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REVIEW

Protective effects of turmeric (*Curcuma longa* L.) supplementation on oxidative stress and metabolic parameters in rats with high-fructose diet-induced metabolic syndrome

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Abstract

Background Metabolic syndrome (MetS) is a growing global health concern characterized by oxidative stress and metabolic dysregulation. Identifying natural compounds with therapeutic potential to mitigate these effects is essential. Antioxidant parameters are crucial in reducing oxidative stress, which is a key factor in the pathophysiology of MetS.

Objective This study aimed to evaluate the protective effects of turmeric (*Curcuma longa* L.) supplementation on oxidative stress markers, biochemical parameters, and histological outcomes in a rat model of MetS induced by a high-sugar diet.

Methods Female Sprague–Dawley rats (n = 32) were divided into four groups: Control, metabolic syndrome (MetS—20% fructose), turmeric (80 mg/kg/day), and MetS + turmeric (80 mg/kg/day). Turmeric was administered orally for 60 days. Oxidative stress markers, lipid profiles, glucose levels, and histological changes were analyzed to assess the effects of turmeric supplementation.

Results Turmeric supplementation significantly reduced body weight, systolic blood pressure, glucose levels, total cholesterol, low-density lipoprotein (LDL) cholesterol, and malondialdehyde (MDA) levels in MetS rats. Additionally, it increased high-density lipoprotein (HDL) cholesterol, vitamin C, vitamin A, vitamin E levels, catalase (CAT) activity, and superoxide dismutase (SOD) activity.

Conclusion Turmeric supplementation at the administered dose demonstrated protective effects against the adverse impacts of a high-fructose diet in MetS development. These effects were attributed to enhanced antioxidant defense mechanisms, improved biochemical parameters, and reduced oxidative stress.

Keywords *Curcuma Longa* L. (Turmeric) · Liver · Metabolic syndrome · Oxidative stress · Vitamins

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Introduction

Metabolic syndrome (MetS) is a complex condition characterized by a range of metabolic disturbances, including type 2 diabetes mellitus, dyslipidemia, hypertension, cardiovascular diseases, and microalbuminuria. Central to its pathophysiology are abdominal obesity and insulin resistance or glucose intolerance, which play critical roles in the development and progression of the syndrome [1]. The global prevalence of MetS is rising, affecting about 40% of adults and imposing significant health, societal, and economic burdens [2]. Although a global consensus on defining MetS is difficult, a significant part of the scientific community agrees that the presence of three specific criteria is decisive. These criteria include abdominal obesity (> 102 cm in men and > 88 cm in women), hypertriglyceridemia (over 150 mg/dL), decreased high-density lipoprotein (HDL) levels (< 40 mg/dL in men, < 50 mg/dL in women), hypertension (characterized by blood pressure exceeding 130/85 mm-Hg), and hyperglycemia (manifested by fasting blood glucose levels exceeding 110 mg/dL) [3].

Fructose is an important monosaccharide found naturally in fruits and is widely used in industry as a sweetener. The rapidly increasing consumption of refined sugar in recent years is thought to be associated with an increased risk of MetS. Increased fructose intake increases triglyceride (TG) synthesis due to the production of fatty acids and glycerol [4]. Furthermore, research on the narcotic-like effects of fructose suggests that this sugar may contribute to unhealthy eating habits and the tendency to overeat. Experimental studies have shown that a high fructose diet induces metabolic disorders in rats, including oxidative stress, non-alcoholic fatty liver disease (NAFLD), hyperglycemia, and dyslipidemia [5].

In the presence of MetS and type 2 diabetes mellitus, hepatic synthesis and storage of TG surge. Elevated TG and hepatocyte lipotoxicity in the liver could result in mitochondrial dysfunction and fatty acid oxidation, triggering the occurrence of reactive oxygen species (ROS) and inflammatory lipid intermediates [6]. These ROS disrupt the regular metabolic processes, modify the utilization of substrates, intensify inflammatory reactions, undermine endothelial function, and hinder glutathione peroxidase activity, consequently diminishing the protective capacity of endogenous antioxidants [7]. Disrupted balance between antioxidant systems results in mild inflammation, endothelial dysfunction, and insulin resistance.

Dietary antioxidants, encompassing vitamins (E, and C), carotenoids, minerals (zinc, manganese, copper, selenium), and polyphenols (flavonoids, phenolic acids, stilbenes, lignans), can impact endogenous antioxidant activity. Internally and externally sourced antioxidants may synergistically work to maintain or restore the body's redox balance. Vitamin C, in collaboration with vitamin E, effectively combats free radicals and restores the reduced form of vitamin E in membranes and lipoproteins [7]. Ascorbic acid is a hydrophilic antioxidant that acts as a chain-breaking antioxidant in aqueous media, scavenging various radicals and singlet oxygen [8]. Meanwhile, the lipid-soluble α-tocopherol safeguards cell membranes from free radical-induced damage, particularly in the lipid-rich membrane interior [9, 10]. Both vitamins E and C, as exogenous antioxidants, play crucial roles in membranes and bodily fluids, countering oxidative stress and preventing peroxidation of polyunsaturated fatty acids. Addressing redox imbalance through antioxidant intervention holds promise for MetS patients [7].

Effective clinical management of MetS is crucial due to its strong association with prolonged and potentially fatal complications. In addition to conventional lifestyle adjustments and pharmaceutical interventions, herbal-derived dietary supplements have emerged as a secure and alternative treatment approach with minimal adverse effects. Spiced foods, known for their rich reservoirs of biologically active substances, are considered particularly beneficial. Herbal therapy is widely adopted in various countries, serving both preventive and therapeutic purposes for addressing MetS risk factors, including blood sugar levels, blood pressure, and lipid profiles [11]. *Curcuma longa* L., a prominent member of the Zingiberaceae botanical family, has gained attention for its biological and pharmacological impact on diverse metabolic irregularities. Its key constituents, collectively known as curcuminoids, include compounds like curcumin, bisdemethoxycurcumin, and demethoxycurcumin. Studies emphasize the potential of curcuminoids to inhibit the formation of ROS, preserving mitochondrial redox potential and functionality [12]. Curcuminoids act through various mechanisms, including the modulation of oxidative stress [13], liver-protective effects [14], inhibition of apoptosis (programmed cell death), and elicitation of anti-inflammatory responses [6].

This study, to investigate the possible protective effects of turmeric (T) (*Curcuma longa* L.) on the changes caused by MetS, in which insulin resistance and oxidative stress play an important role in its pathogenesis, in rat serum and liver tissue by biochemical and histological methods.

Results

The effects of T on serum and liver tissue in high fructose-fed rats were evaluated by determining the changes in various biochemical and histological parameters.

The body weight of the MetS group rats fed with fructose was found to be significantly higher than that of the MetS + T group rats at week 4 (+ 14.82%, $p < 0.01$), and this difference increased by 13.19% at week 9 ($p < 0.01$) (Fig. 1A). In contrast, the MetS + T group rats showed a significantly lower body weight gain, similar to the C group, compared to the MetS group rats fed with fructose at week 9 (−29.91%, $p < 0.01$) (Fig. 1B). These findings demonstrate that T supplementation can control body weight gain in rats fed with fructose and significantly improve obesity. Systolic blood pressure was found to be significantly higher in the MetS group compared to the C group at week 4 (+ 21.66%, $p < 0.01$), and this difference increased by 32.91% at week 9 ($p < 0.01$) (Fig. 1C). In contrast, the MetS + T group rats had significantly lower systolic blood pressure than the fructose-fed MetS group rats at week 9 (−29.34%, $p < 0.001$) (Fig. 1C). In addition, systolic blood pressure was observed to be lower in the MetS + T group rats than in the C group ($p < 0.05$). In the T-only group, blood pressure increased at week 4, but decreased at the end of week 9, reaching similar values to the control group ($p < 0.05$). Figure 1D shows the effect of physiological monitoring of beverage consumption between groups. Fluid intake was significantly higher in the MetS + T group ($p < 0.001$) compared with the C group, followed by the MetS group ($p < 0.001$) while no significant difference was observed in the Z group ($p > 0.05$).

Basal blood glucose and uric acid also increased significantly in the MetS group (128.33 ± 2.62 and 1.35 ± 0.37) compared to the C group (98 ± 1.86 and 0.78 ± 0.54) ($p < 0.0001$ and $p < 0.001$). When the results of the treatment group were analyzed, there were significant decreases in blood sugar levels (119.67 ± 2.49) in the rats in the MetS + T group compared to the rats in the MetS group, while there was no significant decrease in uric acid levels ($p < 0.01$, $p > 0.05$) (Fig. 2A-2B).

When the lipid profile of rats consuming high fructose diet was analyzed, it was observed that TG and total cholesterol levels (MetS; 208 ± 13.8 and 62 ± 4.05 C; 148 ± 13.02,

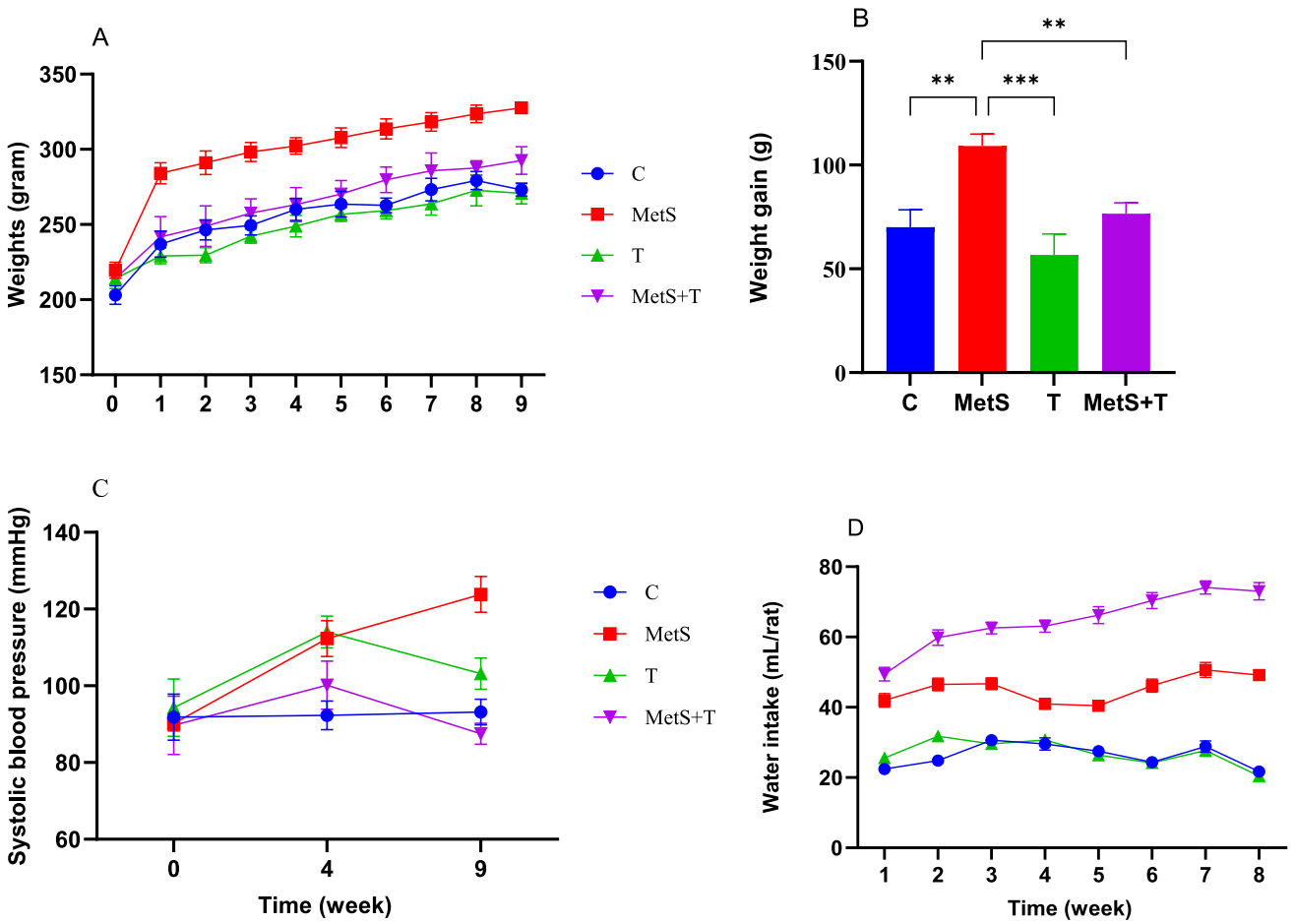

Fig. 1 Effects of T on body weight in different groups of rats. (**A**) Weekly body weight; (**B**) Body weight gain at week 9. Statistical significance values ****, ***, ** and * indicate significance at $p < 0.0001$, $p < 0.001$, $p < 0.01$ and $p < 0.05$, respectively, and $p > 0.05$ indicates non-significance

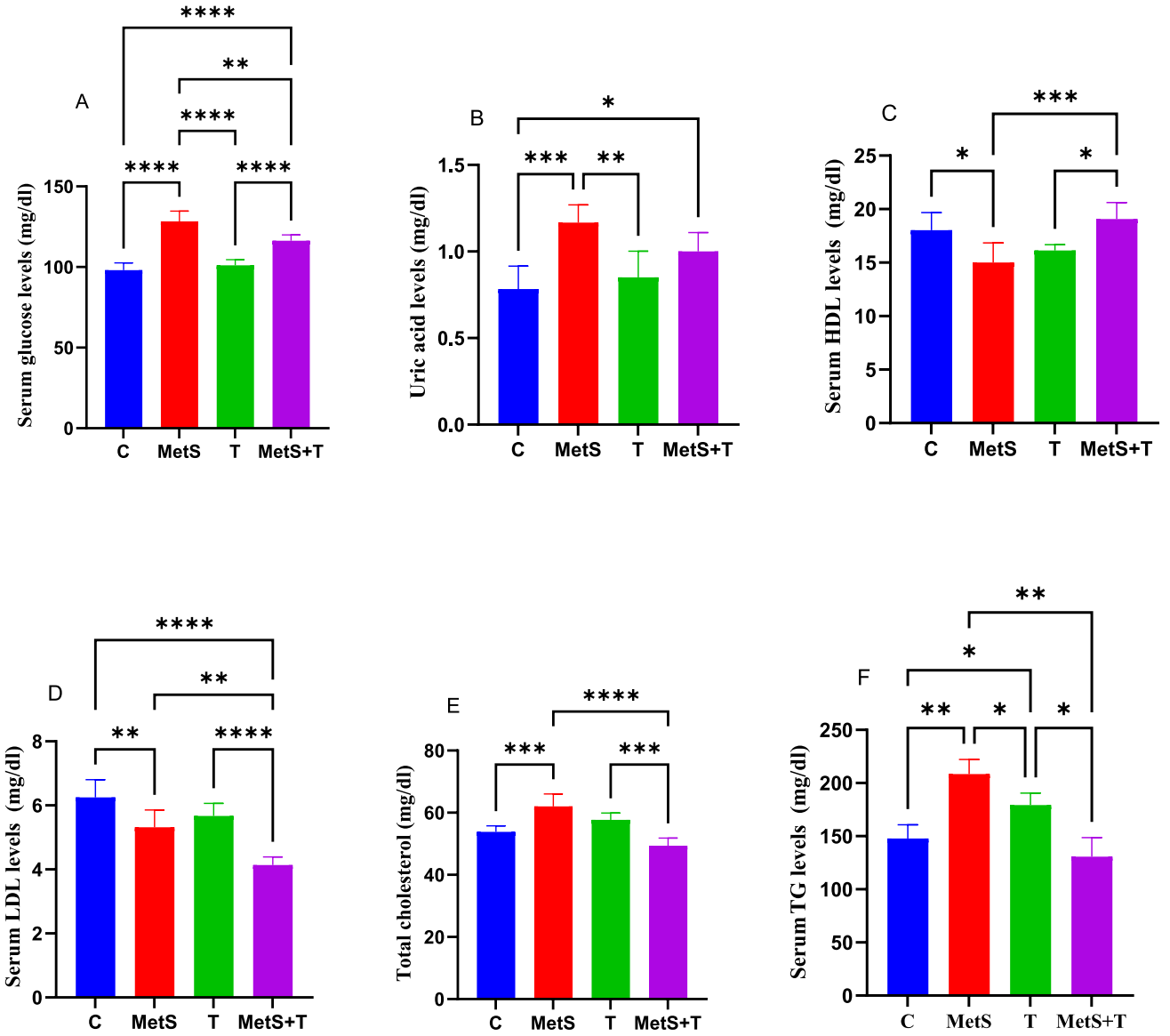

Fig. 2 Biochemical serum levels [(**A**) glucose, (**B**) uric acid, (**C**) HDL, (**D**) LDL, (**E**) total cholesterol, (**F**) triglyceride] Data are expressed as mean ± SD (n = 8) in rats with high fructose-induced metabolic syndrome (MetS) after turmeric (T) treatment. Statistical significance values ****, ***, ** and * indicate significance at $p < 0.0001$, $p < 0.001$, $p < 0.01$ and $p < 0.05$, respectively, and $p > 0.05$ indicates non-significance

53.83 ± 0.79) were significantly increased and LDL levels (MetS; 5.32 ± 0.22, C; 6.25 ± 0.23) were decreased compared to C group rats ($p < 0.001$, $p < 0.05$ and $p < 0.01$). Serum TG, total cholesterol, and LDL cholesterol levels (131.01 ± 8.65 mg/dl, 49.33 ± 2.50 mg/dl, and 4.13 ± 0.24 mg/dl, respectively) were significantly decreased in MetS + T group rats compared to MetS group ($p < 0.01$, $p < 0.001$, $p < 0.01$). HDL levels (MetS; 15 ± 0.75 and C; 18.033 ± 0.67) changed and worsened in the MetS group compared to the C group ($p < 0.05$). MetS + T group rats had significantly increased HDL (19.07 ± 0.63) compared to the MetS group ($p < 0.0001$), while it was not different from C group rats ($p > 0.05$) (Fig. 2).

The preservation of cellular or tissue integrity relies on the equilibrium between the levels of antioxidants and oxidants. This delicate balance dictates the susceptibility of cells or tissues to oxidative stress or free radical attack. The malondialdehyde (MDA) level measures the degree of lipid peroxidation. As shown in Fig. 3, rats exposed to fructose consumption (Serum: 1.535 ± 0.093, Liver: 15.940 ± 1.644) exhibited a statistically significant increase in MDA levels compared to group C rats (Serum: 0.786 ± 0.181, Liver: 9.023 ± 1.0) ($p < 0.0001$). Furthermore, MetS group rats showed a significant decrease in superoxide dismutase (SOD) (102.96 ± 3.39), and catalase (CAT) (101.83 ± 9.93)

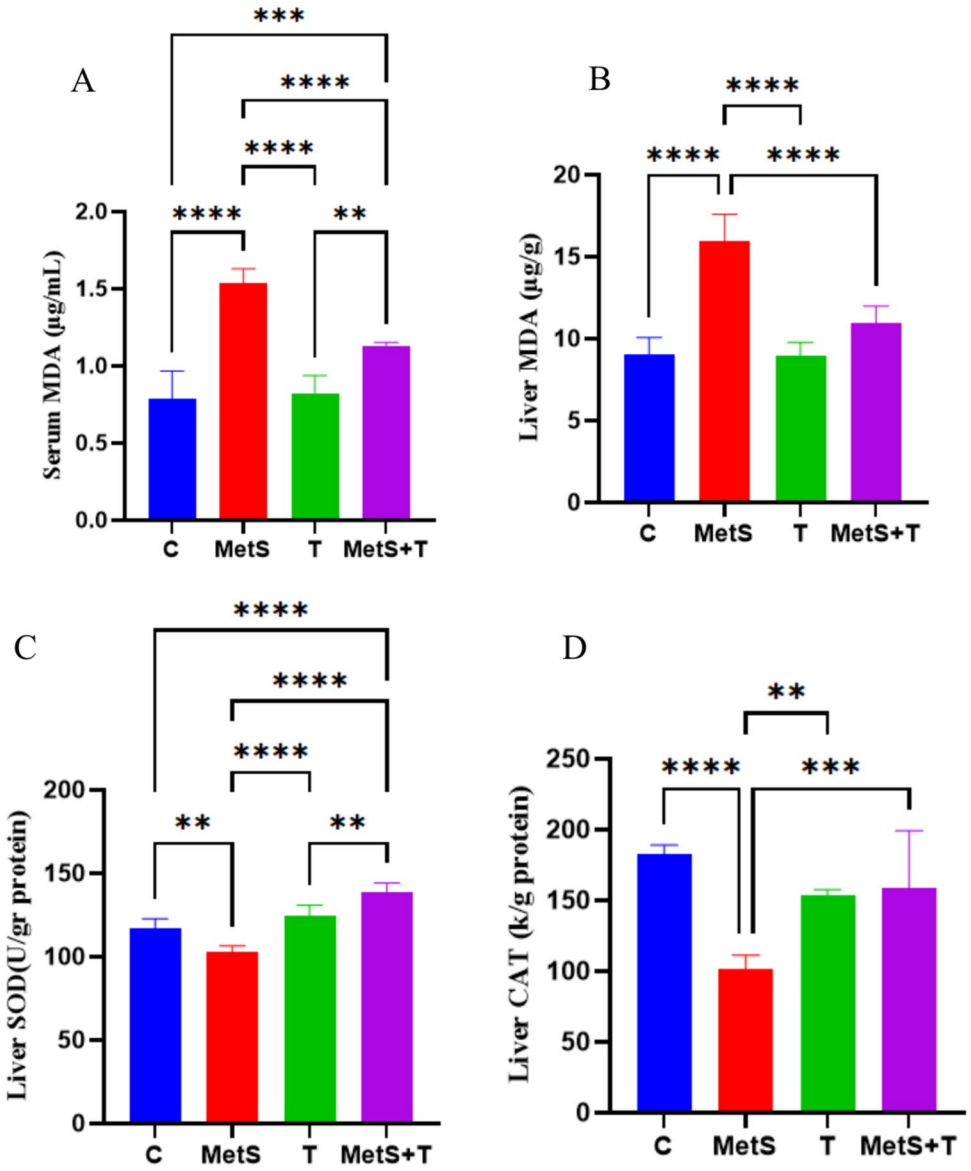

Fig. 3 Levels of oxidative stress markers [(**A**) serum malondialdehyde, (**B**) liver malondialdehyde, (**C**) superoxide dismutase, (**D**) catalase, data are expressed as mean ± SD (n = 8). Statistical significance values ****, ***, ** and * indicate significance at $p < 0.0001$, $p < 0.001$ $p < 0.01$, and $p < 0.05$, respectively, and $p > 0.05$ indicates non-significance

levels in liver tissues compared to C (SOD: 116.78 ± 2.43, CAT: 182.90 ± 2.49) group rats ($p < 0.01$ and $p < 0.0001$). MetS + T group rats showed significant differences in plasma oxidant status of MDA (Serum: 1.13 ± 0.01, Liver: 10.96 ± 0.42), and also caused a significant increase in SOD (140 ± 2.83), and CAT (142.34 ± 5.30) levels.

As shown in Fig. 4, significant antioxidant defense system-related decreases in vitamin A levels in serum, and liver tissues were observed in rats fed a high fructose diet compared to those fed a normal diet (High fructose fat diet: Serum [vit-A]: 1.01 ± 0.19, Liver [vit-A]: 1.19 ± 0.23; Normal diet: Serum [vit-A]: 1.55 ± 0.29, Liver [vit-A]: 2.06 ± 0.14). Furthermore, serum levels of vitamin C were elevated in the high fructose fat diet group (Serum [vit-C]: 0.256 ± 0.03 vs. 0.18 ± 0.01), but levels in liver tissue were significantly decreased (Liver [vit-C]: 146.25 ± 3.33 vs. 193.81 ± 1.87).

Furthermore, a significant decrease in liver vitamin E levels was observed in the MetS group (Liver: 4.44 ± 0.28) compared to the C group (Liver: 18.93 ± 0.93). In contrast, serum vitamin E levels showed a relative decrease in the MetS group (1.82 ± 0.64) compared to the C group (2.23 ± 0.64), but this difference was not statistically significant ($p > 0.05$). Oral administration of T (80 mg/kg/day) increased the levels of these vitamins relatively compared to the control group ($p > 0.05$). T administration at the dose investigated increased the serum vitamin E level (Serum [vit-E]: 3.04 ± 0.178, Liver [vit-E]: 9.23 ± 0.22) in high fructose fed rats, while it increased the levels of other antioxidant vitamins (Serum [vit-A]: 1.82 ± 0.27, Liver [vit-A]: 1.74 ± 0.07; Serum [vit-C]: 0.30 ± 0.03Liver [vit-C]: 189.37 ± 5.65;) reversed the adverse effects of metabolic disorders by significantly elevating the vitamin levels (Fig. 4).

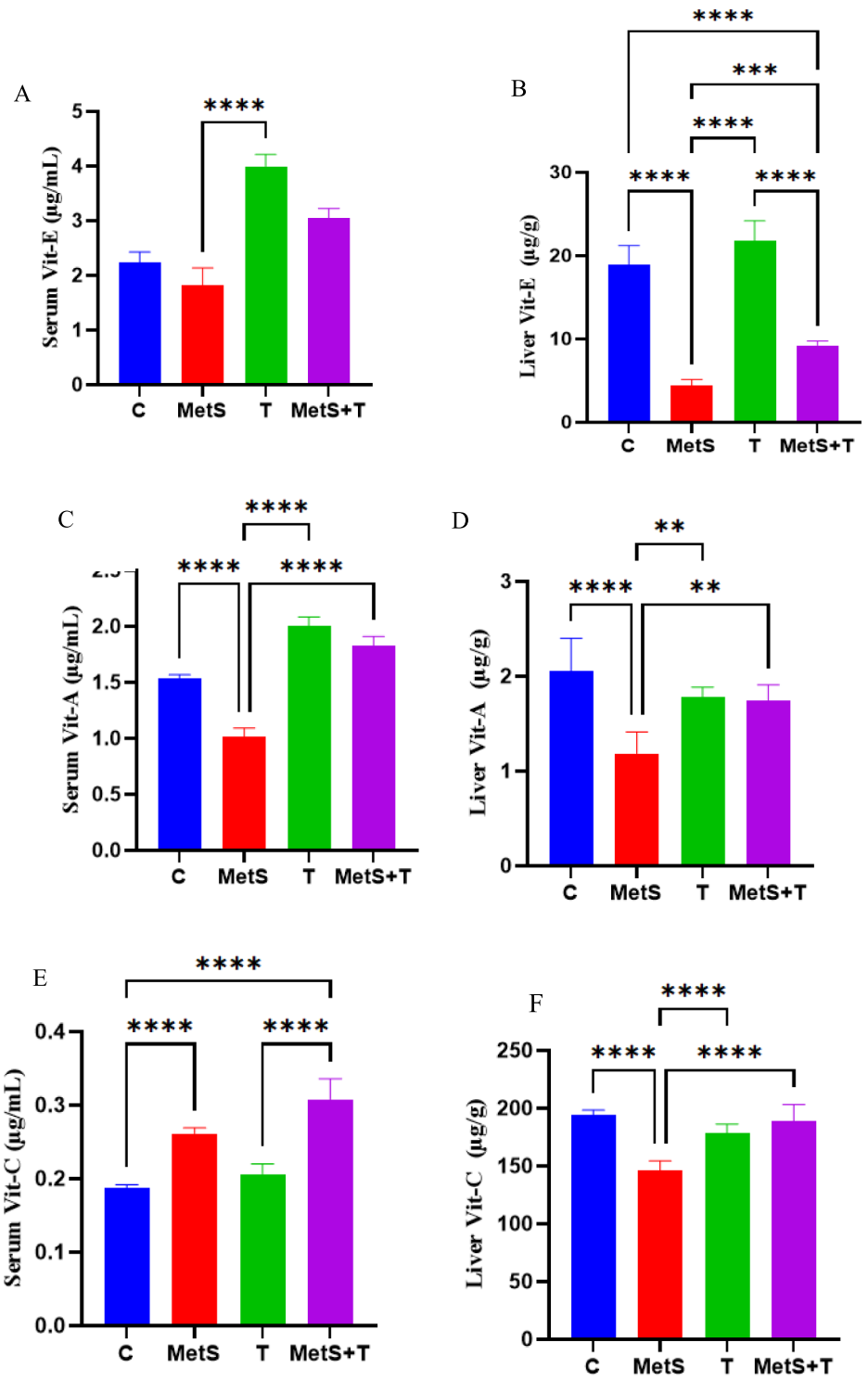

Fig. 4 Effect of turmeric (T) treatment on (**A**) Serum vitamin E, (**B**) Liver vitamin E, (**C**) Serum vitamin A, (**D**) Liver vitamin A (**E**) Serum vitamin C, (**F**) Liver vitamin C levels in rats with high fructose-induced metabolic syndrome (MetS), Data are expressed as mean ± SD (n = 8). Statistical significance values ****, ***, ** and * indicate significance at $p < 0.0001$, $p < 0.001$, $p < 0.01$, and $p < 0.05$, respectively, and $p > 0.05$ indicates non-significance

Histological evaluations

When the liver tissues of the rats belonging to the control group were examined, hepatocytes and sinusoids were observed in normal structure (Fig. 5A). Microvesicular and macrovesicular fat vacuoles and sinusoidal dilatation were detected in hepatocytes in sections belonging to the MetS group (Fig. 5B-5C). Fat vacuoles in macrovesicular form were not found in the sections belonging to the MetS + T group. Fat vacuoles in microvesicular form were very rare. Significant improvement in sinusoidal dilatation was observed (Fig. 5D-5E). Normal-looking hepatocytes and

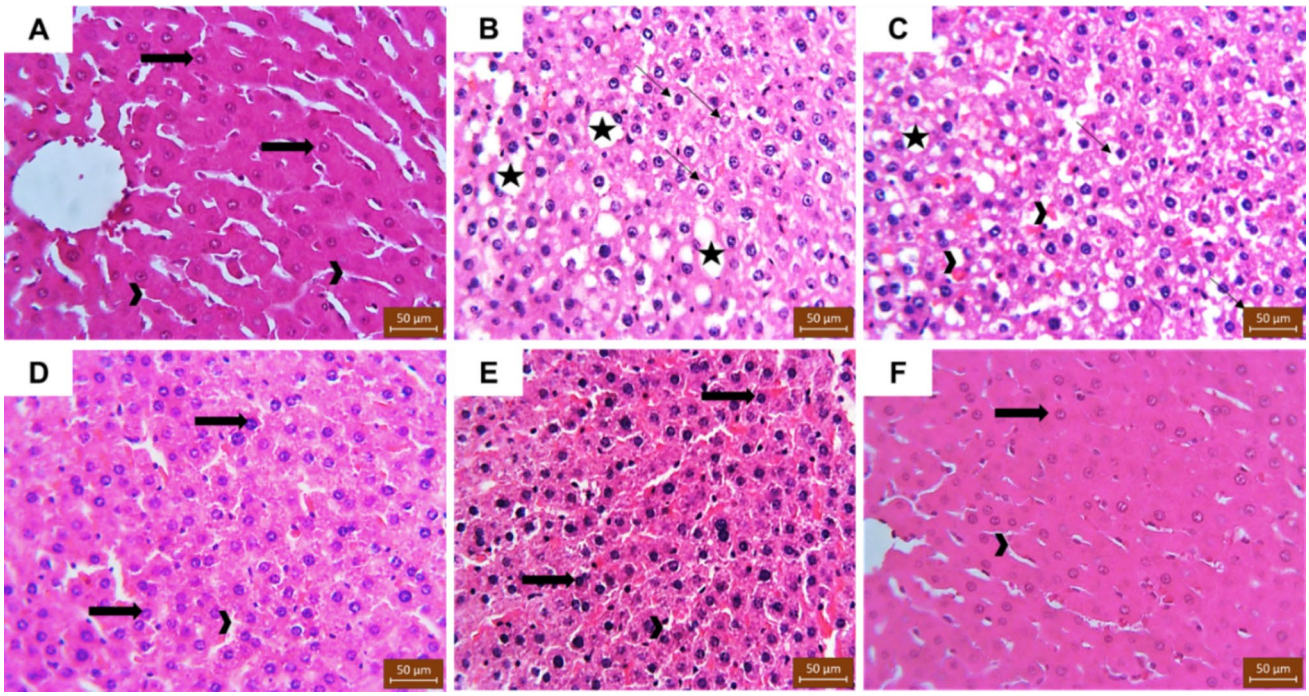

Fig. 5 Histopathology of the liver with H&E stain. **A**. Control group;×40. **B**. MetS group;×40. **C**. MetS group;×40. **D**. MetS + T group;×40. **E**. MetS + T group;×40. **F**. T group;×40. Hepatocytes (thick arrows), sinusoids (arrowheads) and histological changes such as microvesicular (thin arrows) and macrovesicular (stars) fat vacuoles are marked

sinusoids were observed in the turmeric-only group, similar to the control group (Fig. 5F).

Discussion

Metabolic disorders are a major concern for global health, particularly in developed countries, and a relationship has been identified between the increased consumption of fructose and sucrose and the emergence of this syndrome [15]. T, which contains curcumin as its active compound, is believed to exhibit antioxidant and anti-inflammatory properties and, therefore, may have beneficial effects against metabolic diseases. The present study investigated the biochemical and histological effects of T on the serum and liver tissues of female Sprague–Dawley rats fed a high-fructose diet. Previous studies have demonstrated that fructose, included in the diet at different concentrations for 3 weeks [16], 6 weeks [17], and 8 weeks [18] leads to metabolic disorders and the development of oxidative stress. Consistent with this, it has been found that providing drinking water enriched with 20% fructose for 60 days leads to features of MetS such as hypertension and hyperglycemia, weight gain, and an increase in oxidative stress markers. Other anthropometric indicators used to assess MetS are weight gain, body mass index, and waist circumference measurement [19]. In the study by Ajiboye et al. 2016, it was reported that fructose-fed rats exhibited increases in weight gain, BMI, and waist circumference [20]. The weight gain observed in rats subjected to a high fructose regimen aligns with antecedent studies [21]. The current study has demonstrated that T administration reduces fructose-induced weight gain and has the capacity to regulate body weight, suggesting potential beneficial effects in obesity management. Additively, our results also unveiled weight reduction in the T-treated group, as opposed to the C group Additionally, Said et al. 2023 reported that high blood glucose levels, a component of MetS, were observed in rats fed a high fructose diet, and this condition was associated with insulin resistance [22]. The metabolism of fructose after absorption from the intestines, through phosphorylation by the enzyme fructokinase, indicates that fructose follows a different biochemical pathway from glucose. Intermediates such as fructose-1-phosphate are known to support gluconeogenesis, contributing to elevated blood glucose levels [23]. In the current study, an increase in blood glucose associated with high fructose intake was observed, and this condition was reversed with T supplementation. This finding is consistent with previous studies [24, 25]. These results indicate that T exhibits anti-hyperglycemic activity.

Fructose has been shown to promote uric acid production, which contributes to the development and progression of hypertension [26]. The rapid metabolism of fructose leads to cellular ATP depletion and an increase in uric acid. Increased uric acid impairs endothelial function and

increases blood pressure, eventually leading to cardiac dysfunction [27]. The present results suggest that high-fructose intake increases uric acid levels. However, T supplementation was found to be beneficial in ameliorating elevated levels. These results may be explained by the potential of T polyphenols to improve endothelial dysfunction.

The effects of dietary fructose on lipoprotein metabolism are an important issue, and the effects of dietary fructose on circulating triglycerides and circulating total cholesterol, as well as HDL and LDL cholesterol, become important in assessing the metabolic effects of fructose. In the present study, serum concentrations of total cholesterol were significantly higher in the MetS group compared to group C. Triglyceride concentrations were shown to be increased in the fructose-rich diet-fed group compared to group C. Serum HDL concentrations were significantly lower in the fructose-fed MetS group compared to group C. Similar results have been reported in previous studies [28, 29].

Contrary to expectations, the decrease in serum LDL levels observed in the MetS group may be due to increased triglyceride production via de novo lipogenesis (DNL) during the metabolism of fructose in the liver, leading to changes in lipid transport and metabolism by increasing the secretion of VLDL particles, and consequently affecting LDL particle size and metabolic behavior and accelerating the catabolism of LDL particles; such effects may make it difficult to precisely predict changes in serum LDL levels [30].

This disruption in lipid homeostasis remains closely intertwined with cardiovascular diseases and the potential evolution of atherosclerosis [31]. T consumption has demonstrated a capacity to modulate lipid metabolism in diabetic models [25]. For instance, a study involving hamsters subjected to a high-fat diet (comprising 10% coconut oil and 0.2% cholesterol w/w) reported a reduction in TG and LDL cholesterol levels and a corresponding elevation in HDL-cholesterol, thereby enhancing lipoprotein metabolism [32]. The present results show that T can prevent excessive fat accumulation. However, in their study, Yadav and Chaudhary (2016), demonstrated that the administration of T results in the down-regulation of inflammatory cytokines, resistin, and leptin, while concurrently up-regulating adiponectin [33]. This multifaceted action contributes to a favorable impact on lipid metabolism.

While the precise mechanism underlying MetS initiation due to a fructose-rich diet remains enigmatic, oxidative stress is posited to occupy a pivotal role. A perturbation in the coordinated detoxification of ROS has been documented in MetS attributed to heightened fructose consumption, resulting in oxidative stress, redox disturbance, morphological changes, and tissue impairment [20]. High MDA concentration indicates increased ROS in fructose-fed rats [34]. The escalation in lipid peroxidation in fructose-fed rats may partly be attributed to heightened glycemia. Hyperglycemia might directly influence oxidative lipid alteration through glucose autooxidation, the polyol pathway, and the generation of glucose-derived free radicals within the protein glycation process [35]. Extant literature aligns with this notion, citing fructose's propensity to foster peroxidation [36, 37]. The current findings, congruent with precedent research, underscore a noteworthy surge in MDA, an end product of lipid peroxidation, within the liver tissues of fructose-fed rats. T intervention effectively countered the elevation of MDA levels, signifying a mitigation of oxidative stress. This substantiates the potential of T in thwarting liver impairment. These results concur with studies highlighting T's radical-scavenging efficacy [38, 39].

Another oxidant condition is the decreased antioxidant enzyme (SOD, CAT, Glutathione Peroxidase (GSH-Px), Glutathione Reductase (GSH-red), Glucose-6-Phosphate Dehydrogenase (Glc 6-PD) activities in the liver of rats fed a high fructose diet [40, 41]. Decreased activity may lead to tissue damage and cell death. SOD and CAT are two important antioxidant enzymes responsible for superoxide anion radical scavenging activity. SOD, which constitutes the primary enzymatic defense against cellular oxidation, regulates the conversion of superoxide radicals to H_2O_2, which is then detoxified by the CAT enzyme as it passes from the mitochondria to the cytoplasm [42]. Panahi et al. (2017) investigated the effects of curcuminoid supplementation, a class of natural polyphenolic compounds derived from T, on oxidative markers in people with diabetes. Panahi et al. (2017) the effects of curcuminoid supplementation, a class of natural polyphenolic compounds derived from T, on oxidative markers in individuals with diabetes were examined. Through an 8-week human experiment involving curcumin administration, a significant decrease in serum MDA levels as well as increased antioxidant capacity and SOD activity emerged as noteworthy results [43]. Hasimoto et al. examined the therapeutic effect of T in the pathophysiology of fructose consumption-induced NAFLD and demonstrated increased SOD and CAT activities [44]. Consistent with other studies, the present results showed that treatment with T significantly increased liver SOD and CAT activity in the MetS group (Figur 3). The potential of administered T supplementation to ameliorate these changes in fructose-induced MetS emphasizes the protective importance of the plant offering the ability to prevent tissue damage and cell death against the generation of ROS.

In addition to these changes in antioxidant enzyme activities, changes in the levels of exogenous antioxidant vitamins A, E, and C are also important in MetS. These vitamins are essential components of the body's non-enzymatic antioxidant defense system and provide important protection against ROS at appropriate concentrations. Studies have shown that individuals with cardiovascular disease have

lower levels of vitamins A, C, and E in comparison to healthy individuals, even when they have adequate dietary intakes [45, 46].

Supporting these findings, data from the Third National Health and Nutrition Examination Survey (NHANES III, 2003) also show that vitamin C and E concentrations are reduced in MetS patients [47]. This decrease can probably be attributed to the increased need for antioxidants with the effect of the disease and the increased reaction of these vitamins with ROS. A study by Godala et al., encompassing 91 MetS-diagnosed individuals aged 30–65, spotlighted significantly lower plasma concentrations of vitamins A, C, and E in MetS patients relative to controls [48]. In the present study in rats with fructose-induced metabolic syndrome, plasma vitamin A and vitamin E levels were significantly decreased, whereas vitamin C levels were increased. These findings may indicate a protective role of vitamin C in conditions of increased oxidative stress, as well as regenerative functions such as reversal of vitamin E oxidation. Furthermore, the increase in vitamin C may have enhanced the adaptive response of the organism against oxidative damage, exhibiting a supportive interaction with the biological effects of vitamin E [49]. Limited studies have investigated the effects of T on liver exogenous antioxidants in experimental animals affected by MetS. This research demonstrated a significant increase in vitamins A, C, and E levels in MetS subjects following 60 days of T supplementation, highlighting the potential of T to enhance antioxidant capacity (Fig. 4). When oxidative stress occurs, the consumption of specific non-enzymatic antioxidant compounds such as ascorbic acid, α-tocopherol, and carotenoids leads to a decrease of oxidative parameters below their normal range and deterioration of the histopathology of metabolic organs due to the systemic effects of MetS [50]. The effects of T on MetS-induced liver histopathology were investigated to provide additional support for oxidative stress-induced impairments. In the present results, in accordance with the literature, MetS induced a series of irregularities in the histology of rat liver. The current findings suggest that T may have a potential protective effect in preventing and ameliorating MetS-associated histopathological abnormalities such as fatty liver and sinusoidal dilatation. In particular, the complete disappearance of macrovesicular fat accumulation and the rarity of microvesicular fat accumulation suggest that T may exert favorable effects on lipid metabolism. These results support the potential of the anti-inflammatory and antioxidant properties of T to reduce MetS-induced liver injury.

Given this perspective, individuals diagnosed with MetS may be advised to prioritize the recommended daily intake of antioxidant vitamins. This approach would effectively counteract the deleterious effects of oxidative stress by facilitating greater utilization of enzymatic and non-enzymatic antioxidant systems. The present results demonstrate that T administration reduces fructose-induced oxidative stress and emphasises the potential of T as a promising therapeutic agent for managing MetS symptoms and preventing long-term complications, particularly those intertwined with oxidative stress-related problems.

Material and methods

Plant material

Standardized Turmeric (T) was purchased as a food supplement formulation (Solgar®; 400 mg of standardized turmeric extract contained 93% curcuminoids).

Experimental animal design

This research was conducted following the approval granted by the Regional Local Ethics Committee of Fırat University Faculty of Medicine (approval number: 2016/09). The animals used in the study were obtained from the Fırat University Experimental Research Unit. For this investigation, a total of 32 female *Sprague–Dawley* rats, with an age of 8 weeks and an average weight of around 220 ± 20 g, were employed. Rats were kept in special cages under standard conditions (22–24 °C constant temperature and ventilated rooms; 12 h of daylight and 12 h of dark photoperiod) before and during the experiment. Standard rat pellet feed (88% dry matter, 23% protein, 7% cellulose, 8% crude ash, standard rat chow containing 2%HCl insoluble ash, 1.5% calcium, 0.9% phosphorus, 0.7% sodium, 1% salt, 0.3% methionine, and 1% lysine) and drinking water were used in feeding the rats. The rats are divided into 4 groups as C, MetS, T and MetS + T Control (C), T, T + MetS, and MetS.

The standard diet and tap water were given in group C for 60 days. The rats in the MetS group and the MetS + T group were given drinking water containing 20% fructose (D-Fruktoz > %99, Sigma-Aldrich) [29]. Orally, 80 mg/kg/day of T was administered to rats in MetS + T and T groups [51]. Weekly weight measurements of the rats were recorded during the experiment. At the start of the experiment, one month later, and before the animals were decapitated, the systolic blood pressures of the animals were measured with a tail blood pressure measurement system (Tail-Cuff, BIOPAC Systems). Upon completion of the 60-day experimental period, rats from all experimental groups were euthanized under ketamine (75 mg/kg) and xylazine (10 mg/kg) anesthesia [52]. Blood samples and liver tissues were then collected for further analysis.

Preparation of blood samples

Blood samples were collected in biochemistry tubes and centrifuged at 3500 rpm for 10 min using a Nuve NF800R centrifuge. The serum was carefully extracted and stored at −80 °C until further analysis. Total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), glucose, and uric acid levels in serum were measured using an OLYMPUS-AU600 autoanalyzer (Olympus Optical Co., Japan). To determine triglyceride (TG), the direct method proposed by Friedewald et al. [53] was used.

$$LDL = Total\ Cholesterol - \left(HDL + \frac{Triglyceride}{5}\right) \quad (1)$$

Preparation of tissue samples

For superoxide dismutase (SOD) and catalase (CAT) activity measurements, tissue homogenization was performed using 1.15% KCl buffer. For vitamin C and malondialdehyde (MDA) levels, proteins were precipitated with 0.5 M $HClO_4$. For vitamins A and E, ethyl alcohol containing 1% H_2SO_4 and distilled water were added. All homogenization were performed with a Potter–Elvehjem homogenizer.

Catalase activity measurement

CAT activity in hepatic tissue homogenates was measured using the procedure outlined by Aebi (1984) [54]. The principle of this method is based on measuring the enzymatic activity of CAT and H_2O_2 consumption during the first 30 s at 240 nm. CAT enzymatic activity was denoted as catal (k)/g protein per second in diluted liver homogenates.

Superoxide dismutase activity measurement

SOD activity within hepatic tissue homogenates was determined using a reaction dependent on the generation of a blue chromogenic compound resulting from the conversion of nitro blue tetrazolium (NBT) by the xanthine oxidase system [55]. The developed blue hue was quantified at 560 nm, and SOD enzyme activity was quantified as U/g protein in liver tissues.

Determination of liver vitamin C and MDA levels

Following centrifugation of the homogenates at 4500 rpm for 45 min, 20 µl samples were extracted from the supernatants and injected into the high-performance liquid chromatography (HPLC) system. Detection of vitamin C and MDA was executed at a wavelength of 254 nm. The outcome was expressed as µg/g for both MDA content in tissues and vitamin C concentration [56, 57].

Determination of liver vitamin E and vitamin A levels

After centrifugation at 4500 rpm for 15 min, 0.3 mL n-hexane was added, followed by vortexing and centrifugation. The supernatant hexane was collected and additional centrifugation with n-hexane was performed to extract fat-soluble vitamins. The hexane phase was evaporated under nitrogen to leave a residue that was dissolved in 100 µL of methanol. A 20 µL aliquot of this solution was analyzed by HPLC and vitamin A and vitamin E were detected at 326 nm and 296 nm, respectively. The results were reported as µg/g [58].

Determination of serum vitamin C and MDA levels

A 0.3 ml serum sample was mixed with 0.3 mL of 0.5 M $HClO_4$ to precipitate proteins, then vortexed and diluted with water to a final volume of 1 mL. After 15 min, the mixture was centrifuged at 2500 rpm, and 20 µL of the supernatant was injected into the HPLC. Detection for vitamin C and MDA was performed at 254 nm, and results were expressed as µg/mL [57].

Determination of serum vitamin E and vitamin A levels

0.3 mL of serum samples was taken, and 0.3 mL of ethyl alcohol (containing 1% H_2SO_4) was added to precipitate the proteins. The mixture was vortexed and centrifuged at 2500 rpm for 5 min. After centrifugation, 250 µL of n-hexane was added, followed by another vortex and centrifugation. The n-hexane layer was carefully transferred to a glass tube, and an additional 250 µL of n-hexane was added for a final centrifugation. The hexane was evaporated using a nitrogen flow, and the residue was dissolved in 100 µL of methanol. Finally, 20 µL of the sample was injected into the HPLC system. Detection was performed at 326 nm for vitamin A and 296 nm for vitamin E. Results were calculated as µg/mL for vitamins A and E [58].

Histological analysis

Liver specimens underwent fixation in a 10% formaldehyde solution, followed by thorough rinsing under tap water. The tissues were subjected to routine histological processes, involving dehydration and paraffin embedding (P3558-1 kg Sigma-Aldrich Paraplast Embedding Media, U.S.A). Sections measuring 5–6 µm in thickness were obtained from the paraffin blocks and affixed onto prepared slides. Employing

Hematoxylin–Eosin (H&E) dye, the preparations were stained and scrutinized utilizing a light microscope (Novel N-800 M × 20).

Statistical analysis

All data were presented as mean ± standard deviation (SD). Data were analysed by two-way analysis of variance (ANOVA) followed by Bonferroni post-hoc test using SPSS 21.0 software and GraphPad Prism version 9.0.0 software (San Diego, California, USA); statistically significant differences were assessed at $p < 0.05$.

Conclusion

T treatment at 80 mg/kg/day for 60 days during MetS formation showed significant protective effects against oxidative stress by increasing antioxidant enzyme and vitamin levels in rat liver. These effects contributed to the strengthening of antioxidant defense mechanisms and the reduction of oxidative damage in liver tissue. In addition, T treatment significantly decreased body weight, systolic blood pressure, glucose, and LDL cholesterol levels, while a significant increase in HDL cholesterol levels was observed. These findings suggest that turmeric has the potential as an effective nutraceutical agent in the management and treatment of metabolic syndrome. In conclusion, the favorable effects of T on metabolic syndrome may play a prominent role in increasing antioxidant capacity and reducing risk factors. However, a more detailed study of how T penetrates into cells and by which pathways it acts at the molecular level will contribute to a better understanding of its therapeutic potential and increase its usability in future clinical applications.

Author contributions Study design by GOM and KO; animal care and sample collection by GOM, KO and MAK; blood pressure measurements by EO; biochemical analyses and interpretation of results by KO, GOM and MK; histological analyses by NKT and IEO; writing of the original article by GOM, KO. All authors have read and accepted this document.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval This study has been approved by the University Fırat Local Ethics Committee for Experimental Animals (2016/09).

Competing interest The authors declare no competing interests.

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