pharmacy, Cairo University, Egypt, and housed under standard laboratory conditions ($21 \pm 2^\circ\text{C}$, 12-hour light/dark cycle, 50–60% humidity) with free access to food and water. Animals were acclimatized for two weeks before the experiment. All procedures complied with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals and were approved by the Institutional Animal Ethics Committee, Faculty of Science, Beni-Suef University (Approval No. 022-264).

Drugs and experimental protocol

Xanthene (9-xanthene; Sigma-Aldrich, USA) was suspended in 1% Tween 80 and administered subcutaneously at 2 mg/kg/day. Rosuvastatin (Crestor®, AstraZeneca) was administered orally at 10 mg/kg/day, and telmisartan (Micardis®, Boehringer Ingelheim) was administered orally at 8 mg/kg/day. Hyperlipidemia was induced using a high-fat diet (58% fat, 25% protein, and 17% carbohydrate). Treatments were continued daily for four weeks.

Experimental groups

Animals were randomly divided into five groups (n=8 each): Control group: standard chow and vehicle, HFD group: high-fat diet only, Rosuvastatin group: HFD plus

rosuvastatin (10 mg/kg/day), Telmisartan group: HFD plus telmisartan (8 mg/kg/day) and Xanthene group: HFD plus xanthene (2 mg/kg/day).

Biochemical assessment

At the end of the treatment period, rats were fasted overnight and blood samples were collected from the retro-orbital venous plexus under anesthesia. Serum was separated by centrifugation and stored at -20°C until analysis. Serum triglycerides, HDL-C, LDL-C kits were obtained from BioSystems S.A, fasting blood glucose kits obtained from Spinreact, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), angiotensin II (Ang II), and angiotensin-(1–7) kits were obtained from Fine Test, adiponectin kits obtained from Elabscience, United States and measured using commercially available assay kits according to the manufacturers' instructions. Also western blot analysis was done in adipose tissue for measurement of Nrf2 obtained from Santa Cruz Biotechnology, United States, also histopathological examinations were also conducted on adipose tissue to assess the extent of tissue damage and the cellular changes induced by the treatments.

Statistical analysis

Data were expressed as mean $\pm$ SD. Statistical analysis was performed using GraphPad Prism software. Comparisons among groups were conducted using one-way ANOVA followed by Tukey's post hoc test. Probability (p) value <0.05 was considered statistically significant

RESULTS

Table (1): Comparison between the studied groups regarding body weight.

Groups	Body weight before (Mean $\pm$ SD)	Body weight after (Mean $\pm$ SD)	P value
Group1 (control group) (n= 8)	144.666 $\pm$ 10.954	149.777 $\pm$ 14.805	0.452
Group 2 (high fat diet group) (n= 8)	152.200 $\pm$ 14.320	142.800 $\pm$ 12.925	0.068
Group 3 (Rosuvastatin administered group) (n= 8)	138.700 $\pm$ 11.832	141.600 $\pm$ 16.222	0.682
Group 4 (Telmisartan administered group) (n= 8)	138.200 $\pm$ 12.209	156.000 $\pm$ 9.298	0.021
Group 5 (Xanthene administered group) (n= 8)	142.777 $\pm$ 10.639	140.888 $\pm$ 20.404	0.698

The used test was tukey post hoc ANOVA test p value is significant when ≤ 0.05 . p value calculated by Paired sample t-t

There was no significant difference between Xanthene administrated group, high fat diet group, Rosuvastatin administrated group (p value > 0.05). but there was significant increase in Telmisartan administrated group regarding body weight p value =.021 (Table 1).

Table (2): Comparison between the studied groups regarding serum triglycerides, HDL-C, and LDL-C levels.

Groups	Triglycerides (mg/dl) (Mean $\pm$ SD)	HDL-C (mg/dl)	LDL-C (mg/dl)
Group1 (control group) (n= 4)	95.182 $\pm$ 7.022	51.130 $\pm$ 3.431 ^{b d}	52.587 $\pm$ 11.041 ^{b c d}
Group 2 (high fat diet group) (n= 4)	296.422 $\pm$ 6.618 ^{a c d}	31.100 $\pm$ 0.937 ^{a b d}	190.907 $\pm$ 10.002 ^{a c d}
Group 3 (Rosuvastatin administered group) (n= 4)	211.262 $\pm$ 10.151 ^{a b d}	45.650 $\pm$ 5.406 ^b	97.727 $\pm$ 7.500 ^{a b d}
Group 4 (Telmisartan administered group) (n= 4)	204.210 $\pm$ 8.246 ^{a b c}	39.720 $\pm$ 3.543 ^{a b d}	138.337 $\pm$ 7.736 ^{a b c}
Group 5 (Xanthene administered group) (n= 4)	178.127 $\pm$ 3.410 ^{a b c d}	48.587 $\pm$ 2.671 ^{b d}	102.897 $\pm$ 3.690 ^{a b d}
Test	F=378.221	F=20.824	151.200
p value	<0.001	<0.001	<0.001

The used test was Tukey post hoc ANOVA test. p value is significant when ≤ 0.05 . a: significant difference from the control group. b: significant difference from the high-fat diet group. c: significant difference from the Rosuvastatin administered group. d: significant difference from the Telmisartan administered group.

The results showed significant differences among the studied groups regarding triglyceride levels ($F = 378.221$, $p < 0.001$), HDL levels ($F = 20.824$, $p < 0.001$), and LDL levels ($F = 151.200$, $p < 0.001$). The high-fat diet caused a significant increase in triglyceride and LDL levels and a significant decrease in HDL levels compared with the control group ($p < 0.05$). Administration of rosuvastatin, telmisartan, and xanthene resulted in a significant reduction in triglyceride and LDL levels and a significant increase in HDL levels compared with the high-fat diet group ($p < 0.05$). No significant difference was observed in triglyceride levels between the rosuvastatin- and telmisartan-treated groups ($p > 0.05$), while the xanthene-

treated group showed a significant reduction in triglyceride levels compared with both the rosuvastatin- and telmisartan-treated groups ($p < 0.05$). Regarding HDL, the telmisartan-treated group showed a significant decrease compared with the control and xanthene groups ($p < 0.05$), while no significant differences were observed between the rosuvastatin-treated group and the other groups ($p > 0.05$). Regarding LDL, the rosuvastatin- and xanthene-treated groups showed significantly lower levels compared with the telmisartan-treated group ($p < 0.05$), while no significant difference was observed between the rosuvastatin- and xanthene-treated groups ($p > 0.05$). (Table 2)

Table (3): Comparison between the studied groups regarding FBG.

Groups	FBG (mg/dl) (Mean $\pm$ SD)
Group1 (control group) (n= 4)	86.107 $\pm$ 9.940
Group 2 (high fat diet group) (n= 4)	358.257 $\pm$ 8.170 ^{a c d}
Group 3 (Rosuvastatin administered group) (n= 4)	255.265 $\pm$ 12.243 ^{a b}
Group 4 (Telmisartan administered group) (n= 4)	246.805 $\pm$ 10.083 ^{a b}
Group 5 (Xanthene administered group) (n= 4)	215.625 $\pm$ 4.350 ^{a b c d}

A high-fat diet caused a significant increase in fasting blood glucose (FBG) levels compared with the control group (p value < 0.05). Administration of rosuvastatin resulted in a significant reduction in FBG levels compared with the high-fat diet group (p value < 0.05). Telmisartan administration produced a significantly greater decrease in FBG levels

compared with both the high-fat diet and rosuvastatin-treated groups (p value < 0.05). Moreover, the xanthene-treated group exhibited significantly lower FBG levels than the high-fat diet, rosuvastatin-treated, and telmisartan-treated groups (p value < 0.05). (Table 3).

Table (4): Comparison between the studied groups regarding liver enzymes (AST, ALT, and ALP).

Groups	AST (U/L) (Mean $\pm$ SD)	ALT (U/L) (Mean $\pm$ SD)	ALP (U/L) (Mean $\pm$ SD)
Group1 (control group) (n= 4)	32.850 $\pm$ 2.432	26.4525 $\pm$ 1.957	71.942 $\pm$ 5.324
Group 2 (high fat diet group) (n= 4)	102.245 $\pm$ 2.330 ^{a c d}	82.335 $\pm$ 1.839 ^{a c d}	223.912 $\pm$ 5.106 ^{a c d}
Group 3 (Rosuvastatin administered group) (n= 4)	72.855 $\pm$ 3.494 ^{a b}	58.682 $\pm$ 2.819 ^{a b}	159.542 $\pm$ 7.653 ^{a b}
Group 4 (Telmisartan administered group) (n= 4)	70.435 $\pm$ 2.877 ^{a b}	56.722 $\pm$ 2.283 ^{a b}	154.255 $\pm$ 6.302 ^{a b}
Group 5 (Xanthene administered group) (n= 4)	61.422 $\pm$ 1.1759 ^{a b c d}	49.482 $\pm$ 0.946 ^{a b c d}	134.765 $\pm$ 2.717 ^{a b c d}
Test	F=373.363	F=378.150	F=371.351
p value	<0.001	<0.001	<0.001

The used test was Tukey post hoc ANOVA test. P value is significant when ≤ 0.05 . a: significant difference from the control group. b: significant difference from the high-fat diet group. c: significant difference from the Rosuvastatin administered group. d: significant difference from the Telmisartan administered group.

The results showed significant differences among the studied groups regarding AST ($F = 373.363$, $p < 0.001$), ALT ($F = 378.150$, $P < 0.001$), and ALP ($F = 371.351$, $p <$

0.001). A high-fat diet caused a significant increase in AST, ALT, and ALP levels compared with the control group ($p < 0.05$). Administration of rosuvastatin and telmisartan resulted in a significant reduction in AST, ALT, and ALP levels compared with the high-fat diet group ($p < 0.05$). Moreover, xanthene administration resulted in a significantly greater reduction in AST, ALT, and ALP levels compared with the high-fat diet, rosuvastatin-treated, and telmisartan-treated groups ($p < 0.05$). (Table 4)

Table (5): Comparison between the studied groups regarding serum Angiotensin II (AG II) and ACE 1-7 levels.

Groups	AG II (pg/ml) (Mean ±SD)	ACE 1-7 (pg/ml) (Mean ±SD)
Group1 (control group) (n= 4)	36.875 ± 3.569	96.775 ± 21.878
Group 2 (high fat diet group) (n= 4)	168.550 ± 13.417 ^{a c d}	23.750 ± 7.209 ^{a c d}
Group 3 (Rosuvastatin administered group) (n= 4)	63.275 ± 12.217 ^{a b d}	81.175 ± 17.611 ^{b d}
Group 4 (Telmisartan administered group) (n= 4)	108.750 ± 16.901 ^{a b c}	55.075 ± 5.855 ^{a b c}
Group 5 (Xanthenone administered group) (n= 4)	76.400 ± 22.548 ^{a b d}	73.475 ± 5.3680 ^{a b d}
Test	F=45.066	F=17.356
p value	<0.001	<0.001

The used test was Tukey post hoc ANOVA test. p value is significant when ≤ 0.05 . a: significant difference from the control group. b: significant difference from the high-fat diet group. c: significant difference from the Rosuvastatin administered group. d: significant difference from the Telmisartan administered group.

The results showed significant differences among the studied groups regarding AG II ($F = 45.066$, $p < 0.001$) and ACE 1-7 ($F = 17.356$, $p < 0.001$). Angiotensin II (AG II) levels were significantly increased in the high-fat diet group compared with the control group ($p < 0.05$). Treatment with rosuvastatin, telmisartan, or xanthenone significantly reduced AG II levels compared with the high-fat diet group

($p < 0.05$). AG II levels were significantly lower in the rosuvastatin-treated group than in the telmisartan-treated group ($p < 0.05$), while no significant difference was observed between the xanthenone- and rosuvastatin-treated groups ($p > 0.05$). Xanthenone also showed significantly lower AG II levels compared with the telmisartan-treated group ($p < 0.05$). Regarding ACE 1-7, the high-fat diet group showed a significant decrease in ACE 1-7 levels compared with the control group ($p < 0.05$). Rosuvastatin, telmisartan, and xanthenone significantly increased ACE 1-7 levels compared with the high-fat diet group ($p < 0.05$). (Table 5)

Table (6): Comparison between the studied groups regarding serum Adiponectin.

Groups	Adiponectin (µg/ml) (Mean ±SD)
Group1 (control group) (n= 4)	3.371 ± 0.607
Group 2 (high fat diet group) (n= 4)	1.455 ± 0.129 ^{a c}
Group 3 (Rosuvastatin administered group) (n= 4)	2.266 ± 0.290 ^{a b}
Group 4 (Telmisartan administered group) (n= 4)	1.928 ± 0.098 ^a
Group 5 (Xanthenone administered group) (n= 4)	2.223 ± 0.323 ^{a b}

The used test was tukey post hoc ANOVA test p value is significant when ≤ 0.05 . a: significant difference from the control group. b: significant difference from the high fat diet group. c: significant difference from the Rosuvastatin administered group.

Adiponectin levels were significantly reduced in the high-fat diet group compared with the control group (p value < 0.05). Administration of rosuvastatin and xanthenone significantly increased adiponectin levels relative to the high-fat diet group (p value < 0.05). In contrast, telmisartan treatment did not produce a significant change in

adiponectin levels compared with the high-fat diet group (p value > 0.05). However, no statistically significant differences in adiponectin levels were observed among the xanthenone-treated, rosuvastatin-treated, and telmisartan-treated groups (p value > 0.05). (Table 6)

Table (7): Comparison between the studied groups regarding Nrf 2.

Groups	Nrf 2 (relative to B actin) (Mean ±SD)
Group1 (control group) (n= 3)	1.100 ± 0.100
Group 2 (high fat diet group) (n= 3)	0.164 ± 0.127 ^{a c d}
Group 3 (Rosuvastatin administered group) (n= 3)	1.035 ± 0.085 ^{b d}
Group 4 (Telmisartan administered group) (n= 3)	0.504 ± 0.074 ^{a b c}
Group 5 (Xanthenone administered group) (n= 3)	0.906 ± 0.184 ^{b d}

The used test was tukey post hoc ANOVA test p value is significant when ≤ 0.05 . a: significant difference from the control group. b: significant difference from the high fat diet group. c: significant difference from the Rosuvastatin administered group. d: significant difference from the Telmisartan administered group. Western blot analysis showed that Nrf2 protein expression was significantly decreased in the high-fat diet group

compared with the control group ($p < 0.05$). Treatment with rosuvastatin, telmisartan, and xanthenone significantly increased Nrf2 expression versus the high-fat diet group ($p < 0.05$). Nrf2 expression was significantly higher with rosuvastatin and xanthenone than with telmisartan ($p < 0.05$), while no significant difference was observed between xanthenone and rosuvastatin ($p > 0.05$). (Table 7)

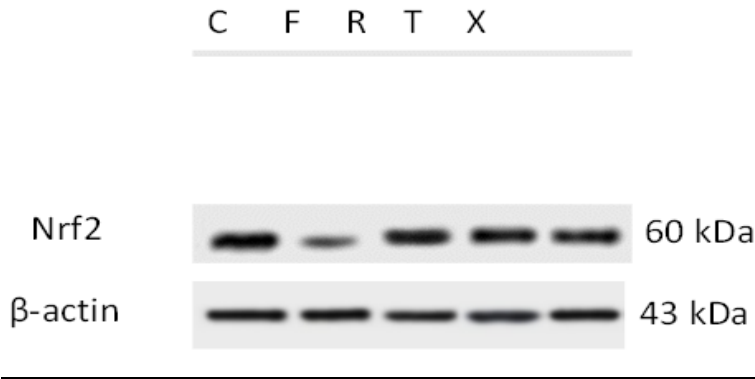


Figure (1): Nrf2 Western Blot analysis in adipose tissue.

Pathological results

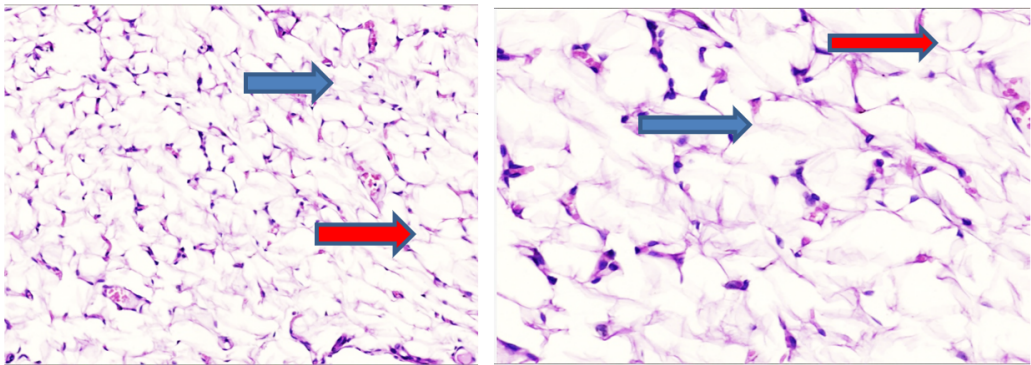


Figure (2): Normal adipose tissue showing normal mature fat cells (blue arrow) separated by delicate fibrovascular connective tissue septa (red arrow) (H&E x200, 400)

Histological examination of adipose tissue sections from the normal control group, stained with hematoxylin and eosin (H&E), revealed normal adipose tissue architecture characterized by mature adipocytes separated by delicate fibrovascular connective tissue septa. (Figure 2)

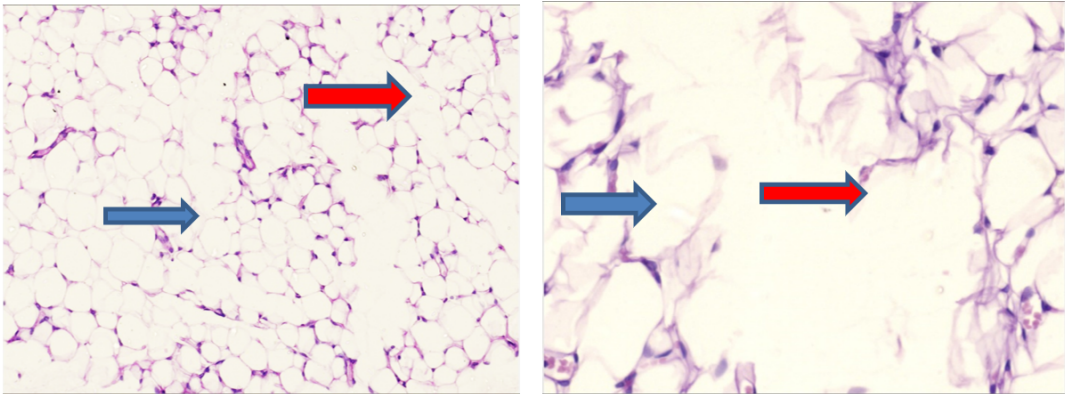


Figure (3): Diseased adipose tissue showing enlarged fat cells with cystic dilatation (blue arrow) separated by delicate fibrovascular connective tissue septa (red arrow) (H&E x200, 400).

In contrast, induction of hyperlipidemia by a high-fat diet resulted in marked pathological alterations in adipose tissue, including pronounced adipocyte hypertrophy with cystic dilatation, while the fibrovascular septa remained evident. (Figure 3)

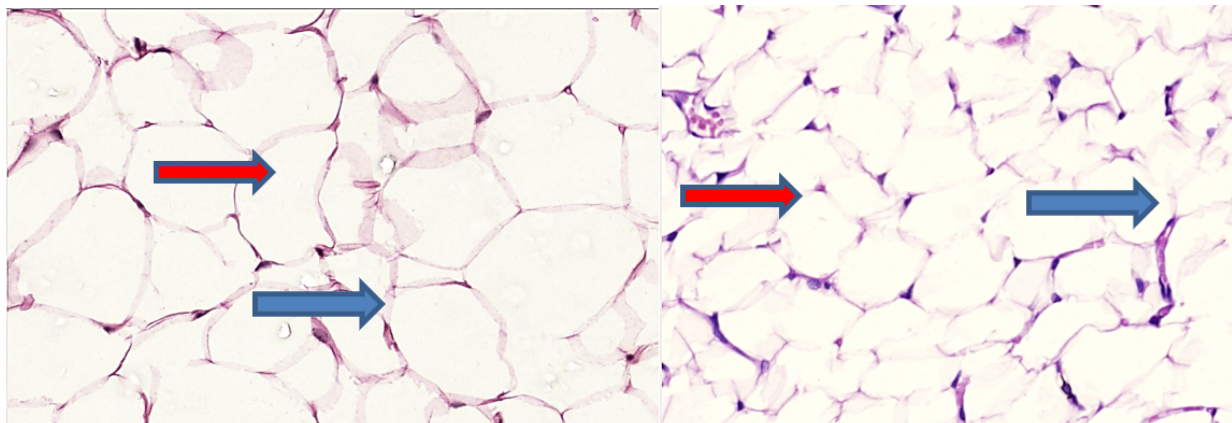


Figure (4): Adipose tissue treated by R drug on the left side and by T drug on the right side showing residual enlarged fat cells (red arrow) separated by delicate fibrovascular connective tissue septa (blue arrow) (H&E x400).

Adipose tissue sections from both rosuvastatin-treated and telmisartan-treated groups demonstrated partial histological improvement, showing residual enlarged adipocytes separated by delicate fibrovascular connective tissue septa. (Figure 4)

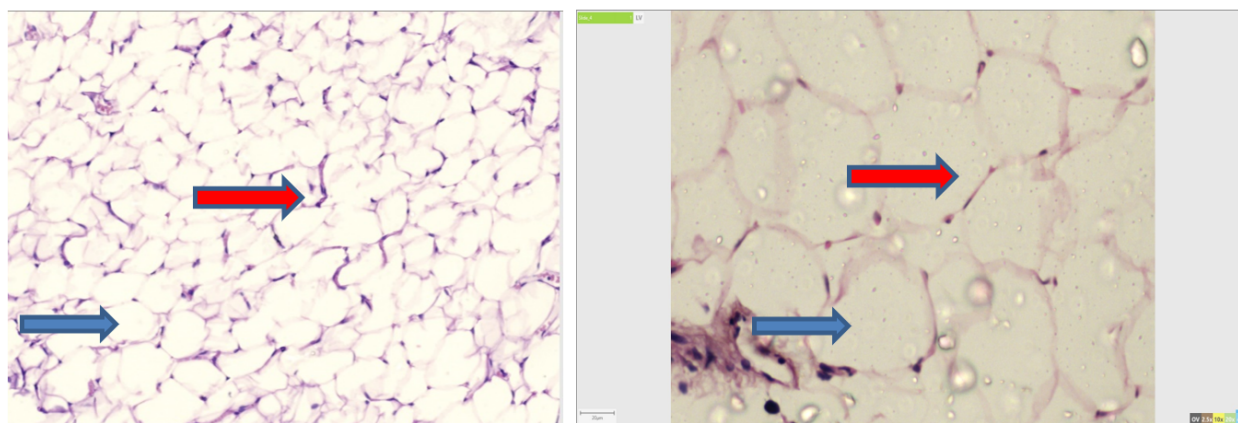


Figure (5): Adipose tissue treated by x drug showing regenerated fat cells (blue arrows) separated by delicate fibrovascular connective tissue septa (red arrows) (H&E x 200, 400).

Notably, adipose tissue from the xanthenone-treated group exhibited marked histological recovery, with regenerated adipocytes and restoration of near-normal adipose tissue architecture. (Figure 5)

DISCUSSION

In the present study, assessment of body weight revealed that administration of a HFD did not result in a statistically significant change in body weight. Similarly, no significant changes in body weight were observed following treatment in all experimental groups, except for the telmisartan-treated group, which demonstrated a significant increase in body weight.

In the present study, significant differences among the studied groups regarding triglyceride levels ($F = 378.221$, $P < 0.001$), HDL-C levels ($F = 20.824$, $p < 0.001$), and LDL-C levels ($F = 151.200$, $p < 0.001$). The HFD caused a significant increase in triglyceride and LDL-C levels and a significant decrease in HDL-C levels compared with the control group ($p < 0.05$). Administration of rosuvastatin, telmisartan, and xanthenone resulted in a significant reduction in triglyceride and LDL-C levels and a significant increase in HDL-C levels compared with the high-fat diet group ($p < 0.05$). No significant difference was observed in

triglyceride levels between the rosuvastatin- and telmisartan-treated groups ($p > 0.05$), while the xanthenone-treated group showed a significant reduction in triglyceride levels compared with both the rosuvastatin- and telmisartan-treated groups ($p < 0.05$). Regarding HDL-C, the telmisartan-treated group showed a significant decrease compared with the control and xanthenone groups ($p < 0.05$), while no significant differences were observed between the rosuvastatin-treated group and the other groups ($p > 0.05$). Regarding LDL-C, the rosuvastatin- and xanthenone-treated groups showed significantly lower levels compared with the telmisartan-treated group ($p < 0.05$), while no significant difference was observed between the rosuvastatin- and xanthenone-treated groups ($p > 0.05$). In the present study, Rosuvastatin was found to control dyslipidemia and insulin resistance induced by HFD. Our findings were in line with the study of Al-Kuraishy and Al-Gareeb. (6) about the effects of rosuvastatin on metabolic profile. They demonstrated that high fat diet group showed

a significant increase in total cholesterol (TC), LDL-C, and TG serum levels ($P = 0.001$), and decrease in HDL-C level ($p = 0.001$) compared to the control. Also, HFD mice showed significant increase in the fasting glucose compared to the control ($p = 0.0001$ and $p = 0.05$), respectively. In addition, HFD mice showed significant increase in the insulin resistance with decrease in β -cell function and insulin sensitivity ($p < 0.05$). Treatment with rosuvastatin caused a significant decrease in LDL-C, TC and TG either at 20 mg/kg or 40 mg/kg ($p = 0.001$). There was significant increase in HDL-C levels in the treated groups ($P = 0.28$). Fasting blood glucose was high in HFD 20 mg/kg (171.00 ± 24.98 mg/dl) ($p = 0.001$) and low in rosuvastatin 40 mg/kg (124.71 ± 13.66 mg/dl) compared to HFD mice ($p = 0.09$). Rondi et al. (7) showed that in the diabetic rats, there was a significant and pathological abnormality in the levels of serum lipids (LDL-C, HDL-C, and triglycerides) when compared with normal control. Treatment with rosuvastatin alone significantly ($p < 0.05$) decreased the levels of LDL-C and the triglycerides, whereas rendered no significant improvement in the levels of HDL-C when compared with diabetic control.

Telmisartan also modulates lipid metabolism by lowering total cholesterol, triglycerides, and LDL-C, while slightly increasing HDL cholesterol. Its anti-inflammatory and antioxidant effects protect pancreatic β -cells and enhance insulin signaling pathways, leading to better glycemic control and lipid profile regulation (8).

Rosuvastatin primarily exerts its metabolic benefits by inhibiting HMG-CoA reductase, reducing cholesterol biosynthesis in the liver, resulting in decreased LDL-C and triglycerides, and increased HDL-C. Beyond lipid lowering, rosuvastatin reduces systemic inflammation and oxidative stress, which improves insulin sensitivity and β -cell function. Its hydrophilic nature allows targeted hepatic action with fewer drug interactions, enhancing overall metabolic homeostasis in dyslipidemia and insulin resistance. The combination of rosuvastatin and telmisartan addresses complementary metabolic pathways, making them effective in controlling high-fat diet-induced glucose and lipid abnormalities (11).

Xanthenone may improve lipid metabolism primarily through its potent antioxidant and anti-inflammatory properties. It activates the Nrf2 signaling pathway, resulting in upregulation of antioxidant enzymes that attenuate oxidative stress, a key contributor to dyslipidemia and lipid peroxidation. By reducing oxidative damage, xanthenone limits hepatic lipid accumulation and attenuates hepatic steatosis. Furthermore, it improves serum lipid profile by decreasing total cholesterol, triglycerides, and LDL-C while increasing HDL-C. These mechanisms collectively support the protective role of xanthenone against high-fat diet-induced dyslipidemia and its associated metabolic complications.

Assessment of LFTs in the present study showed significant differences among the studied groups regarding AST ($F = 373.363$, $p < 0.001$), ALT ($F = 378.150$, $p < 0.001$), and ALP ($F = 371.351$, $p < 0.001$). A high-fat diet caused a significant increase in AST, ALT, and ALP levels compared with the control group ($p < 0.05$). Administration of rosuvastatin and

telmisartan resulted in a significant reduction in AST, ALT, and ALP levels compared with the high-fat diet group ($p < 0.05$). Moreover, xanthenone administration resulted in a significantly greater reduction in AST, ALT, and ALP levels compared with the HFD, rosuvastatin-treated, and telmisartan-treated groups ($p < 0.05$). According to Cao et al. (12), the levels of ALT and AST in serum of HFD rats in their experiment were significantly higher than those of NFD ($p < 0.05$). Also, Jing et al. (2022) revealed that high-fat diet in rats drastically enhanced the levels of AST (131.0 ± 5.507 U/L), ALT (81.0 ± 5.507 U/L), and ALP (165.67 ± 5.783 U/L). The above two findings were consistent with the present study.

The effect of Rosuvastatin on liver functions evaluated by the study of El-Din et al. (13) was comparable to our findings. They reported that the serum levels of ALT, AST, ALP and GGT were significantly increased ($p < 0.05$) in non-alcoholic fatty liver disease induced by high fat diet (NAFLD-HFD) when compared with normal control group. When compared with control group, serum levels of ALT, AST, ALP and GGT were significantly decreased ($p < 0.05$) in the groups treated with Rosuvastatin.

Rosuvastatin alleviates liver injury by inhibiting cholesterol synthesis and reducing systemic inflammation, leading to decreased levels of ALT, AST, ALP, and GGT in liver disease models (13).

In the present study, significant differences among the studied groups regarding AG II ($F = 45.066$, $p < 0.001$) and ACE 1-7 ($F = 17.356$, $P < 0.001$). AG II levels were significantly increased in the HFD compared with the control group ($p < 0.05$). Treatment with rosuvastatin, telmisartan, or xanthenone significantly reduced AG II levels compared with the HFD group ($p < 0.05$). AG II levels were significantly lower in the rosuvastatin-treated group than in the telmisartan-treated group ($p < 0.05$), while no significant difference was observed between the xanthenone- and rosuvastatin-treated groups ($p > 0.05$). Xanthenone also showed significantly lower AG II levels compared with the telmisartan-treated group ($p < 0.05$). Regarding ACE 1-7, the HFD group showed a significant decrease in ACE 1-7 levels compared with the control group ($p < 0.05$). Rosuvastatin, telmisartan, and xanthenone significantly increased ACE 1-7 levels compared with the HFD group ($p < 0.05$). -(1-7). These adverse cardiovascular alterations were markedly reversed by treatment with xanthenone, rosuvastatin, and telmisartan. Intergroup comparisons demonstrated that xanthenone was more effective than telmisartan and exhibited efficacy comparable to rosuvastatin in reducing angiotensin II levels and increasing angiotensin-(1-7) concentrations. The above findings were confirmed in the study of Meeapat et al. (14) who found that HF diet plus 15% fructose solution induced cardiac dysfunction and remodeling as shown by Increases in ACE activity, serum Ang II concentrations and expression of AT1 receptor.

The improvement in Ang II and Ang (1-7) levels following administration of rosuvastatin explained by decreases Ang II levels by improving endothelial function and reducing systemic inflammation, while simultaneously increasing

Ang (1-7), thereby contributing to improved vascular health and reduced fibrosis (15).

Several experimental studies have evaluated the effects of xanthenone on the angiotensin II / ACE2/angiotensin-(1-7) axis and reported findings that are consistent with the present results. Abdel-Fattah et al. (16) investigated the ameliorative effect of xanthenone against gentamicin-induced nephrotoxicity in rats and demonstrated that gentamicin significantly decreased ACE2 and Ang-(1-7) expression (to 59.5% and 51.7%, respectively), while markedly increasing Ang II expression to 1.9-fold compared with the normal control group. Pre-administration of xanthenone (2 mg/kg, s.c.) significantly reversed these alterations, increasing ACE2 and Ang-(1-7) expression to 1.8- and 1.7-fold, respectively, and reducing Ang II expression to 59.2% relative to the gentamicin group.

Similarly, Azouz et al. (17) examined the protective effect of xanthenone against tacrolimus-induced nephrotoxicity and reported that tacrolimus significantly increased renal Ang II levels while reducing Ang-(1-7) content by approximately 129% and 53%, respectively, compared with controls. Co-treatment with xanthenone significantly reduced renal Ang II and increased Ang-(1-7) levels by about 42% and 71%, respectively, compared with the tacrolimus-treated group.

Adiponectin has been found to be highlighted in hyperlipidemia, obesity pathogenesis and its associated complications. Adiponectin serves as a protective factor to prevent hyperlipidemia, obesity occurrence and/or progression by suppressing inflammation, promoting fatty acid oxidation, and improving insulin sensitivity (18).

One of the potential mechanisms underlying the adverse effects of a HFD on lipid and glucose metabolism involves disturbances in adiponectin secretion and free fatty acid (FFA) metabolism. In the present study, HFD feeding resulted in a significant reduction in circulating adiponectin levels accompanied by a significant elevation in free fatty acid concentrations.

Treatment with xanthenone, rosuvastatin, and telmisartan significantly reversed these alterations, as evidenced significant increase in adiponectin levels compared with the HFD group. Intergroup comparisons demonstrated no significant differences between xanthenone, rosuvastatin, and telmisartan with respect to their ability to increase adiponectin levels.

In accordance with our findings several reports showed comparable results regarding the effect of HFD on adiponectin level. Li et al. (19) reported that the level of serum adiponectin was reduced in HFD mice compared with that in the normal control mice.

The impact of high fat diet on oxidative stress could be attributed to its effect on Nrf-2/HO-1/NQO1 pathway. High fat diet caused a significant decrease in the expression of Nrf-2/HO-1/NQO1 expression compared to control group. Xanthenone, Rosuvastatin and Telmisartan reversed the effect of high diet as shown by the significant increase in the expression of Nrf-2. Comparison between groups revealed a higher efficacy of Xanthenone in Nrf-2 expression.

Studies have confirmed that Nrf2 is involved in the control of many oxidative stress-related genes. Nrf2 activates antioxidant factors such as NQO1, HO-1, SOD, and CAT, etc., and also regulates the GSH redox system to inhibit oxidation (20).

Xanthenone exerts its protective and restorative effects on various organs primarily through activation of ACE2. This enzyme converts angiotensin II, a molecule with pro-inflammatory and vasoconstrictive properties, into angiotensin (1-7), which has anti-inflammatory, antioxidant, and vasodilatory effects. By activating ACE2, xanthenone reduces oxidative stress by increasing the activity of transcription factor Nrf2 and influences important molecular pathways which improve endothelial function, decrease cell apoptosis, and protect tissues from injury.

Histopathological examination of rats received high fat diet showed marked degenerative changes, fat accumulation. The adipose tissue showing enlarged fat cells with cystic dilatation separated by delicate fibrovascular connective tissue septa.

In agreement with the present study histological analysis performed by Li et al (19) showed that HFD treatment increased average adipocyte diameters. treatment with rosuvastatin, telmisartan and xanthenone the adipose tissue showed residual enlarged fat cells separated by delicate fibrovascular connective tissue septa.

CONCLUSION

The present study showed that a HFD induced significant metabolic, hepatic and oxidative disturbances. Rosuvastatin, Telmisartan, and Xanthenone improved most of these abnormalities, with Xanthenone showing particularly favorable effects on serum triglycerides, fasting glucose, liver enzymes, AG II, ACE 1-7, and adiponectin as well as visceral adipose tissue Nrf2. Overall, xanthenone demonstrated broad protective effects and, in several parameters, efficacy comparable or superior to standard treatments.

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