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Effects of *Cornus mas* L. on lipid peroxidation and anti-oxidative enzyme activity in high fat diet fed rats

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ABSTRACT: Cornelian cherry (*Cornus mas* L.) has been used for centuries as a traditional herbal medicine in Europe and Asia. In this study, we aimed to describe the effect of *Cornus mas* L. (*C. mas*) on the activity of the antioxidant enzymes and a detoxification agent in rats fed a high-fat diet. Forty-eight adult Sprague Dawley rats were randomly assigned to six groups of eight animals each: Standard diet (Control), High Fat Diet (HFD), HFD + *C. mas* (200 mg/kg/day; 8 weeks), HFD + Atorvastatin (20 mg/kg/day; 8 weeks), HFD post-treated with *C. mas* (200 mg/kg/day; 4 weeks), HFD post-treated with Atorvastatin (20 mg/kg/day; 4 weeks). The activity of the antioxidant enzymes, Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), detoxification agent glutathione (GSH), and oxidative stress parameter thiobarbituric acid reactive substances (TBARS) were measured in the liver tissues. GPx, SOD, and CAT enzyme levels were decreased in HFD groups compared to the control ($p < 0.05$). However, *Cornus mas* L. promoted antioxidant activity by increasing GPx, SOD, and CAT enzymes and It also reduced oxidative stress (as an increase in GSH) both in the HFD + *C. mas* group and the HFD post-treated *C. mas* group compared to the HFD group ($p < 0.05$). Our study showed that feeding a high-fat diet increases oxidative stress. *Cornus mas* L treatment improves antioxidant enzyme activity and oxidative stress parameters in the liver tissues of rats.

KEYWORDS: Cornus mas L.; liver; antioxidant; glutathione; high-fat-diet.

1. INTRODUCTION

A high-fat diet (HFD) significantly contributes to the risk of a wide range of serious diseases, such as obesity, dyslipidemia, cardiovascular disease, Type II diabetes, and non-alcoholic fatty liver disease [1-3]. Accelerated mitochondrial oxidation of FFAs after excessive consumption of fat-rich diets is associated with systemic oxidative stress in humans and rodents through increased production of reactive oxygen species (ROS), enhanced expression of NADPH oxidase, and decreased expression of antioxidative enzymes [4].

Under normal physiological conditions, there is a balance between reactive oxygen species (ROS), which are the types of free radicals in cells, and antioxidant mechanisms [5]. Disruption of the balance between free radicals and antioxidant production in favor of oxidants is defined as oxidative stress and may lead to cell damage at the molecular level [5, 6]. Excessive amounts of ROS may cause damage to cellular lipids, proteins, or DNA, resulting in the inhibition of signal transduction pathways and normal cellular functions. Therefore, it is stated that oxidative stress is associated with the progression of diseases such as cardiovascular and neurodegenerative diseases, cancer, and the aging process [7].

Oxidative stress can be determined by measuring the activity of antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), that are also take part in detoxification [8]. Glutathione, one of the non-enzymatic antioxidants that play a crucial role in removing many reactive species, is a tripeptide that tries to prevent toxicity by binding to GSH-dependent enzymes in the cell [9, 10]. Malondialdehyde (MDA) has been widely used in biomedical research as a marker of lipid peroxidation and is obtained by measuring the amount of thiobarbituric acid (TBA) reactive substances

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(TBARS), the secondary product formed by the TBA reaction [11]. As a result, TBARS serves as a reliable indicator in the measurement of the total level of oxidative stress in a biological sample [10].

Antioxidants that can delay or prevent the oxidation of a particular substrate thus have the ability to reduce oxidative stress, DNA mutations, as well as other parameters of cell damage [12]. Various mechanisms have been developed to counter oxidative stress, with antioxidants produced naturally in the human body or supplied externally through foods or supplements [13].

In general terms, flavonoids or phytochemicals originating from plants (often referred to as polyphenols) support the cell regulatory mechanisms by activating pathways that result in a favorable stress response [14]. Recent evidence suggests that *C. mas* with its fruits and leaves are a good source of antioxidants due to its abundant content of anthocyanins, flavonoids, and other phenolics, iridoids, and vitamins [15-17]. *C. mas* have therapeutic effects on various diseases such as diabetes, microbial infections, oxidative stress, hyperlipidemia, and obesity [18-22]. There are also several reports confirming the hepatoprotective effects of *C. mas* in rats by reducing oxidative stress [23, 24].

Statins, also known as HMG CoA reductase inhibitors, are a class of lipid-lowering medications that positively affect antioxidant, anti-inflammatory, and immunomodulatory mechanisms. Atorvastatin (ATR) is one of the most common synthetic statins used for this purpose [25, 26]. It was observed that treatment with ATR in rats with hepatic liver damage reduced lipid peroxidation due to ATR's free radical scavenging activity and suppression of oxidative stress [27]. Previous research found that the pre-administration of ATR (20 mg/kg/day) significantly decreased the serum level of MDA and significantly increased the activities of SOD, GSH, and GPx in the liver tissues induced by Cadmium chloride [26].

The role of plants rich in antioxidants has received increased attention in the research area in recent years. However, there has been little published research effect of a high-fat diet on liver antioxidant enzymes and the preventive effect of *C. mas* on antioxidant activity. Hence, the aim of the present research was to examine the protective and therapeutic effect of *C. mas* on antioxidant enzyme activity and oxidative stress parameters in rats fed with a high-fat diet.

2. RESULTS

As shown in Figure 1., compared with the control group, rats in the HFD group exhibited decreases in the GSH level. In the HFD + *C. mas* group, the GSH level increased compared to the control group. The GSH level increased in the HFD + *C. mas* group (by 185%) and the HFD post-treated *C. mas* group (by 77%) compared to the HFD group which was statistically significant ($p < 0.05$). The level of GSH in HFD + C. *mas* was found to be higher compared to HFD + ATR while considering the groups treated after treatment post treated ATR was higher compared to post treated C. *mas* group ($p < 0.05$).

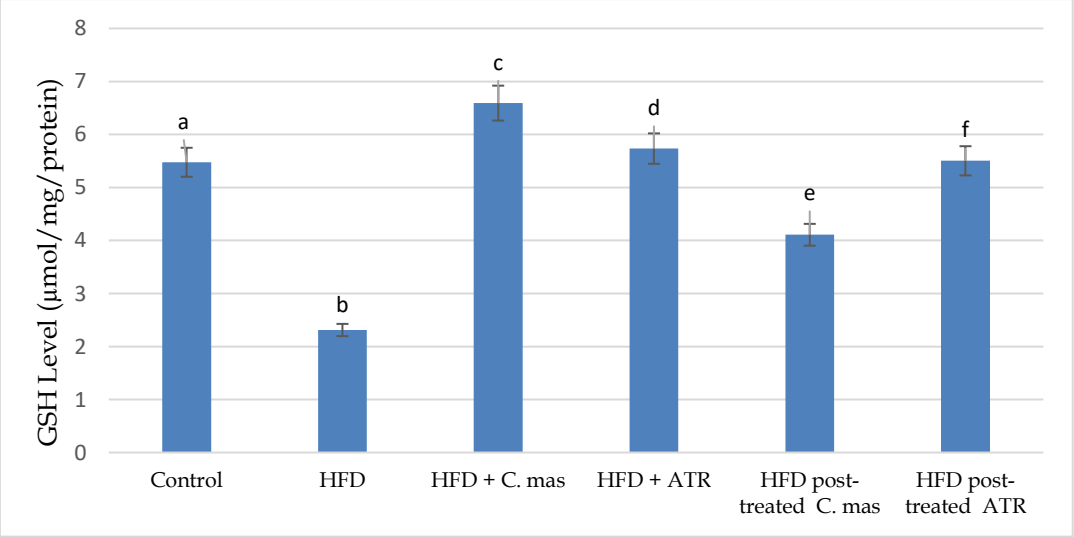

Figure 1. GSH levels (µmol/mg/protein). The letters a, b, c, d, e, and f indicate the differences between the groups. Data showing different letters are significantly different at the $p < 0.05$ level (n = 6).

GPx enzyme activity is given in Figure 2; the enzyme activity decreased by 70% in the HFD group compared to the control group. Compared with the HFD group, the GPx enzyme activity increased both in

the HFD + *C. mas* group (by 295%) ($p < 0.05$). Although the enzyme activity in the HFD + C. *mas* and HDF + ATR groups was higher than in the HFD group ($p < 0.05$)., there was no statistically significant difference between these two groups ($p > 0.05$).

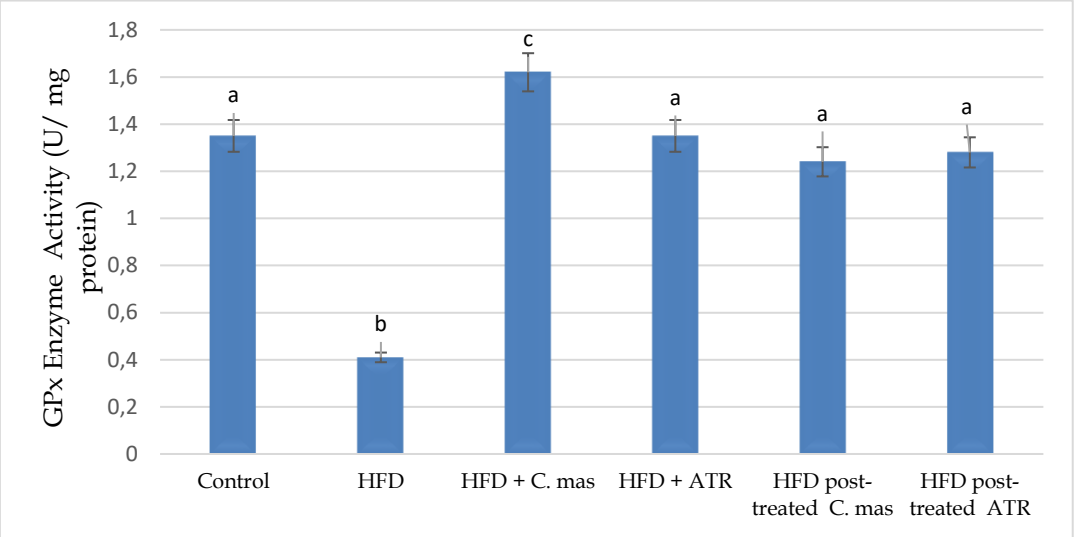

Figure 2. GPx enzyme activity (U/mg protein). The letters a, b, c, d, e, and f indicate the differences between the groups. Data showing different letters are significantly different at the $p < 0.05$ level (n = 6).

Figure 3 shows the SOD enzyme activity; the enzyme activity decreased in the HFD compared to the control group ($p < 0.05$). In addition, the enzyme activity increased significantly in both HFD + *C. mas* (by 105%) and HFD post-treated *C. mas* group (by 129%) compared to the HFD group ($p < 0.05$).

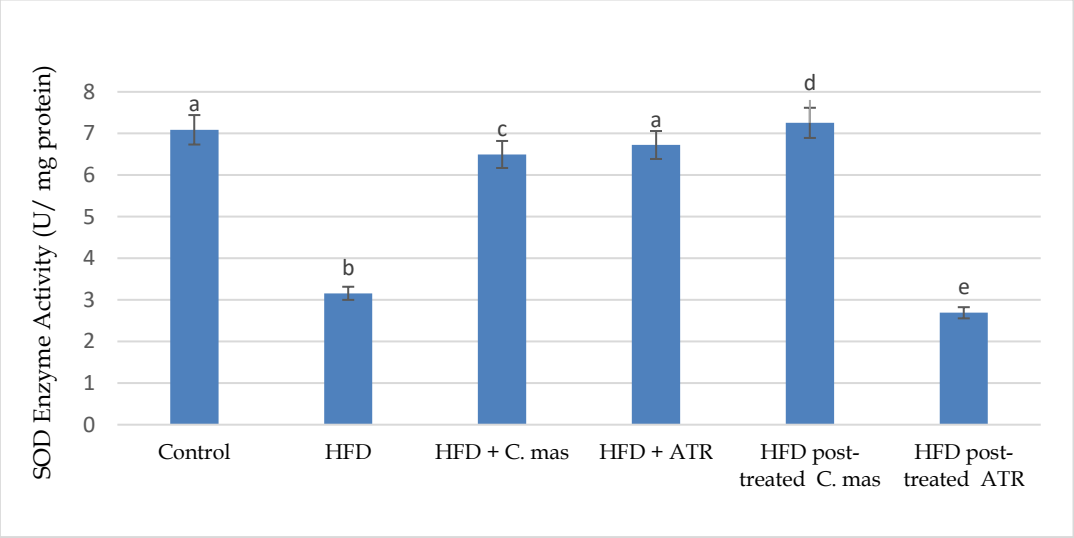

Figure 3. SOD enzyme activity (U/mg protein). The letters a, b, c, d, e, and f indicate the differences between the groups. Data showing different letters are significantly different at the $p < 0.05$ level (n = 6).

The CAT enzyme activity was determined to display significant decreases in the HFD compared to the control group. However, the enzyme activity increased in both HFD + *C. mas* (by 235%) and HFD post-treated *C. mas* group (by 155%) compared to the HFD group (Fig 4., $p < 0.05$). Anti-oxidative enzyme activities (CAT) in the liver of the HFD post-treated *C. mas* group were significantly higher than those in the HFD post-treated ATR group ($p < 0.05$).

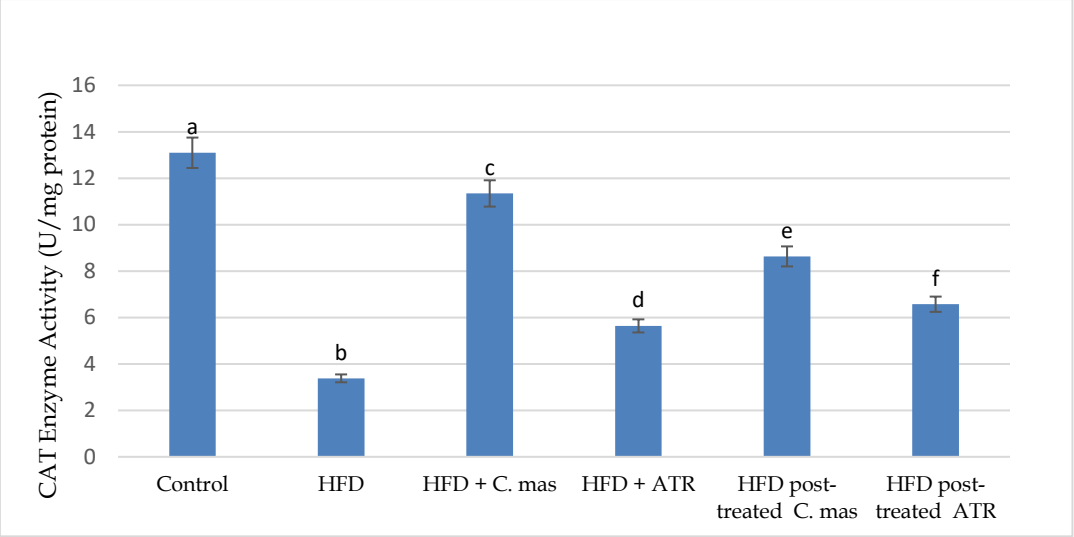

Figure 4. CAT enzyme activity (U/mg protein). The letters a, b, c, d, e, and f indicate the differences between the groups. Data showing different letters are significantly different at the $p < 0.05$ level (n = 6).

Figure 5 shows an increase in TBARS levels in the HFD group compared to the control group. Nevertheless, compared to the HFD group, TBARS levels were similarly decreased in the HFD + *C. mas* group and the HFD post-treated *C. mas* group (by 34% and 40%, respectively); this decrease was statistically significant ($p < 0.05$). TBARS levels in HFD + ATR and HFD then ATR groups were lower compared to the HFD group ($p < 0.05$). Both ATR treatments showed significant decreases in TBARS levels compared to C. *mas* groups ($p < 0.05$).

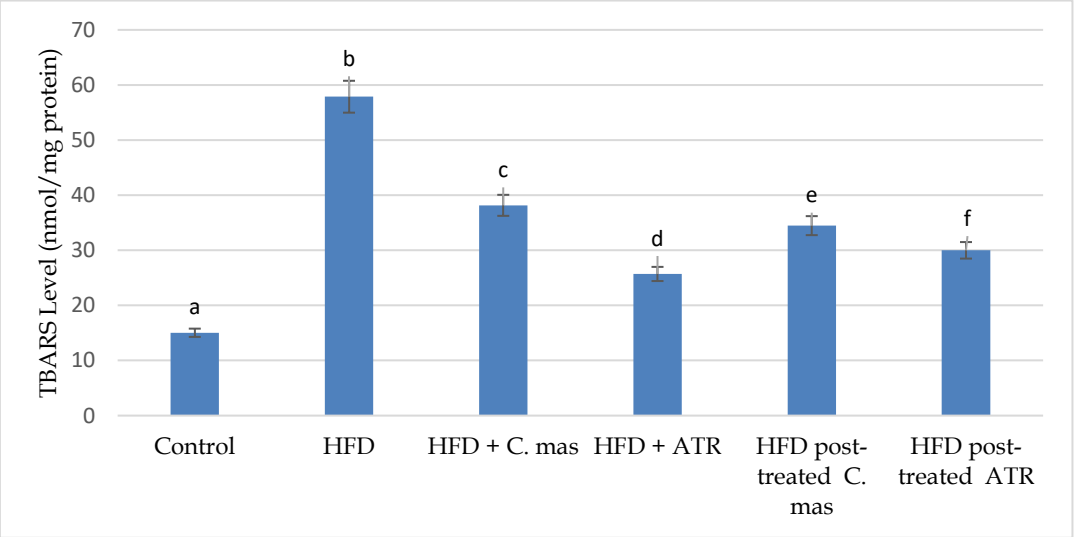

Figure 5. TBARS level (nmol/mg protein). The letters a, b, c, d, e, and f indicate the differences between the groups. Data showing different letters are significantly different at the $p < 0.05$ level (n = 6).

3. DISCUSSION

In the present study, the effects of *C. mas* on the antioxidant system elements of GSH, GPx, SOD, and CAT enzyme activities and lipid peroxidation (TBARS) levels were determined in the liver tissue of rats exposed to the HFD effect.

Antioxidative enzyme activities in the rats' livers decreased in the HFD group compared to the control after eight weeks of high-fat feeding. In addition, the lipid peroxidation (TBARS) level of the HFD group was higher than the control group. Our findings are consistent with the statement that a high-fat diet can cause oxidative stress and lipid metabolism disorders in rats due to long-term dietary fat intake that may lead to

metabolic inflammation and adipose tissue dysfunction [35]. In addition, free fatty acids in circulation can cause lipotoxicity and induce the production of ROS in peripheral tissues, including the liver.

The level of GSH both in the liver of the rats fed with *C. mas* (HFD + C. *mas*) and the group HFD post-treated *C. mas* increased compared to the HFD, revealing that *C. mas* intake was significantly effective. Francik et al. found a decreased GSH level in the high-fat group than the control group and observed that the addition of the *C. mas* diet causes a significant increase in the level of GSH in adipose tissue [36]. The decrease in GSH level in the HFD occurs due to the peroxidation of membrane lipids in the cell membranes. It has been stated that the protective effect and the protection of cell integrity with the addition of *C. mas* to the diet may be due to the increase in GSH level [36]. In the study of Sozanki et al., it was determined that the GSH level in the CH (1% cholesterol) group showed a significant decrease compared to the control group. Furthermore, GSH levels increased in the groups fed with iridoid loganic acid (CH+LA; 20 mg/kg body weight + 1% cholesterol) and anthocyanins (CH+ANT; 10 mg/kg body weight+1% cholesterol) obtained from *C. mas* for 60 days compared to the CH group [37]. A recent study reported that the concentration of GSH in rat serum was decreased in a high-fat diet compared to the control but increased significantly in the serum of rats treated with simple *C. mas* extract compared to the HFD group ($p < 0.05$) [38]. Overall, these studies substantiated our results and highlighted the beneficial effects of *C. mas* on the GSH level.

SOD is in charge of limiting oxidative damage [38] and according to our results, SOD enzyme activity decreased in the HFD compared to the control and increased in the HFD + *C. mas* and HFD post-treated *C. mas* compared to the HFD. The protective effect of *C. mas* extract as an antioxidant was more favorable compared to atorvastatin treatment. Likewise, the same results were seen in the CAT enzyme activity. Francik et al. determined a significant decrease in CAT in rat brain tissue in the high-fat diet group, and *C. mas* showed a protective effect when given with diet [36]. Based on the earlier research, we anticipated that the enhanced activities of enzymes reduce the accumulation of reactive free radicals.

In this study, the increase in GPx enzyme activity in treatment groups was observed as expected in parallel with the rise in the level of GSH; *C. mas* showed protective antioxidant properties in inducing the GPx enzyme, which catalyzes the GSH reaction while contributing to detoxification. Sozanki et al. also reported that while GPx enzyme activity decreased in the CH group, there was no change in the CH+LA and CH+ANT groups in rabbits fed for 60 days [39]. Similarly, there was no significant change in SOD enzyme activity. In the current study, GPx and SOD enzyme activities increased in all groups to which *C. mas* and atorvastatin were added compared to the HFD group ($p < 0.05$). This difference between studies suggests that the use of fruit extract in terms of antioxidant properties has a more beneficial effect on the mentioned enzyme activities.

Reducing harmful oxidative end products such as MDA, measured with the TBA method, presents an alternative mechanism for alleviating the harm caused by oxidative stress [40]. We found a significant increase in TBARS levels was determined in the HFD, HFD + *C. mas*, and HFD + ATR groups compared to the control group. This increase in the amount of TBARS may be due to the decrease in the antioxidant capacity and the increase in the oxidative stress level of the organism. However, a decrease in the amount of TBARS was determined in the HFD + *C. mas* and HFD post-treated *C. mas* groups compared to the HFD group ($p < 0.05$), indicating that adding *C. mas* to the diet has a protective effect of *C. mas* in these groups.

Although some researchers have examined the effects of C. *mas* and statins on liver antioxidant enzymes [37, 30], a previous study has yet to investigate and compare the atorvastatin and C. *mas* effect. The antioxidative effect of atorvastatin has been attributed to its cholesterol-lowering properties and possible inhibition of NADPH oxidase activation, which catalyzes the production of superoxide free radicals [26]. In our study, atorvastatin treatment significantly attenuated the increased TBARS level caused by HFD and compared to C. *mas* treatments, the effect is more favorable. Although it is dose-dependent and associated with elevated liver transaminases that may occur in the first months of statin therapy, it is generally not associated with any long-term hepatic dysfunction [41]. Nevertheless, searching for alternative treatments that do not have harmful side effects is also essential.

Some limitations need to be noted regarding the present study. Although we showed the preventive and therapeutic effects of *C. mas* on oxidative stress, assessing a direct correlation is difficult because other potential factors may influence intracellular antioxidant defense mechanisms. Another limitation is that although the significant anatomical and physiological similarities between humans and animals, the results of our study should be replicated in human studies. Notwithstanding these limitations, the study is unique in investigating the long-term effect of a high-fat diet. The strength of the study is the evaluation of both the preventive and therapeutic effects of *C. mas* on antioxidant activity.

4. CONCLUSION

The current study aimed to determine the effect of *C. mas* on the activity of the antioxidant enzymes in rats fed a high-fat diet. The contribution of this study has been to confirm that a high-fat diet negatively impacts the liver's antioxidant enzyme status. Furthermore, the study has indicated that *C. mas* may be an alternative and reliable source of a therapeutic agent for high-fat diet-induced oxidative stress. Moreover, data show the favorable effect of *C. mas* in preventing and treating oxidative stress. Further research should be carried out to better understand the mechanisms underlying the impact of *Cornus mas* L. on hepatoprotective effect.

5. MATERIALS AND METHODS

5.1. Preparation of the extract

Cornus mas L. stems, flowers, and leaves (with no roots) were collected in the harvest season in August from Mersin (Çamlıyayla population) / Turkey in 2021. The taxonomic definition was made by an expert at Çukurova University, Department of Biology, Botany. The fruits were air-dried for seven days at room temperature, and then finely ground samples were extracted according to the method of Sokmen et al. [28]. For the extraction, the sample weighing about 100 g was extracted with 400 ml of methanol for 6 hours at 60 °C in a Soxhlet. The extract was then filtered through a paper filter and concentrated under pressure at 45 °C to obtain a waxy substance. The extracts obtained were lyophilized and stored in the refrigerator at +4 °C until use.

5.2. Animals and experimental design

Forty-eight adult Sprague Dawley rats (24 male, 24 female), 3-4 months old and weighing 200–250 g, were obtained from the Istanbul University Aziz Sancar Experimental Medicine Research Institute. The rats were housed 4 in per cage with the temperature maintained at 22 ± 2 C, relative humidity at 55 ± 10%, and a 12 h light/dark cycle. All experiments were conducted under the protocol approved by the ethical committee on Animal Experimentation and Research Center, Marmara University, Turkey, according to the Animal Experimentation (46.2021 Mar).

Its therapeutic effect in previous research was considered while determining the extract dose of C-mas [29,30] and atorvastatin (ATR) [26] treatment. After one week of acclimatization, rats were randomly assigned to six groups. For twelve weeks of the experiment, the animals in the control group were fed a standard diet. The other groups High Fat Diet (HFD), HFD + *C. mas* (200 mg/kg/day; 8 weeks), HFD + ATR (20 mg/kg/day; 8 weeks), HFD post-treated with *C. mas* (200 mg/kg/day; 4 weeks), HFD post-treated with ATR (20 mg/kg/day; 4 weeks) received a high-fat diet for eight weeks, and following these weeks, they were fed a standard diet for four weeks. A summary of the experimental procedure is given in Figure 6.

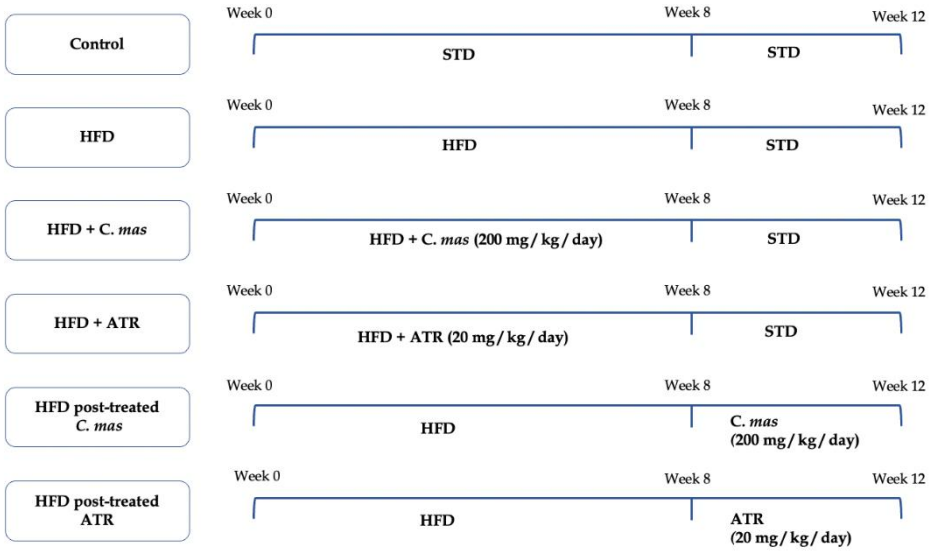

Figure 6. Schematic diagram of the experimental groups and treatment procedure

5.3. Liver tissue biochemistry

The activity of the antioxidant enzymes, SOD, CAT, GPx, and detoxification agent GSH was measured in the liver tissue. For this purpose, liver tissues were homogenized with a phosphate-buffered saline solution containing 2.5 mM ATP at 1/10 (w/v). Homogenates were centrifuged at +4 °C for 15 min at 13000 ×g. SOD [31], CAT [32], GPx [33] enzyme activities; GSH [32], and TBARS [34] were determined with the obtained supernatants.

5.4. Statistical analysis

For statistical analysis, Duncan multiple comparison test was used in one-way ANOVA post-hoc variance analysis. The difference in statistical analysis between the control and treatment groups performed in the SPSS 22.0 (SPSS Inc., Chicago, IL) for Windows and $p < 0.05$ was considered statistically significant.

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Author contributions: Concept – D.K.; Design – D.K., M.E.Ç.; Supervision – Ş.A., M.E.Ç.; Resources – D.K., Ş.A., M.E.Ç., A.N.Y.; Materials – D.K., M.E.Ç., A.N.Y; Data Collection and/or Processing – D.K., M.E.Ç., A.N.Y; Analysis and/or Interpretation – D.K.; Literature Search – D.K.; Writing – D.K., Ş.A..; Critical Reviews – D.K., Ş.A., M.E.Ç., A.N.Y.

Conflict of interest statement: The authors declared no conflict of interest in the manuscript.

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