

Protective Effects of Antioxidant-Rich *Crataegus monogyna* Fruit Extract Against Hydrogen Peroxide-Induced Hepatorenal Oxidative Damage in Rats

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Abstract: The main objective of this study is to investigate the protective potential of antioxidant-rich extract from *Crataegus monogyna* fruit against hydrogen peroxide (H₂O₂)-induced hepatorenal syndrome. Two doses of *Crataegus monogyna* extract (100 and 200 mg/Kg b.wt) were administered to normal (non-stressed) and stressed rats (hydrogen peroxide, 1%) for a period of 6 weeks. Phytochemical composition of *Crataegus monogyna* extract demonstrated the existence of various antioxidant compounds from different chemical classes, represented mainly by rutin (4731.05 mg/kg), epicatechin (1365.50 mg/kg), vanillin (343.10 mg/kg), and quercetin (327.36 mg/kg), among others; reported as having a high antioxidant capacity. Moreover, daily administration of H₂O₂ leads to a significant change in renal biochemical parameters, mainly creatinine, uric acid, and urea, as well as a notable increase in hepatic enzyme levels and a shift in both serum and urine renal electrolytes, a major sign of hepatorenal syndrome. The co-administration of *Crataegus monogyna* fruit extract significantly lessened the detrimental impact of oxidative stress on renal and liver function. Additionally, the extract significantly restored hepatic enzyme levels and renal biomarkers in a dose-dependent manner. Furthermore, the *in vitro* anti-inflammatory activity, evaluated using the albumin denaturation test, showed an IC₅₀ of 321.65±4.12 µg/mL. Hence, it is possible to conclude that *Crataegus monogyna* fruit extract constitutes a promising source of natural antioxidant agents against oxidative stress.

Keywords: *Crataegus monogyna*; hydrogen peroxide; oxidative stress; antioxidant; anti-inflammatory; hepatorenal protection.

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1. Introduction

The pathophysiology of numerous chronic diseases is significantly influenced by oxidative stress, including diabetes, inflammation, cancer, and immune system disorders [1]. An imbalance of redox reactions leads to the overproduction of reactive oxygen species (ROS),

including hydroxyl radicals ($\cdot\text{OH}$) and perhydroxyl radicals ($\text{HO}_2\cdot$), free radicals generated by hydrogen peroxide (H_2O_2). These free radicals can attack essential macromolecules such as proteins, lipids, and DNA, disrupting cellular structure and organ function. The resulting damage impairs cellular organization and aids in the development of illnesses linked to oxidative stress, such as hepatocellular damage [2]. Different internal contributors are implicated in the management of ROS dynamics, including enzymatic and non-enzymatic antioxidative defense systems [3]. However, ROS distribution in different biosystems highlights their critical role in the pathogenesis.

The daily diet contains different components that participate actively in strengthening the antioxidant defenses against oxidative damage [4]. Several natural products, such as aromatic and medicinal plants, have been integrated into the human daily diet since ancient times [5,6]. *Crataegus monogyna* (CM), also known as hawthorn, is a medicinal plant widely used as a natural remedy for multiple diseases. It belongs to the Rosaceae family, genus *Crataegus*, which includes more than 1000 species worldwide. Traditional uses of the plant appear in the medical text Compendium of Materia Medica, reporting its wide range of medical uses in traditional Chinese medicine [7]. Leaf and flower preparations exhibit interesting pharmacological activities, including cardiac strengthening, vasodilation, hypotension, sedation, diuretic, and anticonvulsant effects [7,8]. Recently, CM has gained prominence in scientific research, being recognized for its interesting chemical composition and versatile uses, making it a potential candidate for extracting active ingredients with pleiotropic effects [9]. In fact, a delve into the phytochemical profile of CM revealed the presence of a wide range of physiologically active substances, including organic acids, phenolics, terpenoids, and steroids [7]. A recent study found that the aqueous extract of CM contains different bioactive compounds, such as tannic acid, catechol, gallic acid, and L-histidine, well known for their multiple functionalities [10]. In the same context of evaluating the pharmacological properties of CM, Radi *et al.* showed that this plant's aqueous extract had intriguing antihyperglycemic properties by inhibiting pancreatic α -amylase activity [11]. Furthermore, the ethanolic extract of CM exhibited a significant cytotoxic effect against numerous cancer cells, such as K-562 cells and HL-60 cells, by exerting its effects on key targets, including lipoxygenase, tyrosine kinase, cytochrome P450, and TNFR1-associated death domain protein [12]. Actually, the scientific community has sparked a burgeoning interest in examining the biological properties of natural products, harnessing their potential for the discovery of natural effective agents and their applications as active ingredients in the nutraceutical, cosmetic, and medication industries.

Within this framework, this study hypothesizes that polyphenol-rich *C. monogyna* fruit extract mitigates H_2O_2 -induced oxidative and inflammatory damage in hepatic and renal tissues.

2. Materials and Methods

2.1. Extraction procedure.

The fruit of CM was harvested in October 2023 from Ain Chkef forest (Latitude: 33.9636° N; Longitude: 5.0208° W; Altitude: 499 m), Fez-Meknes region. For extractions of bioactive compounds, 10 g of CM fruit powder was macerated in 300 mL of 70% ethanol-water solution (v/v) with mechanical stirring for one week at room temperature. The final extract was

filtered (Whatman, n°1), freeze-dried after being concentrated in a rotary evaporator. The dried extract was subsequently prepared for further experiments.

2.2. Chemical analyses of the extract.

2.2.1. Quantification of phenolic and flavonoid contents.

The total polyphenol content (TPC) was measured using the Folin-Ciocalteu assay as outlined previously by our research team [13]. Findings were presented as milligrams of gallic acid equivalent (GAE) per gram of CM dry extract (mg GAE/g dry extract).

The quantification of total flavonoid content (TFC) was made using the aluminum chloride colorimetric technique [14]. The findings are presented as mg of quercetin equivalent per gram (mg QE/g dry extract).

2.2.2. Antioxidant components identification and quantification.

The HPLC-ESI-MS (Agilent 1260 series, Palo Alto, CA, USA) with an AB SCIEX Triple Quad 3500 detector (AB Sciex, Foster City, CA, USA) equipped with an electrospray ionization source (ESI) was used to identify the phenolic profile of CM. Two mobile phases (formic acid and acetonitrile with 0.1% formic acid 0.1%) were used in a Luna C18 column (Phenomenex) with an injection volume of 5 µL. The separation process involved the use of 0.1% formic acid (solvent A) and acetonitrile with 0.1% formic acid (solvent B) as eluents in a gradient (98 % of A from 0 to 4.0 min, 98–80 % of A from 4.0 to 7.0 min, 80–10 % of A from 7.0 to 14.0 min, 10 % of A from 14.0 to 15.0 min, 10–98 % of A from 15.0 to 17.0 min) at a flow of 0.3 mL/min.

Nitrogen was used as a collision gas and nebulizer in a positive/negative ionization source using a turbo VTM. The data were collected via multiple reaction monitoring (MRM). Sigma-Aldrich Corporation (St. Louis, Missouri, USA) provided all standards with the highest level of purity (> 96%). The identification of each individual phenolic compound was determined by taking into account the retention time (RT), mass spectra (m/z of the ions), and the concentration was determined using the calibration curve of each corresponding standard.

2.2.3. Antioxidant ability.

The antioxidant capacity of CM extract was assessed using four distinct assays, as detailed by Laaroussi *et al.* [14], namely total antioxidant capacity (TAC), ferric reducing antioxidant power (FRAP), free radical scavenging using 2,2-diphényl 1-picrylhydrazyle assay (DPPH), and radical cation decolorization (ABTS).

For the FRAP assay, a solution of ferrous sulfate ($\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$) was utilized to prepare the standard curve (1000–100 µM, $R^2 = 0.993$). The FRAP values are reported as micromoles of ferrous equivalent per gram of plant extract (mmol Fe^{2+} /g). Total antioxidant capacity of CM extract was evaluated by the phosphomolybdenum method according to the method already described by Laaroussi *et al.* [15]. The combination was then incubated for 90 minutes at 95 °C in a water bath. Ascorbic acid equivalent (AAE) milligrams per gram of sample (mg AAE/g dry extract) was used to express the results.

For the DPPH and ABTS assays, IC_{50} values were determined using different extract concentrations, ensuring inhibition percentages between 20% and 80%. The ABTS and DPPH radical inhibition percentages were determined using equation (1).

The results were expressed as milligrams of *CM* extract per milliliter (mg/mL). Ethanol (70%) was utilized as the control solution in place of the sample.

$$\% \text{ Inhibition} = \frac{\text{Abs control} - \text{Abs sample}}{\text{Abs control}} \times 100 \quad (1)$$

2.2.4. Anti-inflammatory effect of the extract.

The inhibition of albumin denaturation method was used to assess the *CM* extract's anti-inflammatory effectiveness [16]. In summary, 0.5 mL of a 0.2% bovine serum albumin (BSA) solution in Tris buffer (pH 6.8) was combined with 0.5 mL of *CM* extract at varying concentrations or with a standard solution of diclofenac sodium. The mixtures were incubated at 37°C for 15 minutes, then heated to 72°C for another 5 minutes. Following cooling, the absorbance was read at 660 nm, and equation 1 was used to estimate the BSA inhibition percentage. The findings were reported as µg/mL of extract.

2.3. Experimental animal protocol.

In this experiment, 30 Wistar rats were kept in a typical setting with 12-hour light/dark cycles, 23±3°C, and free access to tap water. They were also fed standard rodent chow. The Animal Facility and the Laboratory SNAMOPEQ, University of Sidi Mohamed Ben Abdellah, Fez, Morocco, were responsible for obtaining the ethical approval (S-23-USMBA-SNAMOPEQ 2023–03). In order to prevent and reduce animal suffering and the number of animals used in tests, the care and handling of the animals complied with EU Directive 2010/63/EU.

Rats were randomly allocated into 6 groups of 5 rats. Groups 1 to 3 represent the non-stressed control groups, and groups 4 to 6 were subjected to oxidative stress induced by H₂O₂.

Group DW: Rats received distilled water (10 mL/kg b.wt) via gavage during the period of treatment and had unrestricted access to tap water;

Group CM-d1: Rats received *CM* fruit extract (100 mg/kg b.wt) via gavage and had unrestricted access to tap water;

Group CM-d2: Rats received *CM* fruit extract (200 mg/kg b.wt) via gavage and had unrestricted access to tap water;

Group H₂O₂: Rats received H₂O₂ 1% solution (10 mL/kg b.wt) via gavage and had unrestricted access to tap water;

Group H₂O₂ + CM-d1: Rats received H₂O₂ 1% solution one hour before the oral administration of *CM* fruit extract (100 mg/kg b.wt);

Group H₂O₂+ CM-d2: received H₂O₂ 1% solution daily by gavage one hour before the oral administration of *CM* fruit extract (200 mg/kg b.wt).

The duration of the experiment was six weeks. Animals were fasted for 12 hours following their last meal at the end of the experiment. Urine samples were taken using particular metabolic cages, and each rat's blood was drawn into tubes using retro-orbital bleeding under mild anesthesia. Plasma was then separated by centrifugation (2000 g) for 10 minutes.

2.4. Biochemical analysis.

Urine and blood samples (plasma) were obtained to analyze various kidney and liver biomarkers, including creatinine, urea, uric acid, albumin, total protein, alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and C-reactive protein (CRP). Ion-selective potentiometry was used to assess sodium (Na^+), potassium (K^+), and chloride (Cl^-) in urine and plasma electrolytes (Architect c8000i biochemistry analyzer).

2.5. Statistical analysis.

The means $\pm$ standard deviation (SD) are used to display all data. GraphPad Prism® software (version 8.0; GraphPad Software) was used to perform statistical comparisons between groups using two-way analysis of variance (ANOVA) followed by Tukey's test. Significance was expressed as $p < 0.05$.

3. Results and Discussion

3.1. Phenolic profile and anti-inflammatory activities.

As presented in Table 1, the hydro-ethanolic extract of *CM* fruit demonstrates substantial antioxidant potential, as evidenced by its high phenolic content and powerful antioxidant activity *in vitro*.

The extract showed a TPC of 91.82 ± 6.3 mg GAE/g and total flavonoids of 34.95 ± 1.2 mg QE/g. Considering the eco-regional characteristics of the plant growing area, the extraction solvents/techniques used, and the methods of reporting the results, it is relevant to mention that it remains difficult to compare our data with those previously published [17].

Bahri-Sahloul and coworkers provided a broad overview of phenolic content from *C. monogyna* fruits from 14 genotypes found in Tunisia, showing a range of values between 9.1 and 17.8 mg/g [18], while other studies have reported values from 16.42 to 57.07 mg/g [19,20]. For instance, Mraihi *et al.* extracted bioactive compounds from freeze-dried *C. monogyna* fruits collected from Tunisia using methanol-water (80%, v/v), and showed values of 122.26 mg GAE/100 g and 123.35 mg GAE/100 g in pulp and peel, respectively [21]. In contrast, Bernatoniene *et al.* have quantified the TPC in the water and the hydroethanolic extract (ethanol-water, 70/30 v/v), and reported a content of 182 mg GAE/100 mL for the hydroethanolic extract, roughly three times more than that of the water extract [22]. These discrepancies highlight the impact of geographical origin and methodological differences on reported phenolic content.

Flavonoids are a valuable subclass of phenolic compounds. In the current study, the reported value for total flavonoids (34.95 ± 1.2 mg QE/g) is in line with the values reported in the literature, where TFC values in hawthorn fruits range from 4.46 to 147 mg QE/g [23].

Furthermore, HPLC-ESI-MS was used to identify and quantify the individual bioactive compounds in the *CM* extract, and the results are displayed in Table 1.

A total of nineteen bio-compounds belonging to different chemical classes, such as phenolic acids (3,4-dihydroxybenzoic, *p*-coumaric, gallic, 4-hydroxybenzoic, vanillic, syringic, ferulic and salicylic acids), flavonoids (rutin, epicatechin, quercetin, catechin, naringenin and luteolin), phenolic aldehydes (syringaldehyde and vanillin) and alkaloids (methylxanthine family, like caffeine, theophylline and theobromine) were identified in the *CM* extract.

Identifying these bioactive molecules is essential for a comprehensive discussion of their *in vitro* antioxidant activities as well as for understanding their potential contributions to the observed hepato-protective effects *in vivo*. Rutin (4731.05 µg/g), epicatechin (1365.50 µg/g), and 3,4-dihydroxybenzoic acid (562.85 µg/g) were identified as the most abundant molecules. Additionally, vanillin (343.10 µg/g), quercetin (327.36 µg/g), *p*-coumaric acid (177.13 µg/g), and gallic acid (153.87 µg/g) were found in moderate amounts, while caffeine (4.06 µg/g), salicylic acid (5.93 µg/g), and theophylline (0.56 µg/g) were quantified in lower concentrations. The other compounds were found in concentrations between 11 and 90 µg/g. Prior research revealed the existence of other phenolic acids, flavanols, flavonols, lignans, and anthocyanins families of different origins [24]. This variability of individual bioactive molecules highlights the crucial need for their identification to correlate better the biological activities of *CM* extract with its specific bio-compounds and to propose a possible underlying mechanism of action.

Table 1. TPC, TFC, individual phenolic compounds, antioxidant activity (DPPH, ABTS, FRAP, and TAC), and anti-inflammatory activity of *Crataegus monogyna* fruit extract.

TPC and TFC	
TPC (mg GAE/g dry extract)	91.82±6.3
TFC (mg QE/g dry extract)	34.95±1.2
Individual antioxidant compounds (µg/g)	
Rutin	4731.05±164.95
Epicatechin	1365.50±61.50
3,4-Dihydroxybenzoic acid	562.85±17.45
Vanillin	343.10±6.80
Quercetin	327.36±12.96
<i>p</i> -Coumaric acid	177.13±4.72
Gallic Acid	153.87±1.27
Catechin	87.81±3.40
Syringaldehyde	84.89±3.15
4-Hydroxybenzoic acid	64.57±1.45
Vanillic acid	54.45±1.75
Theobromine	32.75±1.75
Syringic acid	18.68±0.46
Naringenin	15.22±0.46
Ferulic acid	12.71±0.59
Luteolin	11.70±0.90
Salicylic acid	5.93±0.50
Caffeine	4.06±0.12
Theophylline	0.56 ±0.01
Antioxidant activity	
DPPH IC ₅₀ (mg/mL)	3.33±0.12
ABTS IC ₅₀ (mg/mL)	2.12±0.09
FRAP (mmol Fe ²⁺ /g dry extract)	0.59±0.04
TAC (mg AAE/g dry extract)	168.62±1.72
Anti-inflammatory activity	
IC ₅₀ (µg/mL)	321.65±4.12

The extract's overall antioxidant capacity is increased by phenolic components, which include both flavonoid and non-flavonoid chemicals, which significantly contribute to scavenging free radicals and reducing oxidative stress.

The obtained extract exhibited interesting antioxidant capacity, showing free radical scavenging activities with an IC₅₀ value of 3.33±0.12 and 2.12±0.09 mg/mL for DPPH and ABTS assays, respectively. As shown by the lower IC₅₀ value for ABTS compared to the DPPH

test, this probably results from the different interactions between the specific individual chemical constituents of the extract and these radicals. The ABTS assay measures the ability of the extract to scavenge the ABTS radical cation, which is a more diffusible and water-soluble species, potentially allowing for greater interaction with the extract's antioxidant compounds. Conversely, the DPPH radical is a more stable, non-polar radical, which might be less accessible to some of the extract's hydrophilic antioxidants. The higher efficiency in scavenging ABTS radicals suggests that the extract contains components that are particularly effective against water-soluble radicals or that its antioxidant profile includes compounds with a higher affinity for ABTS compared to DPPH. This selectivity highlights the importance of both the radical specificity and the specific antioxidative properties of the phytochemicals present in *CM*.

Moreover, *CM* extract showed an antioxidant reducing power value of 0.59 ± 0.04 mmol Fe^{2+} /g dry extract and total antioxidant activity of 168.62 ± 1.72 mg AAE/g dry extract. These results are in agreement with recent literature associating the antioxidant properties of plant extracts with their rich and diverse content of antioxidant components [17], making them valuable for potential applications in health and food formulation, such as a preservative.

The *in vitro* anti-inflammatory activity, conducted using an albumin denaturation test as a functional approach, is displayed in Table 1. Accordingly, *CM* extract has a lower inhibition of albumin denaturation effect than the control drug diclofenac sodium, with IC_{50} values of 321.65 and 152.18 $\mu\text{g/mL}$, respectively. The *CM* extract may exert its anti-inflammatory effects through indirect mechanisms rather than direct inhibition of protein denaturation. For instance, the extract could influence inflammatory pathways through antioxidant activity, modulation of cytokine levels, or inhibition of other inflammatory mediators. These pathways might not directly result in high protein denaturation inhibition, thereby affecting the reported IC_{50} value. Amarti *et al.* found that the administration of 1000g/kg exhibited the highest anti-inflammatory effect by inhibiting 99.10% of edema[12].

3.2. Effect of hydrogen peroxide and *Crataegus monogyna* fruit extract on liver biochemical changes.

The liver plays a central role in a variety of metabolic processes essential for maintaining systemic balance. It is responsible for the metabolism of approximately 70% to 80% of xenobiotics, including drugs and toxins, through a two-phase process involving oxidation and conjugation, which allows them to be eliminated from the body. Additionally, the liver regulates nutrient metabolism by converting carbohydrates, proteins, and fats into energetic substrates. However, its pivotal functions are compromised in several health disorders characterized by excessive exposure to oxidant molecules, lipid accumulation, hepatocyte dysfunction, and chronic inflammation[12].

Within this framework, an experimental animal model was used to examine the protective ability of *Crataegus monogyna* fruit extract against hydrogen peroxide-induced hepatorenal syndrome. The results showed that the levels of liver enzymes (ALT, AST, and ALP) were considerably elevated after 6 weeks of H_2O_2 -1% administration and protein C-reactive as credible biomarkers of liver function (Figure 1). The elevated levels of hepatic enzymes confirmed the hepatotoxicity of H_2O_2 , which causes histological damage to the hepatic tissue, impairing the liver's normal physiological function. It has been confirmed that hydrogen peroxide at elevated concentrations perturbs redox balance, which contributes to

oxidative stress [25,26]. In contrast, the administration of *C. monogyna* fruit extract counteracted the harmful effect of H₂O₂ by normalizing hepatic enzyme levels and C-reactive protein compared with the control group. Interestingly, the studied extract did not induce any signs of toxicity in normal rats and significantly reduced C-reactive protein compared with the control group. H₂O₂ disrupts hepatocyte physiological processes by penetrating cell membranes and producing hydroxyl radicals [27]. It induces oxidative stress, inflammation, and cell damage that promote enzyme leakage into the blood circulation [28].

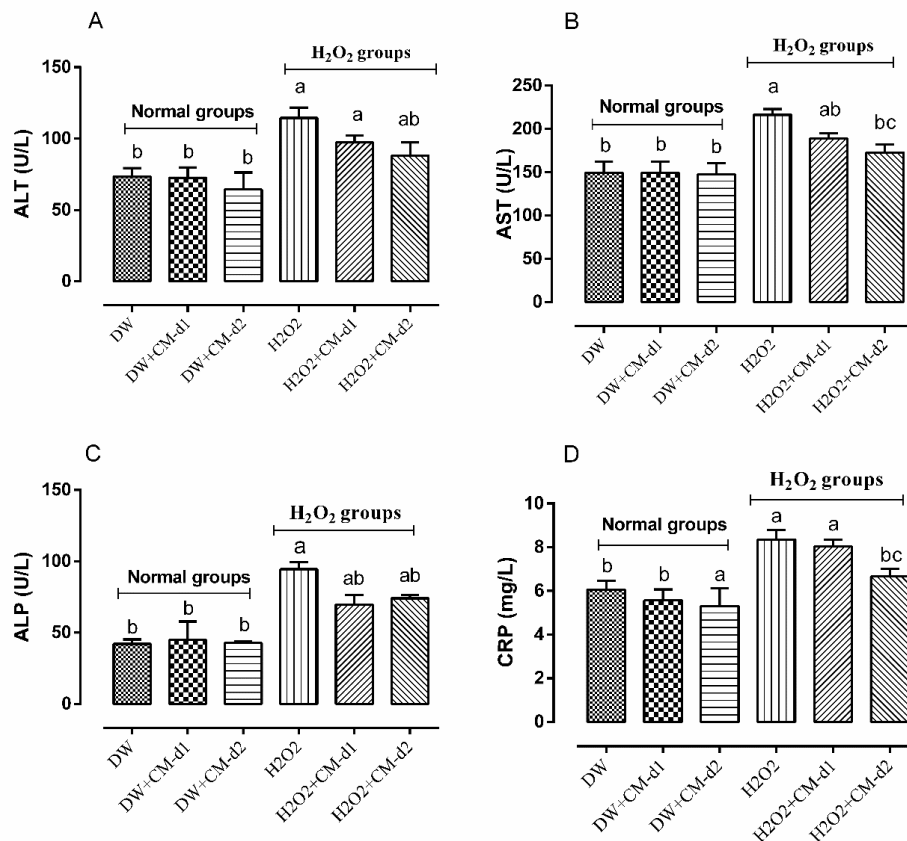


Figure 1. Effect of *Crataegus monogyna* fruit extract on hydrogen peroxide-induced changes in (A) alanine aminotransferase (ALT); (B) aspartate aminotransferase (AST); (C) alkaline phosphatase (ALP); (D) C-reactive protein (CRP) in Wistar rats.

Natural remedies provide multiple active ingredients significantly implicated in the proper functioning of the body's physiological functions. These protective effects are attributed to the complex chemical composition of natural products like *C. monogyna* products. It contains various phytoactive components, including rutin, epicatechin, 3,4-dihydroxybenzoic acid, quercetin, vanillin, and other compounds at different concentrations (Table 1). Rutin, in particular, has been shown to alleviate liver injuries and hepatotoxicity by improving various functional biomarkers, reducing oxidative stress, and modulating inflammatory responses. It works by decreasing lipopolysaccharide levels, enhancing intestinal barrier integrity, and inhibiting inflammatory pathways such as the MyD88-independent NF- κ B signaling pathway [29].

It has been reported that the daily co-administration of rutin (28 mg/kg b.wt) attenuated liver injuries and hepatotoxicity related to vortioxetine. Accordingly, rutin significantly improved functional biomarkers, including antioxidant enzymes, hepatic enzymes, oxidative stress parameters, and inflammatory markers [30]. Moreover, a recent study documented that

the combination of rutin with iron oxide nanoparticles resulted in the attenuation of hepatotoxicity by reducing hepatic enzyme levels (ALT and AST) and cardiotoxicity by decreasing creatine kinase-myocardial B fraction and LDH levels, upregulation of heat shock protein 70 (HSP70), and downregulation of tumor necrosis factor- α (TNF- α) expression in liver and heart tissues [31]. Substantial evidence shows that rutin alleviates inflammation by decreasing lipopolysaccharide levels in serum and liver, boosting the production of short-chain fatty acids, and enhancing intestinal barrier integrity. Moreover, rutin also inhibits the MyD88-independent NF- κ B signaling pathway [32]. In the same context, He *et al.* [33] found that rutin exhibits its protective effects by controlling the TLR4/MyD88/NF- κ B inflammatory signaling pathway.

Epicatechin, another important biomolecule of *C. monogyna*, offers protective effects against toxic agents like methotrexate and carbon tetrachloride. It is effective against the harmful effects of methotrexate by enhancing antioxidant defense systems (glutathione, catalase, superoxide dismutase, and glutathione peroxidase) and reducing inflammatory reactions [34]. Furthermore, epicatechin exhibited considerable hepatoprotective effects against carbon tetrachloride by decreasing hepatic malondialdehyde levels and upregulating antioxidant defense systems, such as glutathione peroxidase (GPx), glutathione S-transferase (GST), nitric oxide synthase (NOS), catalase (CAT), and cytochrome P450 (CYP450) levels [35]. These findings suggest that the documented effects of *C. monogyna* are likely due to the synergistic actions of its diverse active compounds. These compounds collectively contribute to its ability to combat oxidative stress, inflammation, and liver damage, highlighting the potential of *C. monogyna* as a valuable natural remedy for oxidative stress management and liver protection.

3.3. Effect of *Crataegus monogyna* fruit extract on kidney function.

3.3.1. Effect of interventions on renal biomarkers.

Hydrogen peroxide, while not a free radical itself, is a precursor to highly reactive free radicals that drive oxidative damage in renal cells. Upon cellular entry, H_2O_2 is converted into more reactive species, including $\bullet OH$ and $HO_2\bullet$. The hydroxyl radical, generated from the reaction of H_2O_2 with transition metals like iron or copper, is one of the most reactive and damaging species, causing severe oxidative stress by attacking lipids, proteins, and DNA, thus compromising overall cellular integrity. This results in lipid peroxidation and the formation of harmful by-products like malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), which further propagate cellular damage and thereby contribute to renal dysfunction [36].

The oxidative stress induced by H_2O_2 also activates inflammatory pathways, significantly amplifying renal injury. Specifically, oxidative stress stimulates the nuclear factor kappa B (NF- κ B) signaling pathway, which is a major regulator of inflammation. Pro-inflammatory cytokines, including NF- κ B activation, lead to the transcription of pro-inflammatory cytokines such as TNF- α and interleukin-6 (IL-6), which are transcriptionally triggered by NF- κ B activation, exacerbating renal inflammation and promoting fibrosis [37].

The overproduced ROS and pro-inflammatory cytokines might lead to glomerular and tubular damage, manifesting in altered biomarkers of renal function. Specifically, oxidative stress caused by H_2O_2 helps raise the amounts of creatinine and urea in the blood, as these are indicative of impaired glomerular filtration rate (GFR) and compromised renal excretory function [38]. Additionally, oxidative damage disrupts renal tubular function, leading to

elevated uric acid levels due to impaired renal clearance. The structural damage to nephrons and increased proteinuria result in reduced serum albumin and total protein levels, while liver damage or altered renal clearance can cause elevated total bilirubin levels [39,40].

The current data presented in Figure 2 indicated that 1% H₂O₂ for 6 weeks led to kidney impairment, evidenced by a notable increase in blood levels of urea, uric acid, and creatinine, alongside a significant reduction in total protein level.

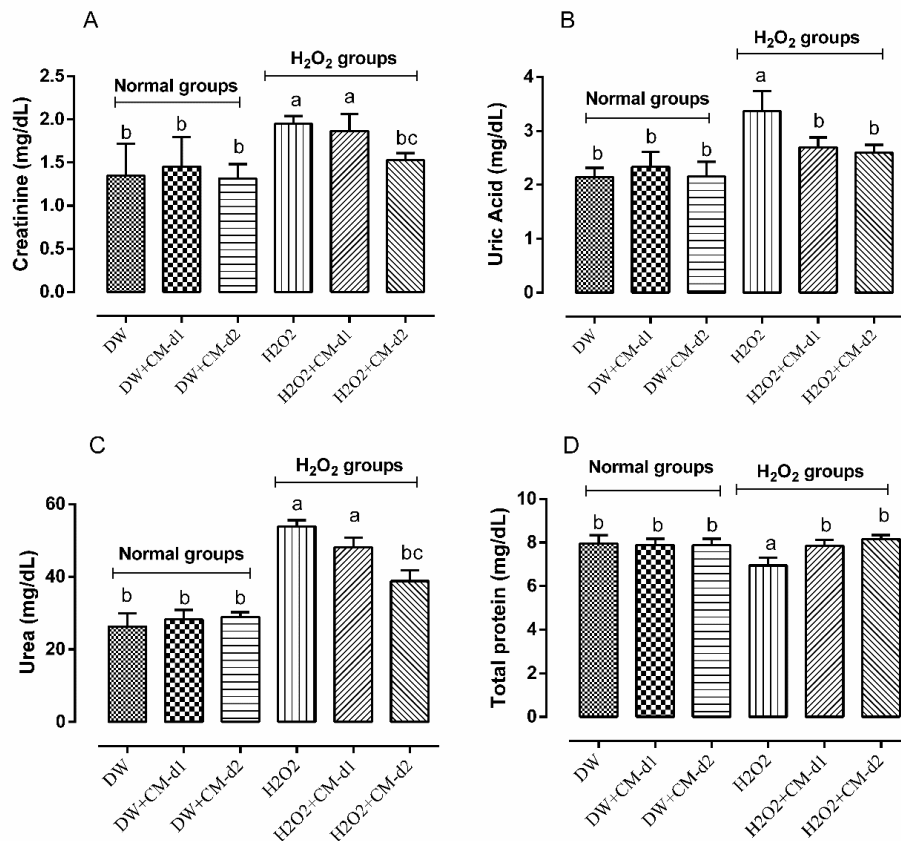


Figure 2. Effect of *Crataegus monogyna* fruit extract on H₂O₂-induced changes in (A) plasmatic creatinine; (B) uric acid; (C) urea; (D) total protein in Wistar rats.

However, treatment with CM extract, especially at a higher dose (200 mg/kg b.wt), significantly improved the elevation of serum creatinine, urea, and uric acid levels in models of renal dysfunction induced by H₂O₂. Moreover, CM treatment in normal groups doesn't promote biochemical changes in animals. This effect aligns with the extract's known antioxidant and anti-inflammatory properties, which likely regulate inflammatory pathways and reduce oxidative stress-induced renal damage, thereby improving overall renal function [12].

Albumin and total proteins are important indicators of renal function. In fact, hypoalbuminemia, or low serum albumin levels, can be a sign of nephrotic syndrome or significant proteinuria. It has been established that H₂O₂ generates oxidative modifications such as carbonylation and nitrosylation, which impair enzyme function and structural integrity [41]. Reduced total protein levels may also reflect compromised kidney function, as the kidneys play a vital role in maintaining protein balance. The plasmatic levels of these biomarkers were improved following the CM administration in a dose-dependent manner.

Our findings are consistent with recent research highlighting the renal protective effects of antioxidant-rich *Crataegus monogyna* extracts. Recent studies have demonstrated that CM

possesses significant antioxidant activity that helps mitigate oxidative stress, a key factor in renal damage. For instance, Wahabi and co-workers highlight the ability of *CM* extracts to enhance renal function by reducing oxidative markers and improving antioxidant defense mechanisms in kidney tissues [42]. In a related study, Amrati *et al.* reported that the phenolic fraction of *CM* collected from Morocco plays a significant role in protecting liver and kidney function by reducing inflammation pathways and oxidative stress in experimental kidney disease models [12]. Accordingly, the documented effects are potentially related to its functional ingredients, mainly quercetin, verbascoside, and procyanidin. These findings align with the current results and emphasize the potential of *C. monogyna* in safeguarding/protecting renal integrity.

The improvement of the investigated renal parameters by *CM* fruit extract could be due to its rich composition in anti-inflammatory and antioxidant bioactive molecules, including rutin, epicatechin, theobromine, vanillin, quercetin, *p*-coumaric acid, and many other active components (Table 1). As already mentioned, these molecules are known for their ability to reduce the expression of pro-inflammatory cytokines and eliminate the excess of free radicals. Previous investigations revealed that secondary plant metabolites, including nitrogenous compounds, phenolic compounds, tannins, and glycosides, have protective actions against oxidative stress and associated damage in oxidative stress animal models [13,43].

It has been reported that rutin, a major compound quantified in the evaluated *CM* extract (4731.05 mg/kg), a flavonoid molecule with potent anti-inflammatory and antioxidant properties, plays a crucial role in mitigating inflammation and oxidative stress. Rutin's mechanism of action involves scavenging free radicals and upregulating endogenous antioxidant defense systems by enhancing the activity of key antioxidant enzymes such as GSH, GPx, SOD, and CAT, thereby reducing oxidative damage in vital organs, including renal tissues [44]. Moreover, rutin also exhibits anti-inflammatory effects by inhibiting the activation of NF- κ B and reducing the production of pro-inflammatory cytokines, which further helps in alleviating renal inflammation and proteinuria [45].

Likewise, Quercetin, a flavonol-based phytochemical present in numerous fruits and vegetables, demonstrates significant nephroprotective effects through multiple mechanisms. These include the activation of the AMP-activated protein kinase (AMPK) signaling pathway, contributing to metabolic regulation and decreased oxidative stress [46]. It also alleviates inflammation and endoplasmic reticulum (ER) stress by inhibiting critical inflammatory mediators and ER stress pathways [47]. Notably, quercetin suppresses the activation of NF- κ B and modulates mitogen-activated protein kinase (MAPK) pathways, which are involved in the regulation of inflammatory responses and cellular stress [48]. These combined effects highlight quercetin-rich plants as a promising therapeutic agent for protecting the kidneys and managing renal disorders.

According to another study, epicatechin, another key phenolic compound, offers significant protection against oxidative damage by scavenging free radicals and enhancing endothelial function, thereby preventing renal injuries and supporting their function [49].

Together, these biovaluable active ingredients may interact synergistically to counteract inflammation and reduce free radical-related oxidative stress, leading to the observed improvements in renal biomarkers. This study underscores the therapeutic potential of *CM* extract as a natural intervention for oxidative stress-related renal disorders, affirming further investigation into its clinical applications.

3.3.2. Effect of interventions on plasma and urinary electrolytes.

The kidneys are vital organs responsible for maintaining acid-base balance and regulating electrolyte homeostasis, which are crucial for overall physiological stability. They achieve this integrity by filtering blood to excrete excess acids and bases, as well as by modulating the blood levels of electrolytes such as sodium (Na^+), potassium (K^+), and chloride (Cl^-) due to their involvement in various physiological processes, including fluid balance, nerve function, and muscle contraction [50]. These electrolytes serve as important biomarkers for renal function, reflecting the kidney's capacity to maintain equilibrium and its response to various interventions.

In order to evaluate the effect of CM extract alone, hydrogen peroxide alone, or co-treated with CM extract on electrolyte balance, plasma and urinary concentrations of sodium (Na^+), potassium (K^+), and chloride (Cl^-) were measured across all experimental groups. This approach allows us to determine how these treatments influence electrolyte homeostasis and offers insights into the protective (CM extract) or disruptive (H_2O_2) effects on renal function.

The data presented in Table 2 showed that CM extract administration did not change any electrolytes in serum and urinary analysis samples. In serum samples, H_2O_2 treatment significantly lowered serum sodium levels compared to the normal animals (H_2O_2 untreated rats); however, K^+ and Cl^- concentrations were not changed either in the untreated H_2O_2 groups (DW) or treated H_2O_2 groups. In addition to its hepatorenal dysfunction, it has been proven that H_2O_2 specifically generates free radicals and induces hyperglycemia by damaging pancreatic β -cells [51]. Owing to its high osmolality, glucose in hyperglycemia conditions prompts water excretion and consequently reduces plasma sodium levels by dilution [52]. Uncontrolled hyperglycemia can also cause hypovolemic hyponatremia due to osmotic diuresis [52]. Furthermore, low plasma sodium ion concentration may also be related to the translocation of Na^+ - K^+ -ATPase pumps from the basolateral membrane of proximal tubules to the cytosol, which reduces sodium pumping from renal tubules to the blood circulation.

Table 2. Effect of *Crataegus monogyna* fruit extract on serum and urinary electrolytes (sodium, potassium, and chloride) in normal and H_2O_2 -induced Wistar rats.

Experimental groups	Serum parameters (mEq/L)			Urinary parameters (mEq/L)		
	Sodium	Potassium	Chloride	Sodium	Potassium	Chloride
DW	131.94 $\pm$ 2.9 ^b	5.03 $\pm$ 0.05	106.37 $\pm$ 3.01	84.09 $\pm$ 6.89 ^b	56.60 $\pm$ 2.90 ^b	106.64 $\pm$ 5.16 ^b
DW+CM-d1	129.17 $\pm$ 2.9 ^b	5.03 $\pm$ 0.05	100.08 $\pm$ 2.53	88.65 $\pm$ 1.57 ^b	45.68 $\pm$ 2.99 ^b	103.32 $\pm$ 6.21 ^b
DW+CM-d2	131.42 $\pm$ 1.3 ^b	5.98 $\pm$ 0.22	103.55 $\pm$ 7.35	82.10 $\pm$ 4.05 ^b	49.27 $\pm$ 7.42 ^b	100.10 $\pm$ 12.08 ^b
H_2O_2	117.78 $\pm$ 2.80 ^a	5.57 $\pm$ 0.12	104.76 $\pm$ 9.91	117.56 $\pm$ 18.45 ^a	84.62 $\pm$ 4.76 ^a	129.05 $\pm$ 6.30 ^a
H_2O_2 +CM-d1	111.64 $\pm$ 3.80 ^{ab}	5.60 $\pm$ 0.40	103.30 $\pm$ 1.65	96.16 $\pm$ 7.96 ^{ab}	75.86 $\pm$ 1.92 ^{ab}	127.11 $\pm$ 2.87 ^{ab}
H_2O_2 +CM-d2	105.70 $\pm$ 3.1 ^{abc}	5.78 $\pm$ 0.05	101.30 $\pm$ 5.21	75.50 $\pm$ 13.63 ^{ab}	75.03 $\pm$ 6.84 ^{ab}	114.61 $\pm$ 9.62 ^{bc}

Values in the same column followed by the same letter are not significantly different by Tukey's multiple range test ($p < 0.05$).

H_2O_2 rats co-treated with CM extract at both low (100 mg/kg Bw) and high (200 mg/kg Bw) doses for 6 consecutive weeks did not exhibit significant normalization of plasma Na^+ levels. Although this result seems unexpected, it suggests that CM extract's impact on electrolyte homeostasis could be complex and multifaceted. According to the outcome of a previously published study by Dizaye [53], the intravenous injection of procyanidins (50 mg/kg Bw) extracted from CM demonstrates a significant diuretic effect characterized by increased

urine flow and elevated urinary sodium and potassium electrolytes as compared to the untreated group. The author reports that the compounds present in the extract act as a diuretic agent, which may be due to their targeting of the Na-K-2Cl co-transporter [53]. This supports our findings, suggesting that *CM* extract may exert a comparable diuretic effect through a similar pathway.

Regarding urinary electrolytes, H₂O₂ administration leads to a significant excretion of all evaluated urinary electrolytes (Na⁺, K⁺, Cl⁻), which indicates electrolyte imbalance (see Table 2). Increased urinary excretion of sodium, potassium, and chloride ions has also been documented by Chen *et al.* [54] in streptozotocin-induced Type 1 diabetes. Also, Eteng *et al.* [55] reported that electrolyte loss in uncontrolled diabetes mellitus is most often related to osmotic diuresis. Interestingly, in our study, the treatment with *CM* extract, especially at a high dose of 200 mg/kg Bw, markedly lowered urinary electrolyte leakage (Table 2). Several active compounds have been found in *Crataegus monogyna* fruit extract

These compounds exhibit excellent diuretic effects, including rutin and epicatechin [56–58].

Overall, the current results reveal that *CM* fruit extract potentially counteracts the renal toxicity induced by hydrogen peroxide, restoring kidney function and stabilizing both renal biomarkers and electrolyte levels.

3.4. Effect of interventions on body and organ weight changes.

The results summarized in Table 3 showed that the normal group received only distilled water (DW) and presented the largest body weight changes (from initial to final body weight), with an increase of approximately 43.7 g. The normal group treated with the *CM* extract doses (DW+*CM*-d1 and DW+*CM*-d2), although they also recorded weight gains, showed a less pronounced increase than the control group (23.7 and 19.6 g, respectively). However, the H₂O₂ group showed a weight loss of -12.5 g relative to the initial body weight with a percent change of -111.21. In contrast, the H₂O₂+*CM*-treated groups had a slight body weight increase (6.7 and 10.7 g for 100 mg/Kg Bw and 200 mg/Kg Bw treated animals, respectively).

Table 3. Effect of *Crataegus monogyna* fruit extract on body weight changes in normal and H₂O₂-induced Wistar rats.

Experimental groups	Initial BW (g)	Final BW (g)	BW changes (g)
DW	168.90 ± 4.22	212.56 ± 4.41	43.66 ± 0.19 ^b
DW+CM-d1	149.37 ± 7.13	173.02 ± 5.07	23.66 ± 1.05 ^{ab}
DW+CM-d2	181.95 ± 4.15	201.56 ± 7.24	19.60 ± 3.09 ^{ab}
H₂O₂	217.34 ± 4.73	204.84 ± 3.45	-12.51 ± 0.51 ^a
H₂O₂+CM-d1	156.81 ± 6.15	163.51 ± 5.28	6.7 ± 1.87 ^{abc}
H₂O₂+CM-d2	147.14 ± 6.33	157.87 ± 5.21	10.73 ± 1.06 ^{ab}

Values in the same column followed by the same letter are not significantly different by Tukey's multiple range test ($p < 0.05$).

These results could be explained by several hypotheses supporting the preventive effect of *CM* extract against weight loss, which depends mostly on its rich composition of bio-functional ingredients. For instance, it's well-established that polyphenols quench and scavenge the overproduced free radicals following the H₂O₂ administration, thus preventing cellular and organ damage, a well-known contributor to body and organ weight loss [59]. Moreover, some other identified molecules, such as gallic acid and rutin, improve the metabolic status by

enhancing mitochondrial function and preserving the integrity of muscle cells by up-regulating the SIRT1-associated pathway in C2C12 myotubes [60], thus promoting better nutrient utilization. Additionally, the upregulation of SIRT1 improves fatty acid oxidation and enhances insulin sensitivity, facilitating better nutrient utilization and fat storage. Overall, the discussed published mechanisms may explain the potential effect of CM active ingredients in neutralizing oxidative stress and contributing to weight loss prevention, highlighting their significant role as natural and effective ingredients for maintaining the well-being and managing health issues.

The weight loss shown in rats exposed to H₂O₂-induced oxidative stress was previously observed in other studies [61,62]. Multiple interrelated mechanisms explain this body weight loss. First, oxidative stress, which can cause metabolic deregulation and interfere with normal metabolic functions, can suppress appetite and change nutrient absorption [63]. Secondly, the elevated production of ROS and other free radicals leads to cellular deterioration in diverse organs, including skeletal muscles, which are essential for energy metabolism and utilization [64]. Lastly, H₂O₂ can affect the hormonal status, particularly insulin. Oxidative stress-induced insulin resistance may result in less fat being stored and more fat being mobilized.

The absolute and relative organ weights (kidney, liver, and pancreas) of different groups are displayed in Table 4. The findings demonstrated that the H₂O₂-untreated groups' kidney weight increased while their liver and pancreas weight decreased, in comparison with the other groups.

Table 4. Effect of *Crataegus monogyna* fruit extract on absolute and relative organ weight changes in normal and H₂O₂-induced Wistar rats.

Experimental groups	Kidney weight (g)	Liver weight (g)	Pancreas weight (g)	Kw/100g Bw	Lw/100 g Bw	Pw/100 g Bw
Dw	1.57±0.06	6.22±0.39	0.62±0.03	0.74±0.016 ^b	2.92±0.012 ^b	0.29±0.001 ^b
Dw+CM-d1	1.30±0.02	4.97±0.22	0.48±0.08	0.75±0.008 ^b	2.87±0.00 ^a	0.27±0.005 ^b
Dw+CM-d2	1.45±0.05	5.94±0.78	0.58±0.10	0.73±0.009 ^b	2.94±0.015 ^b	0.28±0.003 ^b
H ₂ O ₂	1.65±0.08	4.83±0.39	0.48±0.01	0.80±0.01 ^a	2.35±0.017 ^a	0.23±0.005 ^a
H ₂ O ₂ +CM-d1	1.17±0.10	4.69±0.36	0.41±0.11	0.71±0.007 ^b	2.86±0.014 ^{ac}	0.25±0.008 ^{ac}
H ₂ O ₂ +CM-d2	1.16±0.07	4.78±0.72	0.45±0.09	0.73±0.01 ^b	3.02±0.024 ^{ab}	0.28±0.001 ^b

Values in the same column followed by the same letter are not significantly different by Tukey's multiple range test ($p < 0.05$).

It has been demonstrated that the exposure of the liver to oxidative stress leads to ROS generation. This can seriously damage cells. Free radicals can oxidize proteins, lipids, and nucleic acids, which can ultimately lead to cell death via different processes such as necrosis and apoptosis [65]. The accumulation of necrotic cells contributes to the onset of inflammation and worsening liver damage [66]. Over time, hepatocyte mass may decrease as a result of this process, lowering total liver weight [67].

Additionally, oxidative stress can impair normal hepatic metabolic processes. It disrupts the liver's vital function in fat and carbohydrate metabolism [48,68]. For instance, the disruption of lipid metabolism may lead to steatosis (fat accumulation) or liver cell atrophy [69]. Derangements in metabolism that follow may be a factor in the reduction of liver size and function. In addition, the release of glycogen reserves and disruptions in protein synthesis can lead to an overall decrease in liver weight due to decreased hepatocyte size [70].

Furthermore, the consequences of persistent oxidative stress and the weight loss that goes along with it could put the liver at risk for additional diseases like cirrhosis and hepatic carcinoma [71]. The secretion of insulin and the production of digestive enzymes are two

metabolic pathways that the pancreas regulates. Its structural integrity and weight are essential to its correct functioning [72]. Numerous investigations have exhibited a relationship between decreased pancreatic weight and oxidative stress [73,74].

The activation of pro-inflammatory pathways by oxidative stress results in persistent inflammation of the pancreas [75]. A conditioned immune response brought on by this inflammation may harm pancreatic cells, especially islet and acinar cells. These damaged cells may experience atrophy or apoptosis, which lowers the mass of the pancreas as a whole [76]. For example, several studies have demonstrated that prolonged exposure to high glucose levels can cause oxidative stress, which in turn triggers the release of inflammatory cytokines like TNF- α and IL-6, aggravating pancreatic damage [77,78].

Pancreatic tissue may experience fibrotic alterations in response to oxidative stress, which is typified by the accumulation of extracellular matrix elements and a decrease in the number of functional cell types. Because fibrous tissue replaces functioning cells in the pancreas during fibrotic remodeling, there may be a decrease in pancreatic weight, which would be detrimental to the pancreas's overall function [79].

Regarding the kidney, numerous researchers have documented a direct relationship between elevated kidney weight and oxidative stress. For instance, elevated kidney weight is frequently seen in diabetic models alongside oxidative stress markers, suggesting that hyperglycemia may intensify oxidative damage and cause renal hypertrophy [80,81]. Furthermore, research on animals has demonstrated that exposure to heavy metals like cadmium increases the weight of the kidneys due to oxidative damage, inflammation, and subsequent hypertrophy [82,83]. When signals that support cell growth and survival are cut off by oxidative stress, the kidneys respond by becoming more hypertrophic, which enlarges the organ [84].

4. Conclusions

The phytochemical analysis of *Crataegus monogyna* fruit extract revealed the presence of various bioactive molecules, including phenolics like rutin, epicatechin, 3,4-dihydroxybenzoic acid, vanillin, quercetin, *p*-coumaric acid, gallic acid, etc., well known for their antioxidant and anti-inflammatory effects. The action of *Crataegus monogyna* fruit extract in a rat model of oxidative stress showed powerful hepatorenal protective effects against hydrogen peroxide-induced renal and liver damage, evidenced by significant improvement of key biochemical markers and organ weight changes.

These findings suggest that polyphenol-rich *Crataegus monogyna* fruit extract may protect against oxidative hepatorenal dysfunction, likely via synergistic antioxidant and anti-inflammatory mechanisms. Further studies are needed to elucidate molecular pathways and validate safety in clinical models.

Author Contributions

Conceptualization, N.S. and H.L.; methodology, N.S.; data curation, D.O.; M.B.; and P.F.; writing—original draft preparation, N.S.; H.L., and D.O.; writing—review and editing, M.B., P.F.; K.K., O.D., and Z.O.; supervision, B.L., All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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