

## Effect of curcumin on plasma TBARS and IL-6, adipose tissue AFABP-4 and liver FGF-21 in fructose-induced metabolic syndrome rats

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Elucidation of the positive effects of curcumin on oxidative damage and inflammation, as well as clarifying the parameters related to adipose tissue and liver, would contribute furthermore to literature. Here, we have demonstrated the potential healing effects of curcumin in rats with metabolic syndrome (MetS). Twenty-four adult male Wistar albino rats were selected for the study. Only corn oil was administered to the control group rats, while corn oil and 20% fructose were administered to the MetS group rats for eight weeks. The curcumin dose groups were administered 100 and 200 mg/kg of curcumin dissolved in corn oil along with 20% fructose. Plasma TBARS, IL-6, adipose AFABP-4 and liver FGF-21 levels were determined using the ELISA method. It was observed that plasma TBARS and IL-6 levels were significantly decreased in the 100 and 200 mg/kg curcumin dose groups compared to the MetS group ( $P \leq 0.008$ ). Adipose tissue A-FABP-4 levels in the 200 mg/kg curcumin dose group were significantly decreased compared to the MetS group ( $P \leq 0.008$ ). FGF-21 levels in the 100 mg/kg and 200 mg/kg curcumin dose groups were significantly increased compared to the MetS group ( $P \leq 0.008$ ). The healing effects of curcumin administration on MetS were effective on inflammation and lipid peroxidation. Curcumin administration decreased the adipose tissue AFABP-4 levels and increased the liver FGF-21 levels.

**Keywords:** *Curcuma longa*, Fructose administration, Inflammation, Oxidative stress, Turmeric

Metabolic syndrome (MetS) refers to a combination of conditions, including visceral obesity, hypertension, atherogenic dyslipidemia, insulin resistance and glucose intolerance<sup>1,2</sup>. Fructose is a highly lipogenic carbohydrate with serious metabolic effects. In the past 40 years, fructose consumption has increased dramatically, leading to diseases such as obesity and MetS. Excessive use of fructose contributes to the development of MetS<sup>3,4</sup>. *Curcuma longa* L., commonly known as the Turmeric, produces rhizomes, from which the active ingredient curcumin is obtained. Previous *in vitro* and *in vivo* studies have revealed that curcumin possesses antioxidant, anti-inflammatory, and anticancer properties<sup>5,6</sup>.

Lipid peroxidation is a free radical-induced state that causes oxidative degradation of polyunsaturated lipids and leads to dysfunction via disruption of the fluidity of biological membranes. Thiobarbituric acid (TBARS) is generated as a by-product in the lipid peroxidation reaction<sup>7</sup>. IL-6 is a membrane cytokine in the glycoprotein structure synthesized to maintain

homeostasis<sup>8</sup>. IL-6 is produced immediately upon infection or tissue injury and contributes to the body's defense in the acute phase and immune response<sup>9,10</sup>.

Adipocyte fatty acid-binding protein (AFABP-4) is a member of the mammalian intracellular fatty acid binding protein family, which is present in the adipose tissues and macrophages. An increase in the levels of AFABP-4 may exert adverse effects on energy metabolism, insulin resistance, and obesity-associated cancer<sup>11,12</sup>. Fibroblast growth factor-21 (FGF-21) has been isolated from the liver tissue and indicated to play a crucial role in cell growth, differentiation, and development<sup>13</sup>.

In the present study, we investigated the healing effect of curcumin administration on oxidative damage and inflammation, as well as a potential effect on AFABP-4 release in the adipose tissue and the levels of liver FGF-21 in MetS induced rat model.

### Materials and Methods

#### Experimental animals and design

The study involved observing 24 adult male Wistar albino rats (206 ± 10). All rats in the experimental

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groups were maintained at room temperature (21°C). All rats received normal tap water and standard rodent feed. The rats were divided into four groups, with six rats in each group. Only corn oil was administered to the control group. MetS was established by administering 20% of D-fructose to the experimental rats for eight weeks, which led to insulin resistance, hypertension, and dyslipidemia<sup>14,15</sup>. The MetS group of rats was then administered corn oil and 20% fructose. In previous studies, the administration of 100 and 200 mg/kg of curcumin has been demonstrated to exert a protective effect against oxidative stress and inflammatory response<sup>16</sup>. The 100 mg/kg Curcumin group was administered 100 mg/kg of curcumin dissolved in corn oil along with 20% fructose. The 200 mg/kg Curcumin group was administered 200 mg/kg of curcumin dissolved in corn oil along with 20% fructose. After eight weeks, the rats were sacrificed under the effect of ketamine–xylazine anesthesia. The blood samples were extracted from the heart via a syringe and then centrifuged to obtain the corresponding plasma samples. The obtained plasma samples were stored at –80°C. The liver and adipose tissues were homogenized with PBS buffer in a ratio of 1:10 (100 mg of the liver tissue + 900 µL of PBS, pH = 7.4). The supernatants were obtained through centrifugation at 3000 rpm for 20 min and then stored at –80 °C. The total protein in each tissue sample was quantified. The method is based on combining the oxidation of aromatic protein residues with the reaction of copper ions with peptide bonds under alkaline conditions<sup>17</sup>. Necessary ethical approval (G.Ü.ET-18.082) was obtained from the Animal Experiments Local Ethics Committee, Gazi University.

#### Measurement of parameters

The levels of plasma TBARS, IL-6, liver FGF-21 and adipose tissue AFABP-4 were measured using the ELISA kit from Bioassay Technology Laboratory. According to the instructions of the kit, the complex

formed upon binding to TBARS, IL-6, FGF-21 and AFABP-4 antibodies was labeled with biotin, followed by incubation and washing steps. It was observed that the addition of the substrate solution changed the color of the solution from blue to yellow in proportion to the amounts of TBARS, IL-6, FGF-21 and AFABP-4. This color change was measured spectrophotometrically. TBARS levels were expressed in nmol/mL, IL-6 in ng/L, FGF-21 in pg/g protein and AFABP-4 in ng/g protein.

#### Statistical analysis

IBM SPSS 25 (Statistical Package for Social Sciences) was employed to determine the differences between groups. Post-analysis, the obtained median and interquartile range values were presented. The level of significance of the difference between the groups was determined by performing the Kruskal–Wallis test under non-parametric test conditions. In order to determine the significant differences, the Mann-Whitney U test and Bonferroni Correction were used. In this analysis, four groups were compared six times, along with the division of the p-value ( $P \leq 0.05$ ) into 6. The p-values equal to or below 0.008 were considered significant. The correlation between the parameters was determined using Spearman's correlation analysis. In the correlation analysis, a p-value equal to 0.05 and below was considered significant, while a p-value equal to or below 0.01 was considered strongly significant.

## Results

#### Plasma TBARS and IL-6

The TBARS levels in all groups presented a significant difference ( $p = 0.006$ ). The plasma TBARS levels were significantly higher in the MetS group compared to the control group ( $p = 0.006$ ). The TBARS levels in the 100 and 200 mg/kg dose groups were significantly lower compared to the MetS group ( $p = 0.006$  and  $p = 0.004$ , respectively) (Fig. 1 and Table 1).

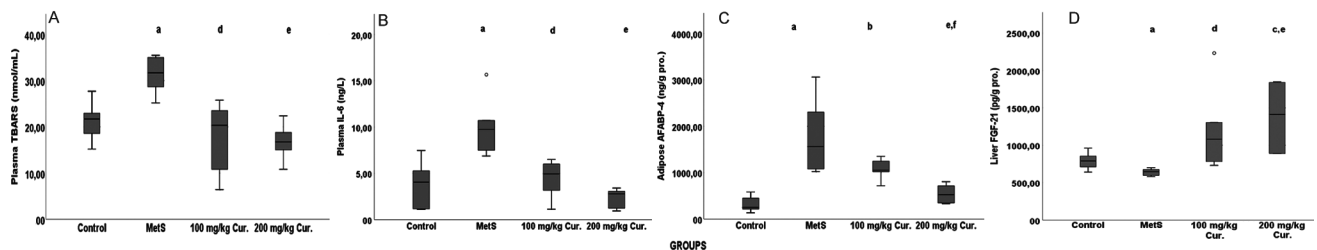


Fig. 1 — Box plot graphs of (A) Plasma TBARS; (B) Plasma IL-6; (C) Adipose tissue AFABP-4; and (D) Liver FGF-21. [T: maximum value; ⊥: minimum value; —: median; ○: extreme value]

Table 1 — Median (interquartile) values of TBARS, IL-6, AFABP-4, FGF-21 of groups and significance between groups

Groups/parameters	Control group	MetS group	100 mg/kg curcumin group	200 mg/kg curcumin dose group
TBARS (nmol/mL)	21,71 (17,7-24,1)	31,7 (27,8-35,1) <sup>a</sup>	20,3 (9,7-24,06) <sup>d</sup>	16,8 (14-20) <sup>e</sup>
IL-6 (ng/L)	4,04 (1,15 - 5,82)	9,74 (7,34-11,9) <sup>a</sup>	4,94 (2,66-6,13) <sup>d</sup>	2,79 (1,17-3,15) <sup>e</sup>
AFABP-4 (ng/g pro.)	252,4(196,8-484)	1560(1067-2493) <sup>a</sup>	1054(945-1273) <sup>b</sup>	525,5(345 -736,9) <sup>e,f</sup>
FGF-21 (pg/g pro.)	789 (694-882)	646 (594-681) <sup>a</sup>	1081 (770-1536) <sup>d</sup>	1412 (890-1843) <sup>e,e</sup>

[Value of  $P \leq 0.008$  was considered statistically significant () between (a) control and MetS groups (b) control and 100 mg/kg curcumin groups (c) control and 100 mg/kg curcumin groups (d) MetS and 100 mg/kg curcumin groups (e) MetS and 200 mg/kg curcumin groups (f) 100 mg/kg curcumin groups and 200 mg/kg curcumin groups]

The serum IL-6 levels were observed to differ significantly ( $p = 0.002$ ) between all groups. The plasma IL-6 levels in the MetS group were significantly higher than those in the control group ( $p = 0.006$ ). On the other hand, the plasma IL-6 levels in the 100 and 200 mg/kg dose groups were significantly decreased compared to the MetS group ( $p = 0.004$  and  $p = 0.004$ , respectively) (Fig. 1 and Table 1). A positive correlation was observed between plasma TBARS and IL-6 levels ( $r = 0.506$ ,  $p = 0.012$ ).

#### Adipose tissue AFABP-4

The adipose tissue AFABP-4 levels differed significantly ( $p = 0.001$ ) among all groups. The AFABP-4 levels in the MetS and 100 mg/kg curcumin dose groups were significantly increased compared to the control group ( $p = 0.004$  and  $p = 0.004$ , respectively). No significant differences were observed between the MetS group and the 100 mg/kg curcumin dose group ( $p = 0.093$ ). However, the AFABP-4 levels in the 200 mg/kg curcumin dose group were significantly decreased compared to the MetS group and the 100 mg/kg curcumin dose group ( $p = 0.006$  and  $p = 0.008$ , respectively) (Fig. 1 and Table 1).

#### Liver FGF-21

The liver FGF-21 levels differed significantly among the four groups ( $p = 0.01$ ). The FGF-21 levels in the MetS group were significantly decreased compared to the control group ( $p = 0.008$ ). The FGF-21 levels in the 200 mg/kg curcumin dose group were increased significantly compared to the control group ( $p = 0.008$ ). In addition, the levels of FGF-21 in the 100 and 200 mg/kg curcumin dose groups were increased significantly compared to the MetS group ( $p = 0.002$  and  $p = 0.002$ , respectively) (Fig. 1 and Table 1).

#### Discussion

MetS is a term that refers to a set of conditions, including central obesity, high blood pressure, insulin resistance, hyperinsulinemia, hyperglycemia, and

dyslipidemia<sup>18,19</sup>. In a previous study by our research group, the successful establishment of the MetS model was confirmed by determining high cholesterol, VLDL-C, LDL-C, TG, obesity, hypertension, and insulin resistance in the fructose group. However, the obesity condition and the systolic blood pressure were not measured in the 100 mg/kg dose administration group. The curative effects were evidently observed in the 200 mg/kg curcumin dose administration group<sup>20</sup>.

Excessive nutrient intake and a sedentary lifestyle lead to excessive activity of the mitochondria in the cells, resulting in excess ROS generation and, ultimately, oxidative stress<sup>21</sup>. The administration of high doses of fructose increases blood glucose and malondialdehyde levels, which are, therefore, used as parameters to indicate lipid peroxidation. In addition, the administration of high doses of fructose reduces the levels of antioxidant biomolecules, such as glutathione peroxidase and reduced glutathione<sup>22</sup>. IL-6 is a proinflammatory cytokine that is involved in the pathogenesis of several diseases<sup>23,24</sup>. An unregulated excessive generation of IL-6 may lead to acute systemic inflammatory response syndrome and chronic immune response, ultimately causing diseases<sup>25</sup>. Excessive fructose consumption causes obesity, hyperglycemia, hypertension, and dyslipidemia, along with increased oxidative stress and inflammation, resulting in metabolic syndrome<sup>26</sup>. Curcumin administration has been demonstrated to attenuate oxidative stress and inflammatory injury<sup>27,28</sup>. In a study, supplementation with 500 mg of curcumin in the adolescent diet significantly decreased the levels of parameters related to inflammation and oxidative stress<sup>29</sup>. Animal experiments were conducted to unravel the underlying mechanism, which revealed that curcumin treatment could have suppressed the liver toll-like receptors (TLRs)/nuclear factor-kappaB (NF- $\kappa$ B)<sup>30</sup>. Activated nuclear factor-like 2 (Nrf2) protects cells against injury by inhibiting the NF- $\kappa$ B signaling pathway. Nrf2 also induces the antioxidant-responsive element (ARE). ARE induces antioxidant

molecules, such as reduced glutathione, glutathione peroxidase, glutathione S-transferase, and NADPH: Quinone reductase, in addition to decreasing proinflammatory parameters<sup>31</sup>.

In the present study, TBARS levels were observed to be significantly increased in the MetS group, while the reverse occurred in the 100 mg/kg and 200 mg/kg curcumin dose groups ( $p \leq 0.008$ ). The IL-6 levels were increased significantly in the MetS group and decreased significantly in the 100 mg/kg and 200 mg/kg curcumin dose groups. These results indicated that curcumin administration inhibited the proinflammatory cytokine IL-6 ( $p \leq 0.008$ ). The positive correlation revealed between the plasma TBARS and IL-6 levels indicated that increased inflammation was caused by an increase in lipid peroxidation and that curcumin administration exerted a healing effect on inflammation and lipid peroxidation.

Previous studies have reported the association of increased plasma AFABP-4 levels in type 2 diabetes mellitus (T2DM) patients with insulin resistance<sup>32,33</sup>. Similarly, it has been indicated that increased plasma AFABP-4 levels lead to insulin resistance and inflammation in gestational diabetes<sup>34</sup>. Curcumin treatment has been demonstrated to reduce AFABP-4 levels by reducing adipogenesis in obese mice<sup>35</sup>. It is indicated that curcumin reduces the levels of AFABP-4 by modulating activated protein kinase (AMPK)<sup>36</sup>. FGF-21 led to valuable outcomes in terms of glucose-insulin sensitivity and maintenance of islet  $\beta$ -cell function in animal models<sup>37</sup>. In addition, hepatic FGF-21 expression increased with a decrease in the endoplasmic reticulum stress<sup>38</sup>. Therefore, FGF-21 is considered one of the biomarkers in T2DM and MeTS<sup>39</sup>. Curcumin has beneficial effects on FGF-21. It is reported that curcumin increases liver FGF-21 expression in mice fed with a high-fat diet<sup>40</sup>. It is reported that curcumin administration increases gluconeogenesis and liver FGF-21 expression in dexamethasone-induced mice, leading to improved sensitivity of insulin signaling<sup>41</sup>.

The results of the present study indicated that adipose tissue AFABP-4 was increased significantly in the MeTS group, while a slight decrease was observed in the 100 mg/kg curcumin dose group ( $P > 0.008$ ). Conversely, a significant decrease was observed in the 200 mg/kg curcumin dose group ( $P \leq 0.008$ ). These results indicated that the

administration of 200 mg/kg curcumin evidently reduces the levels of adipose tissue AFABP-4 cytokine in rat models. In addition, the liver FGF-21 levels were decreased significantly in the MetS group and increased significantly in the 100 and 200 mg/kg curcumin dose groups ( $P \leq 0.008$ ). These results demonstrated the protective effects of curcumin administration on liver FGF-21 levels.

### Conclusion

The above results have demonstrative potential help effects of turmeric on metabolic syndrome. TBARS and IL-6 levels were significantly increased in the 20% fructose-induced MetS group and significantly decreased in the 100 mg/kg and 200 mg/kg curcumin dose groups, which played a protective role against 20% fructose induction of MetS. While inflammation and lipid peroxidation were increased in the MetS rat groups, the healing effects of curcumin administration on inflammation and lipid peroxidation could be observed. Adipose tissue AFABP-4 levels were increased significantly in the MeTS group and decreased in the 200 mg/kg curcumin dose group. In contrast to the AFABP-4 levels, the liver FGF-21 levels were significantly increased in the MetS group and significantly decreased in the 100 mg/kg and 200 mg/kg curcumin dose groups. Adipose tissue AFABP-4 levels decreased with the metabolic syndrome, while the FGF-21 levels increased with curcumin administration. These results indicate that the administration of curcumin would be beneficial in public health protection against MetS. The findings of the present study would serve as a contribution to the literature, to be used as references for the levels of TBARS, IL-6, adipose tissue AFABP-4, and liver FGF-21 in MetS rats induced with 20% fructose and the rats that receive two different doses of curcumin, in future studies in the field of pharmacological research.

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### Conflict of Interest

Authors declare no competing interests.

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