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Synergistic effect of ferulic acid and caffeic acid on metabolic syndrome and immune response in rats

Synergistic ferulic and caffeic acids: Metabolic and immune modulation in hfd-fed rats

Nesrin I. Tarbiah[1], Fares K. Khalifa[1,2], Nuha A. Alkhattabi[1], Abeer A. Banjabi[1], Reem F. Ghazali[3], Reem Y. Alzahri[4], Norah Abdu Almerabi[5], Ahd A. Mansour[6]
[1] Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia
[2] Department of Biochemistry and Nutrition, Faculty of Women for Arts Science and Education, Ain Shams University, Cairo, Egypt
[3] Department of Clinical Biochemistry, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
[4] Department of Biology, College of Science, University of Jeddah, Saudi Arabia
[5] Department of Pharma. D, Faculty of Pharmacy, Ibn Sina National College for Medical Studies, Jeddah, Saudi Arabia
[6] Department of Medical Laboratory Sciences, MLS program, Fakeeh College for Medical Sciences, Jeddah, Saudi Arabia

Abstract

Aim: The aim of the study is to evaluate the synergistic modulatory effects of ferulic acid (FA) in combination with caffeic acid (CA) on the immune response and metabolic syndrome in male rats fed high-fat diets (HFD).

Material and Methods: Forty-five adult male albino rats (Sprague-Dawley) were divided into five groups: G1, controls fed basal fat diet (BFD); G2, high-fat modified diet containing 20% fat (HFD); G3, rats fed HFD and received FA (150 mg/day) orally; G4, rats fed HFD supplemented with CA (0.8 g/ 100 g diet), and G5, Rats fed HFD and received both FA (150 mg/day) and CA (0.8 g/ 100 g diet).

Results: Serum concentrations of TG, TC, LDL-c, glucose, insulin, oxidative stress biomarkers, and proinflammatory cytokines were elevated in rats fed a high-fat diet compared with the BFD group. Significant adjustments were observed after the administration of FA and CA. The maximum improvement was viewed in rats administered with CA in combination with FA.

Discussion: FA and CA significantly counteracted the pronounced oxidative stress effect of HFD by the inhibition of lipid peroxidation, restoration of antioxidant status, and metabolic syndrome biomarker levels. In conclusion, these findings indicate the synergistic protective effect of FA and CA on risk factors that can lead to metabolic syndrome and immune response imbalance during HFD-associated oxidative stress in rats.

Keywords

High-Fat Diet, Metabolic Syndrome, Immune Response, Oxidative Stress, Caffeic Acid, Ferulic Acid, Phenolic Acids

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Corresponding Author: Nesrin I. Tarbiah, Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia.
E-mail: ntarabah@kau.edu.sa P: +96 650 567 12 53
Corresponding Author ORCID ID: https://orcid.org/0000-0002-8706-2663
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Introduction

Metabolic syndrome (MetS) is a condition where the body metabolizes proteins, fats, carbohydrates, and other substances in a disorderly manner. It is characterized by a combination of risk factors, including diabetes, high cholesterol levels, high blood pressure and obesity [1]. The primary culprits behind MetS are lifestyles and unhealthy eating habits like consuming high-calorie diets. It is proved that 20 -30% of adults are affected by MetS [2]. Therefore, it is crucial to identify strategies to combat this issue. Extensive research has demonstrated that incorporating wholegrain foods and dietary fiber into our diets can have positive impacts on lowering the risk of MetS and its correlated disorders [3].

Nutritional supplements frequently contain phenolic acids, like caffeic acid (CA) and ferulic acid (FA), which are characterized by antioxidant properties, hypoglycemic, hypolipidemic [4,5], anti-inflammatory, and immunomodulatory roles [6]. FA is a phenolic acid compound, found in cereals, fruits, vegetables, and other edible plants [7]. It is recognized for its anti-inflammatory properties, which contribute to its ability to perform several beneficial functions in the body. These include regulating glucose tolerance and lipid metabolism, which leads to improving liver health [8].

CA is a secondary metabolite that is derived from natural sources, such as olives, berries, potatoes, and carrots, also it is predominantly obtained from coffee beans. It belongs to the family of hydroxycinnamic acid, which is a major constituent of the daily human diet [9]. Numerous in vitro and in vivo experiments demonstrated that CA possesses anti-atherosclerotic, immunostimulant, cardioprotective anti-proliferative benefits [10] as well as its ability to improve inflammation and oxidative stress in chronic metabolic diseases. The strategy of synergistic effects aims to enhance potency through treatment with a combination of therapeutic agents. Successful combinations involving agents and natural products can effectively attain desired outcomes while reducing toxicity levels [11]. Based on this, the aim of this study is to examine the synergistic modulatory effects of FA in combination with CA on the immune response and MetS in male rats fed high-fat diets (HFD).

Material and Methods

Ethical approval

The study was conducted from March 2023 to May 2023. The Research Ethics Committee of Ain Shams University evaluated and approved the experimental procedures of this study (Code sci1432309001) before starting the experiment (1 March 2023).

Chemicals

CA (≥95%) was purchased from Sigma-Aldrich (St Louis, MO, USA.). FA (purity >98%) was purchased from Source Naturals Co., Miami, FL, USA. Commercial assay kits including glucose, total cholesterol (TC), triacylglycerols (TG), high-density lipoprotein-cholesterol (HDL-c), low-density lipoprotein-cholesterol (LDL-c), free fatty acid (FFA) were obtained from Siemens Healthcare Diagnostics, USA. Malondialdehyde (MDA), superoxide dismutase (SOD), and reduced glutathione (GSH) kits were purchased from BioVision Inc. Co., USA. Insulin, tumor necrosis factor-α (TNF-α), nuclear factor kappa B (NF-kB), interleukine-6 (IL-6), and interferon-γ (IFN-γ) were analyzed by enzyme-linked immunosorbent assay (ELISA) kits obtained from BioVision Inc. Co., USA. Also, pyruvate carboxylases (PC) assay colorimetric kits, and phosphoenol pyruvate carboxy kinase (PEPCK) were purchased from (BioVision Inc. Co., USA).

Animals and Experimental Design

Fifty adult male albino rats (Sprague-Dawley) weighing 127.2-134.3 g were used in this study. Animals were kept in stainless steel cages in an air-conditioned animal house at 24°C and fed a basal diet, allowed water ad libitum throughout the experimental period (8 weeks). The rats were randomly divided into five groups (10 rats/group) as follows:

G1: Rats fed a basal fat diet (BFD).

G2: Rats fed a high fat diet (25%) (HFD).

G3: Rats fed HFD and received FA (150 mg/day) by oral gavage (HFD+FA).

G4: Rats fed HFD supplemented with CA (0.8 g /100 g diet) (HFD+ CA).

G5: Rats fed HFD supplemented with CA (0.8 g /100 g diet) and FA orally (150 mg/day) (HFD +FA + CA).

Sample Collection and Biochemical Assessment:

After eight weeks, blood was drawn from the hepatic portal vein of ether-anesthetized rats that had fasted overnight. Blood tubes were centrifuged at 4000 x g for 15 minutes at 25°C to separate the serum. Serum samples were collected in sterile plastic tubes and kept frozen at -20 ºC for later biochemical testing. The liver was separated, rinsed, and washed with saline solution (NaCl 0.9%), then blotted on filter paper. The liver was rapidly freeze-clamped and stored at -20 ºC for liver enzyme analysis. Liver enzymes (PC and PEPCK) and serum biochemical parameters were determined according to analytical methods. The oral glucose tolerance test (OGTT) was operated on with oral gavage of glucose (2 g/kg b.w.) after 12 hours of fasting on the first day of week eight. Blood glucose concentrations were monitored by the tail blood using a glucometer with one-touch ultra test trips at 0 (before glucose infusion), 30, 60, 90, and 120 (post-infusion) of gavage.

Statistical Analysis

Data were statistically evaluated. Data were presented as mean ± standard error of the mean (SEM), and one-way analysis of variance (1-way ANOVA) test. Differences were considered significant at $P \leq 0.01$.

Results

Serum concentrations of TG, TC, and LDL-c were elevated significantly ($p \leq 0.01$) in rats fed a high-fat diet compared with the BFD group and gradually normalized by FA and CA supplementation. The level of serum HDL-c was significantly lowered ($p \leq 0.01$) in the HFD group compared to BFD and gradually increased by adding FA and CA (G3-G5). The maximum improvement in serum levels of lipid profile was observed in rats administered with CA in combination with FA (Figure 1). Glucose administration raised glucose levels after 30 minutes. Then, it gradually returned to baseline levels within 90 minutes. However, when rats were fed HFD for 56 days, their glucose levels peaked at 30 minutes after receiving glucose. All groups showed normalized blood glucose levels within 60-90 minutes

except for rats fed a high-fat diet (G2). However, when CA was supplemented alone or in combination with FA, blood sugar levels significantly approached normal levels (Figure 2). HFD rats had significantly increased serum FFA, fasting glucose and insulin levels compared with the BFD group (p≤ 0.01). Supplementation of FA combined with CA significantly lowered the values of FFA, glucose and insulin by 45.2%, 26.6 and 22.1.1%, respectively compared with HFD rats (Table 1). Results revealed the reduction of hepatic PC and PEP-CK activities in rats fed HFD (by -28.3% for PC, and -41.3% for PEPCK, respectively) compared to control rats. Supplementation with FA and CA modulated the activities of both enzymes as compared to rats fed a high-fat diet. The maximum improvement in liver activities of both enzymes was observed in rats fed a diet supplemented with CA in combination with FA (by +42.1% for PC, and +58.3% for PEPCK respectively) compared with the HFD group (Table 2). In this study, SOD activity was significantly decreased (p≤ 0.01) in HF diet-fed rats compared to the control group. Serum levels of MDA, GSH, and SOD activities were significantly (p ≤ 0.01) restored by CA and FA supplementation compared with HF diet-fed rats (Figure 3). Compared with the control group, an apparent increase of the values of IFN-γ, TNF-α, IL-6, and

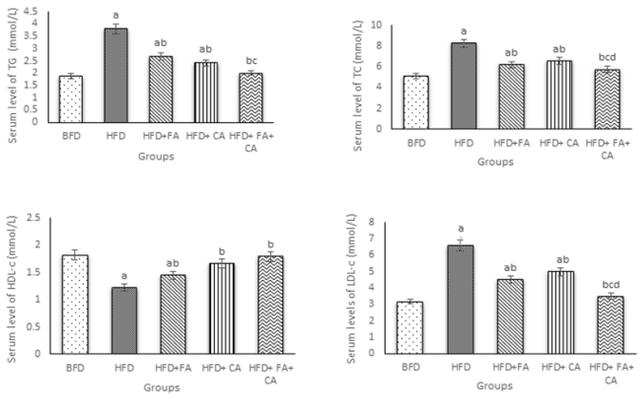

Figure 1. Effect of all treatments on serum lipids profile. BFD: basal fat diet (control); HFD: high fat diet; FA: Ferulic acid; CA: Caffeic acid. Alphabetical superscripts mean: a: significance against control; b: significance against HFD group; c: significance against HFD +FA group; d: significance against HFD + CA.

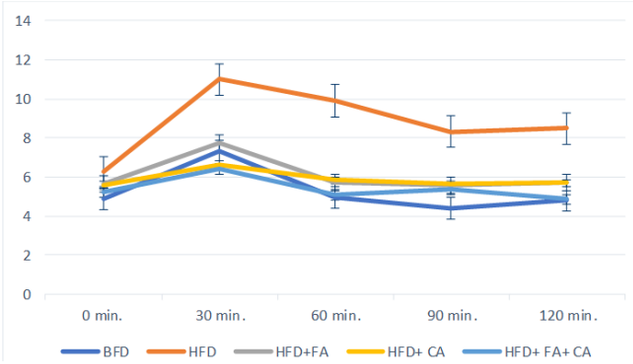

Figure 2. . Oral glucose tolerance test (OGTT) after treatments. BFD: basal fat diet (control); HFD: high-fat diet; FA: Ferulic acid; CA; Caffeic acid.

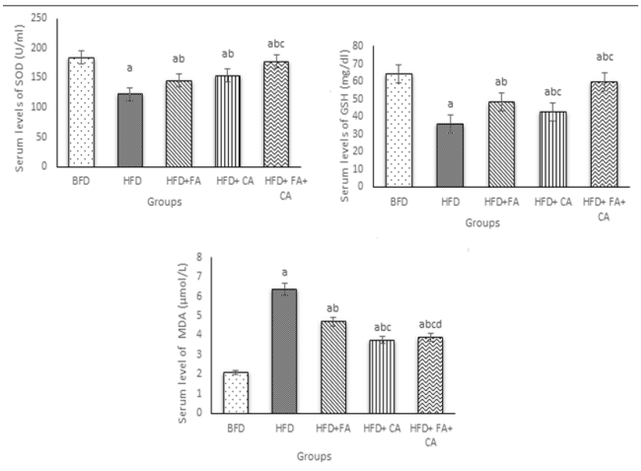

Figure 3. Effect of various treatments on serum levels of oxidative stress biomarkers. BFD: basal fat diet (control); HFD: high-fat diet; FA: Ferulic acid; CA; Caffeic acid. The alphabetical superscripts mean: a: significance against control; b: significance against HFD group; c: significance against HFD +FA group; d: significance against HFD + CA.

Table 1. Effect of various treatments on serum glucose, insulin, and free fatty acids (FFA)

Groups	Glucose (mmol/L)	Insulin (mIU/L)	FFA (µmol/ml)
BFD	4.85±0.75	12.80 ± 0.9	0.830 ±0.08
HFD	6.95 a ±1.01	15.03 a ± 1.1	2.01 a ± 0.05
HFD+FA	5.55 ab ±0.37	10.30 b ± 0.5	1.55 ab ±0.08
HFD+ CA	5.65 ab ±0.45	12.40 bc ± 0.3	1.35 abc ±0.04
HFD+ FA+ CA	5.10 bcd ±0.55	11.70 bc ± 0.8	1.10 bcd ±0.06

Values are expressed as means ± SD. (n= 9), a = significance against control; b= significance against HFD group; c= significance against HFD +FA group; d= significance against HFD + CA. at P ≤ 0.01

Table 2. Effect of various treatments on liver Pyruvate Carboxylase (PC) and Phosphoenolpyruvate Carboxykinase (PEPCK) activities

Groups	PC (Pmol/min/mg protein)	PEPCK (nmol PEP/min/mg protein)
BFD	152.30 ±9.2	72.50 ±3.7
HFD	109.1 a ±7.3	42.5 a ±1.9
HFD+FA	126.5 ab ±8.0	51.3 ab ±5.1
HFD+ CA	136.5 abc ±6.5	53.0 ab ±4.7
HFD+ FA+ CA	155.1 abcd ±9.3	67.3 abcd ±6.9

Values are expressed as mean ± SD. (n= 9), a = significance against control; b= significance against HFD group; c= significance against HFD +FA group; d= significance against HFD + CA. at P ≤ 0.01

Table 3. Effect of various treatments on serum levels of proinflammatory cytokines

Groups	IFN-γ (pg/mL)	TNF-α (pg/ml)	IL-6 (pg/ml)	NF- kB (pg\ml)
BFD	2.95±0.55	8.73 ± 1.1	10.30 ± 0.95	45.0 ±3.03
HFD	10.33 a ±0.41	24.30 a ±4.3	25.00 a ±2.75	99.6 a ±6.50
HFD+FA	7.55 ab ±0.30	16.4 ab 5 ±2.1	15.25 ab ± 1.3	63.34 ab ±7.34
HFD+ CA	6.10 abc ±0.33	12.33 abc ±3.0	15.13 ab ± 1.2	67.1 abc ±5.66
HFD+ FA+ CA	4.20±0.62	8.82 ±2.3	11.25 bcd ± 1.0	55.2 abcd ±4.50

Values are expressed as mean ± SD. (n= 9), a = significance against control; b= significance against HFD group; c= significance against HFD +FA group; d= significance against HFD + CA. at P ≤ 0.01

NF- kB was observed in the HFD group by 3.5, 2.7, 2.4 and 2.2-fold, respectively. The levels of IFN-γ, TNF-α, IL-6, and NF-kB displayed a significant decrease after administration with FA separately or combined with CA. The results postulated that FA combined with CA exhibited an improving effect in HFD-caused inflammation in rats (Table 3).

Discussion

High-fat and high-energy diet is widely recognized as a factor contributing to the onset of various health issues. This study demonstrates that rats administered HFD suffered from glucose intolerance, dyslipidemia, and oxidative stress in their livers with a parallel increase in serum glucose and lipid levels, including cholesterol and triglycerides levels. Dyslipidemia refers to abnormal levels of lipids circulating in the body [12].

Meanwhile, supplementing FA and CA decreased serum lipid levels in the rat group fed high fat, thus avoiding glucose intolerance. Supplementation of CA combined with FA also reduced oxidative stress and lipid peroxidation in both serum and liver by repairing the cellular antioxidants.

Hyperglycemia-related oxidative stress is considered as one of the main reasons for metabolic and hormonal imbalances. Overnutrition may result in insulin resistance in tissues, which generally respond to insulin for glucose uptake [13]. Over time this resistance leads to increased fasting glucose levels and diminished insulin-mediated glucose clearance. As a result, there will be negative feedback signaling inadequate insulin response prompting the pancreatic β-cells to produce more insulin. If this state of insulin resistance persists without correction it eventually causes hyperglycemia and type 2 diabetes that leads to type 2 diabetes [14].

Administering CA and FA enhanced glucose utilization in the current study, as shown by OGTT results, and the results are supported by previous experiments [15]. It was suggested that FA diminished HFD-induced glucose synthesis possibly by suppressing glucose-6-phosphatase, consequently slowing hepatic gluconeogenesis. Furthermore, PC and PEPCK are considered as key enzymes that regulate hepatic gluconeogenesis and glucose production. Results of the present study showed that CA and FA displayed tremendous synergistic effects on modulation of the glucose metabolism by management of PEPCK and PC activities in high fat-fed rats. Son et al. [16] exposed that FA boosted the level of glycogenesis by decreasing PEPCK levels. These results suggest that FA can adjust glucose homeostasis by restoring hepatic glucose metabolism disturbance. A previous study showed that administrating FA reduced insulin resistance and diminished levels of TG, free fatty acids, cholesterol, and phospholipids in rats fed HFD. In addition, the modulatory effect of FA on lipid homeostasis was correlated to decreased lipogenic enzymes such as fatty acid synthase and acetyl-CoA carboxylase [8].

CA elevated insulin sensitivity by reducing proinflammatory cytokines and increasing adiponectin under the hyperglycemic state. One previous work showed that MetS diet in rats increased blood glucose, TG, and LDL-c, and decreased the HDL-c, the group that received CA showed a reduction in serum insulin, TNF-α, and IL-6. Similarly, CA-supplemented rat groups showed the highest liver levels of SOD, CAT, and GPx antioxidant enzymes, after four weeks of caffeic acid administration compared to FA, gallic acid, and protocatechuic acid [17]. This suggests that CA showed high scavenging activity and effectiveness among the recorded phenolic acids that keep against hyperglycemic injuries.

In a recent in vivo study, CA supplementation reduced body weight and prevented fat accumulation on HFD obese mice exposed that CA was able to reduce body weight and fat accumulation also it improved lipid profile with an increased HDL-c [18]. This suggests that CA is capable of reducing FFA production, thus demonstrating its hepatoprotective capability. Results showed that the co-treatment of FA and CA was able to reduce the serum level of TC by 47.1% from the positive control group (HFD), which was much higher than the mono treatment groups (FA by 29.2% and CA by 36.3%). Similarly, the combination of FA and CA reduced the serum level of LDL-c by 47.1% versus 31.1% by FA and 24.5% by CA. Thus, both CA and FA exhibited excellent synergistic effects on modulation of the lipid profile in high-fat-fed rats.

CA has shown potential antihyperglycemic effects. It also possesses antioxidant and anti-inflammatory properties. The protective effects of CA may be attributed to its ability to activate and defend cellular antioxidant enzymes due to its role in transferring hydrogen atoms and single electrons while also chelating metal ions [19]. As demonstrated in the current study, rats fed a high-fat diet had higher levels of the lipid peroxidation product MDA. The decreased SOD activity and GSH observed in the current study could be related to the rise in oxidative stress. According to the findings of this study, there was an increase in MDA levels in rats fed a high-fat diet. This increase was linked to the reduction in activities of SOD and GSH. These results agreed with studies, which suggested that the tissue antioxidant defenses may be compromised when animals are fed a high-fat diet [20].

Administrating FA clearly reduced the MDA production and boosted antioxidant enzymes (SOD and GSH) activities, this enhances scavenging free radicals [21], helping to reduce lipid peroxidation and oxidative stress caused by HFD in the liver. Additionally, the levels of TNF-α, NF- kB, and IL-6 were significantly reduced after FA consumption. Additionally, FA may decrease lipid peroxidation, resulting in decreased levels of MDA and LDL-C [22].

Inflammation develops after ingestion of HFD in the peripheral tissues including the liver, adipose tissue, and skeletal muscles. Alterations in the gut microbiota brought on by HFDs and direct effects of FFAs on intestinal cells may be the initial step in the development of chronic systemic inflammation. The second step may involve increasing intestinal lipopolysaccharide (LPS), pro-inflammatory cytokines, and FFA transport into the systemic circulation and portal circulation, which would result in systemic low-grade inflammation [23]. Elevated serum FFAs and LPS can upregulate the expression of Toll-like receptors in circulating macrophages, allowing macrophage activation, which in turn produces pro-inflammatory cytokines.

In the inflammatory process, cytokines are crucial mediators in the body's immune response. An extremely crucial factor in determining the proper immune response is the interaction between pro-inflammatory and anti-inflammatory cytokines

throughout homeostasis and inflammation associated with diseases. The results of the present study showed that HFD resulted in a significant increase in IFN-γ, TNF-α, IL-6, and NF- kB serum levels. IFNγ is predominantly produced by natural killer T cells during the innate immune response and by CD4+ T helper (Th1) cells and CD8+ cytotoxic T cells in the humoral immune response, that are essential for the detection of tumor cells, immunoregulation, and inflammation [24].

Our experimental results demonstrated that each of CA and FA showed a strong synergistic antioxidant and anti-inflammatory activity. The immunomodulatory role of antioxidants is demonstrated in the capability of these molecules to influence important signaling pathways responsible for inflammation. NF-kB regulates the expression of many genes directly related to inflammation. According to recent research, certain polyphenols can alter the activity of NF-kB and lessen cellular inflammation [25]. Suppression of NF-kB is dependent on the action of polyphenolic compounds. The reduction of the expression of certain pro-inflammatory cytokines is one of the most prevalent ways in whereby polyphenols exert their immunomodulatory effects.

Conclusion

Several disease conditions primarily require combination therapy due to their complex pathophysiology and progression. The combination of CA with different compounds has been widely examined for various types of disorders. CA, owing to its free radical scavenging property, was able to increase the antioxidant efficacy of agents such as FA for better treatment outcomes. As the results of the present study showed, CA was exhibited to be synergistic with FA for modulation of MetS and immune response. Through this study, we can conclude that CA and FA possess excellent promise for managing MetS through their anti-obesity properties, and antidiabetic, and hypolipidemic, activities. Although there are a lot of studies on CA and other phenolic acids, no previous research indicated that CA and FA had synergistic effects against immune disturbance and metabolic implications induced by HFD.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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This study was approved by the Ethics Committee of Ain Shams University evaluated and approved the experimental procedures of this study (Date: 2023-03-01, No: sci1432309001)