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LISINOPRIL PROTECTS THE LIVER AGAINST FUNCTIONAL DISORDERS AND HISTOLOGICAL DAMAGES INDUCED BY FERROUS SULFATE IN RATS

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Iron Overload, Lisinopril, Oxidative stress, Hepatotoxicity, Free radicals

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ABSTRACT: Iron overload has toxic effects on the body. Hepatotoxicity is a common finding in iron-overloaded patients, resulting from iron deposition in hepatocytes. Angiotensinιι is involved in developing hepatic damage through its pro-oxidative properties. Therefore, the current study aimed to investigate the therapeutic effect of the ACE inhibitor, lisinopril, against ferrous sulfate-induced hepatic functional disorders and histological damages in rats, due to its inhibitory effect on angiotensin II and its ability to scavenge free radicals *in-vitro*. 23 male adult rats were randomly classified into three groups and treated as follows: Normal control group: received daily 1 ml/day distilled water as an intraperitoneal injection for 14 days, Iron overload non-treated group: received ferrous sulfate at a daily dose of 30 mg/kg/day i.p. for 14 days, Iron overload treated with lisinopril group: received ferrous sulfate at a dose of 30 mg/kg/day followed by lisinopril at a dose of 1 mg/kg/day daily i.p. for 14 days. Compared to the control group, administration of ferrous sulfate resulted in liver dysfunction, as evidenced by significantly higher serum hepatic markers levels, increased malondialdehyde levels, and histological damages. Treatment with lisinopril significantly reversed the elevated serum hepatic enzyme levels and lipid peroxidation marker in the liver. All these changes were corroborated by histological observations of the liver ($P<0.05$). Our study suggests that lisinoprilprotects against iron overload-induced hepatotoxicity through inhibition of lipid peroxidation.

INTRODUCTION: Iron is one of the most abundant minerals in the human body and is categorized as an essential element for biological function [1]. Iron occupies this position due to its affinity to oxygen and facile redox chemistry, enabling it to switch between its two more stable oxidation states Fe^{+3} and Fe^{+2} in redox cycle [2]. However, excess iron can be toxic, because in the presence of molecular oxygen, "Free" iron leads to the generation of oxygen-derived free radicals such as hydroxyl radicals and other reactive oxygen species (ROS) [3, 4] *via* Fenton reaction [5], which initiates lipid peroxidation from cell membranes and cause oxidative damage to protein and nucleic acids [6]. Iron overload is a pathological phenomenon that occurs in conditions such as hereditary hemochromatosis and transfusion-dependent anemia, including sickle cell disease and beta-thalassemia [7], in which the supply of iron exceeds cell demands [8]. Eventually, it leads to iron accumulation in several organs, including the liver, the major site for storing iron [9].

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Therefore, the liver is considered the key organ to be adversely affected by iron overload toxicity [10]. Excess iron deposition within hepatocytes induces hepatic tissue damage through oxidative stress [11, 12]. Resulting in fibrosis, cirrhosis, and subsequently raising the morbidity and mortality rate [11]. Based on these data, hepatotoxicity was induced in the

present study using an iron overload model to simulate such clinical conditions [13]. More recently, it was observed that angiotensin II and other major components of RAS are locally expressed in the diseased liver [14] and influence the progression of hepatic injury through inducing oxidative stress [15]. Ang II promoting oxidative stress and ROS formation is mediated *via* activation of NADPH oxidase through phosphorylation of its regulatory subunit, p47 phox [16]. ROS in turn, activates the NFκβ, which ends in the secretion of pro-fibrogenic cytokines, TNF-α and TGF-β, that are key mediators in liver injury [17, 18]. Accordingly, inhibition of angiotensin II *via* ACEIs may benefit ameliorating hepatic injury induced by ferrous sulfate. Lisinopril, an Angiotensin-converting enzyme inhibitor (ACEIs), has been shown to have safety profiles and low economic cost in treating blood pressure [15]. Over the anti-hypertensive treatments, several additional effects of lisinopril may be found via reducing angiotensin-II mediated oxidative stress and its ability to scavenge the hydroxyl radical (•OH) [19]. Nevertheless, the protective role of ACE inhibition oniron overload-induced hepatotoxicity has not been investigated. In this regard, the current study aimed to evaluate the potential benefits of lisinopril against Ferrous sulfate-induced functional and histological damage in ratsliver [15].

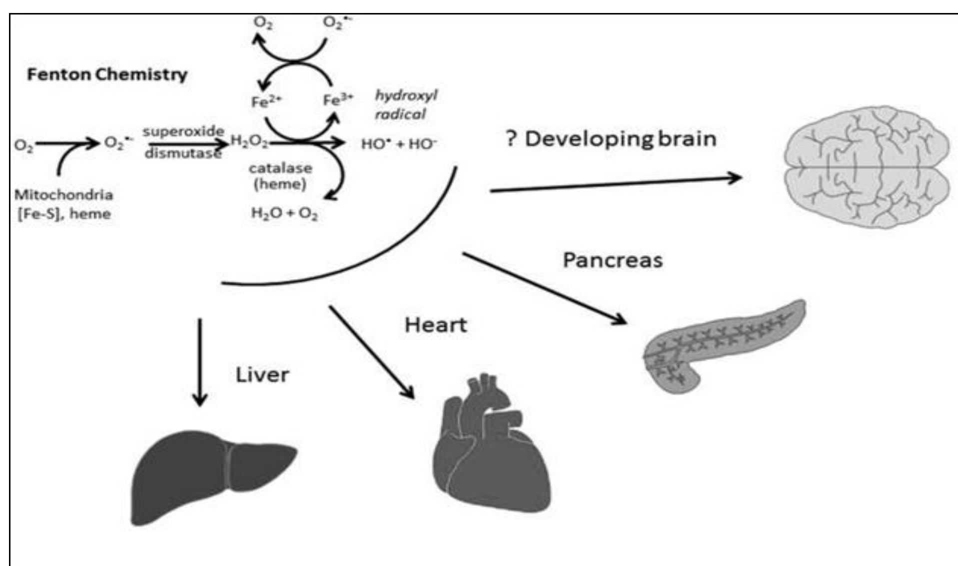


FIG. 1: IRON MECHANISM IN CAUSING TISSUE INJURY [4]

MATERIALS AND METHODS:

Materials: Lisinopril was purchased from Nutra Specialties Private Limited, India. Ferrous sulfate (Feso4) was purchased from HIMEDIA Laboratories, India. Diethyl ether $(C_2H_5)_2O$ was purchased from Merck Pharmaceutical industry, United States of America. Thiobarbituric acid was purchased from Titan Biotech, India. Standard assay kits for ALT and AST were purchased from Medichem Company, Aleppo, Syria

Experimental Animals: Twenty-three male albino rats (average bodyweight 150-300 gm), were obtained from the animal house of the Scientific Research Center in Syria. The animals were acclimatized under standard laboratory conditions for 2 weeks before treatment. They were maintained under standard conditions of temperature (25ºC) and light/ dark cycles. All the experimental studies were conducted in conformity with our College ethical protocol's guidelines for care and standard experimental animals. The animals were used in this study divided into three groups; they were treated as follows:

Group I: (control group n=8): received daily dose of distilled water (1 ml/day) intraperitoneally for 14 successive days [20].

Group II: (Iron overload non-treated group n=8): received ferrous sulfate at a daily dose of 30 mg/kg/day intraperitoneally for 14 successive days [20].

Group III: (Iron overload treated with lisinopril group n=7): received daily dose of ferrous sulfate

(30 mg/kg/day) [20] followed by lisinopril at a dose of 1 mg/kg/day i.p [21], for 14 successive days.

Samples Preparation

Serum Preparation: All the animals were anesthetized under light diethyl ether anesthesia and blood samples were collected in clean test tubes by intracardiac puncturing. Then, blood samples were allowed to coagulate at room temperature, thencentrifuged at 4000 g for 10 min. The clear serum was separated and stored into eppendorff tubes at – 80 °C to be used for analysis of biochemical parameters, including ALT and AST.

Liver Tissue Preparation: After sacrificing, the abdominal cavities were opened and the livers were separated and washed with ice-cold saline. Hepatic lobes were separated. Parts of hepatic tissue were preserved in 10 % formaldehyde for future histological examination and the rest was immediately stored at -80 °C to determine hepatic malondialdehyde (MDA) content.

Estimation of Liver Function: In serum samples, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined using commercial kits provided by Medichem middle east (Syria) according to the method of Reitman and Frankel (1957) [13].

Assessment of Hepatic Oxidative Stress: 1 g of hepatic tissue was homogenized with 10 volumes of phosphate buffer (PBS) using a homogenizer (tissue lysser II). Estimation of lipid peroxidation marker, Malondialdehyde (MDA) in hepatic tissue was assayed following the protocol described by Ohkawa *et al.* (1979) where thiobarbituric acid reacts with the hepatic content of Malondialdehyde (MDA) in acidic pH to give a stable dye with an absorption maximum at 540 nm [22].

Preparation of Slides for Histopathological Examination: Liver tissues were separated and immersed in buffered formalin solution for 24 h. Then, dehydrated with a graded alcohol series and cleared in xylol. The hepatic sample was then embedded in paraffin and stained with hematoxylin and eosin. Each section was examined in at least 10 randomly selected non-overlapping fields under a light microscope. The hepatic histopathology was quantified for apoptosis, swelling, fatty degeneration, cytoplasmic vacuolation, enlarged nuclei of hepatocytes, infiltration of inflammatory cells, and vascular dilation. The sum of all numerical scores of each rat in each group was taken as the total histopathological score.

Data Analysis: Data were subjected to statistical analysis using GraphPad Prism 8.0.1.Data were expressed as the mean values mean± standard error (SE) of samples. For the parametric data, the Statistical significance of the differences between various groups was determined by LSD (Least Significant Difference). For the non-parametric data, the Statistical significance of the differences between various groups was determined by the Kruskal-Wallis test. Differences were considered statically significant for p-value < 0.05

RESULTS:

Liver Coefficient (Liver/Body Weight Ratio): Table 1 shows that iron overload markedly increased the liver/ body weight ratio when compared with control rats ($p<0.001$). Treatment with lisinopril significantly reduced the liver/body weight ratio when compared with the iron group ($P<0.05$) **Fig. 2.**

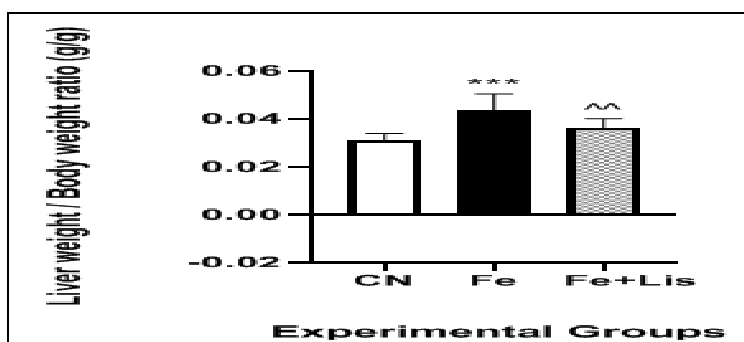


FIG. 2: EFFECT OF LISINOPRIL ON LIVER COEFFICIENT (LIVER WEIGHT/BODY WEIGHT) (G/G). Values given represent the mean (± s.e). ***p < 0.001 *vs* control group. ^p < 0.05 vs iron overload group. Control group (cn), iron overload group (fe), iron overload treated with lisinopril group (Fe+Lis).

Hepatic Functional Markers: Daily injection of ferrous sulfate for 14 days significantly increased the serum ALT and AST activities when compared with the control group (P<0.001). A significant improvement was reported in the levels of ALT, and AST activity of the lisinopril treated group when compared with the iron overload group (P<0.05) **Table 1** and **FIG. 3.**

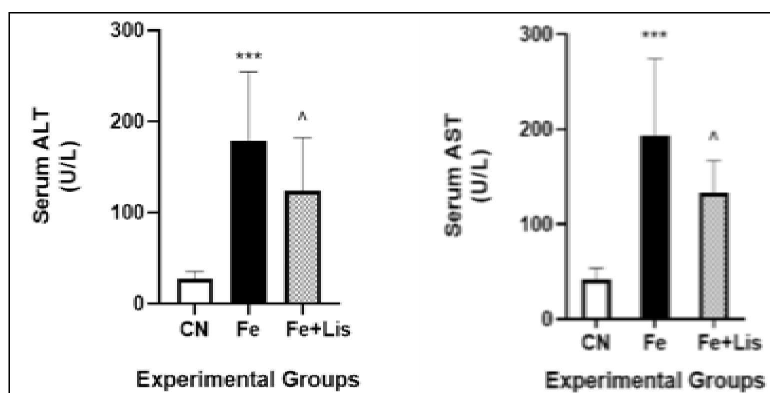


FIG. 3: EFFECT OF LISINOPRIL ON LIVER ENZYMES ACTIVITY ALT, AST (U/L). Values given represent the mean (± S.E). ***p < 0.001 *vs* control group. ^p < 0.05 *vs* iron overload group. Control group (CN), iron overload group (Fe), iron overload treated with lisinopril group (Fe+Lis).

Oxidative Stress in the Liver: The current study aimed to investigate the anti-oxidant activity of lisinoptil against oxidative stress induced by ferrous sulfate. Iron overloads caused a significant increase in the levels of hepatic malonyldialdehyde (MDA) (P<0.01), a biological compound used as an indicator of oxidative stress [11]. Whereas, a significant reduction in hepatic MDA levels was observed in the lisinopril treated group (P<0.05) **Table 1** and **Fig. 4.**

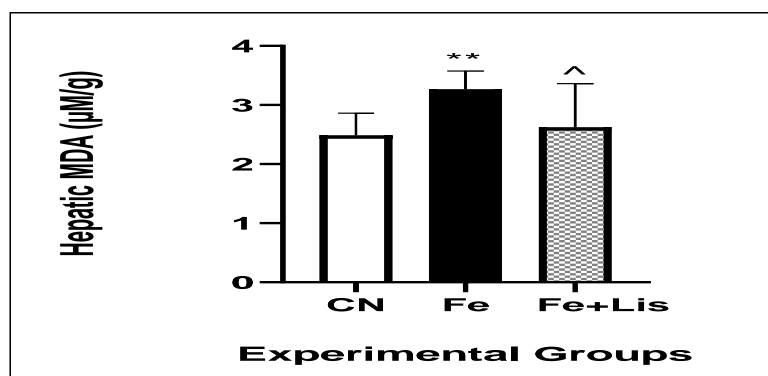


FIG. 4: EFFECT OF LISINOPRIL ON HEPATIC MDA CONTENT (µM/g). Values given represent the mean (± S.E). ***p < 0.001 vs control group. ^p < 0.05 *vs* iron overload group. Control group (CN), iron overload group (Fe), iron overload treated with lisinopril group (Fe+Lis).

TABLE 1: EFFECT OF LISINOPRIL ON THE LEVELS OF HEPATIC FUNCTION PARAMETERS, LIVER COEFFICIENT AND LIPID PEROXIDATION MARKER IN EXPERIMENTAL GROUPS

Parameters	Control	iron overloaded	Treatment with Lisinopril
Liver coefficient (g/g)	0.03123±0.0009619	0.04375±0.002403***	0.03643±0.00143^^
ALT (U/L)	27.09±3.055		110.1±12.58^
AST(U/L)	41.79±4.226	178.9±26.73***	133.7±12.53^
(M/gµ)Hepatic MDA	2.488±0.1315		2.624±0.2784^

Values are expressed as means ± (SEM). ***p < 0.001 *vs.* control group. ^ p< 0.05 vs. iron-overloaded group. ^^ p < 0.01 *vs.* iron-overloaded group.

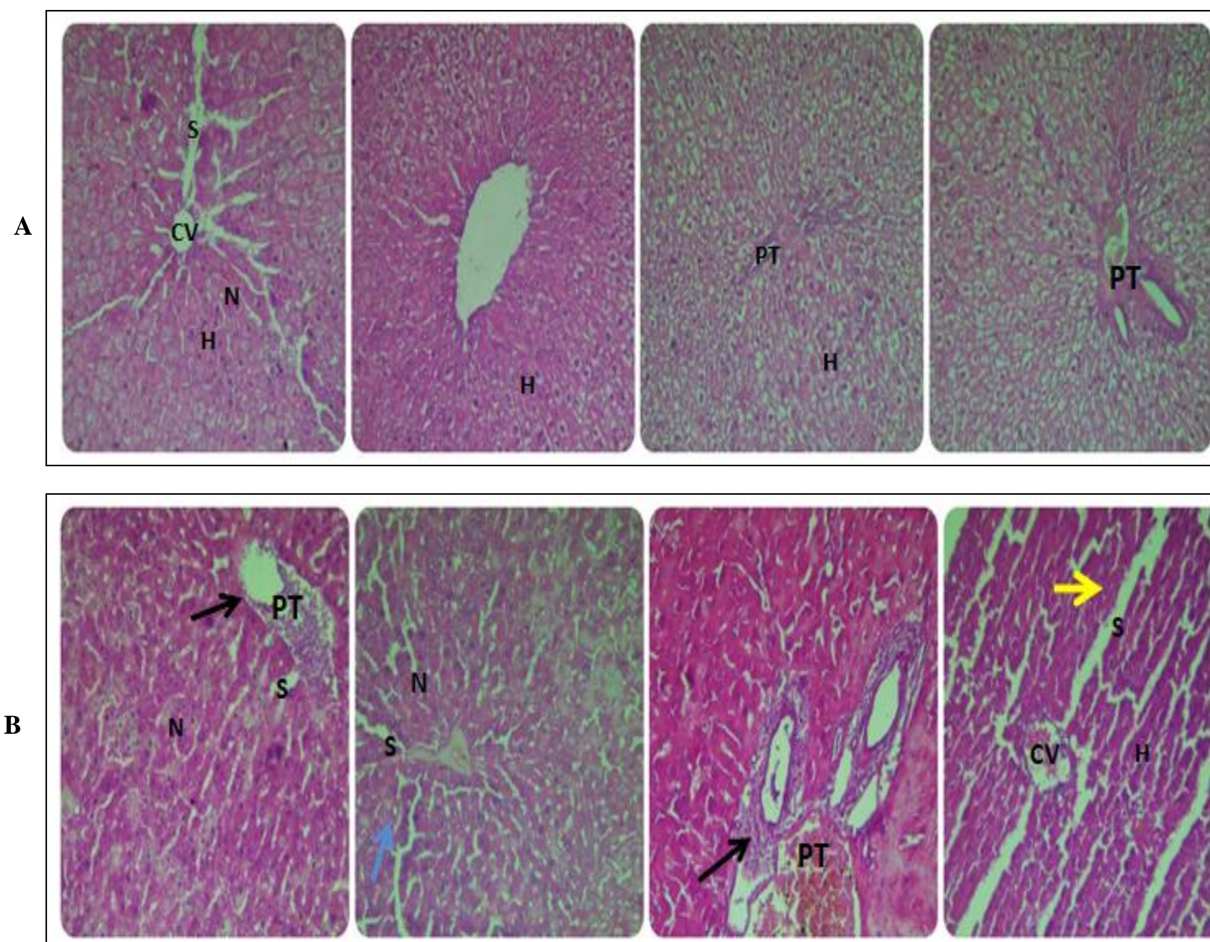
Histological Damages in the Liver: Results of the histological studies of the liver were in agreement with the measured activities of hepatic enzymes. Hepatic sections stained with hematoxylin and eosin obtained from the normal control group showed normal cell morphology's characteristic hepatic architecture, including radiating cords of normal hepatocytes with central rounded vesicular

nuclei, separated by blood sinusoids. The hepatic sinusoids were regularly distributed. The hepatic lobule structure was well preserved. The central vein and portal triad were prominent with no cellular infiltration (CV) **Fig. 5A.** Iron exposure resulted in changes in liver architecture and distortion of the normal hepatocytes **Table 2** as indicated by enlarged hepatocytes nuclei, apoptosis of the hepatic cells and fatty degeneration of hepatocytes. Infiltration of inflammatory cells in the portal triad, near the central vein and between hepatocytes compared to the control group **Fig. 5B.** The most prominent lesions in the iron overload group were dilation of the central vein (CV), dilation of the hepatic sinusoids, and the portal triad. Furthermore, the hepatic lobule structure appeared disintegrated compared to the control group **Fig. 5B.** Livers of iron overloaded rats treated with lisinopril showed improved histological pictures, as shown by the total histopathological score **in Table 2**, with relatively less intense lesions in hepatocytes nuclei and less hepatic apoptosis cells reduced fatty degeneration of hepatocytes. Furthermore, the hepatic lobule structure was preserved compared to the iron overload group **Fig. 5C.** Lisinopril treatment markedly reduced accompanying infiltration of inflammatory cells near the central vein and between hepatocytes compared to the control group. However, there was occasional infiltration of inflammatory cells in the portal triad. In addition, congested dilated central vein (CV), dilated, congested hepatic sinusoids, and congested portal triad was seen in the liver of the lisinopril treated group, similar to the iron overload group **Fig. 5C.**

TABLE 2: TOTAL HISTOPATHOLOGICAL SCORE OF EXPERIMENTAL GROUPS

Experimental Groups	Histopathological scores of liver tissue
Control	0.63±0.26
Iron overload	9.88±0.55***
Treatment with lisinopril	4.08±0.38^

Values (sum of histopathological scores in each group) are expressed as mean ± SEM ***P<0.001 as compared to the control group ^P<0.05 as compared to the Fe group.



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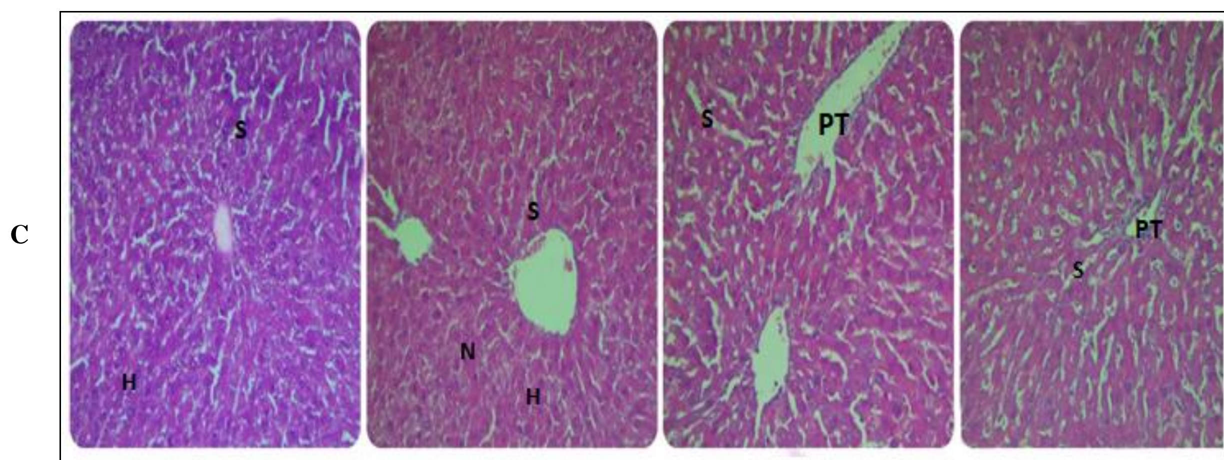

FIG. 5: PHOTOMICROGRAPHS OF LIVER SECTION OBTAINED FROM DIFFERENT GROUPS (H&E; 400) (a) Normal control group showing normal hepatic architecture with central vein (CV) and normal portal triad (PT). Radiating cords of normal hepatocytes (H) with central rounded vesicular nuclei and prominent nucleoli (N). Hepatic cords are separated by blood sinusoids (S). (b) Ferrous sulfate group showing loss of radial arrangement (H), enlargement nuclei of hepatocytes(N), dilated congested central vein (CV), dilated congested portal triad (PT), dilated congested blood sinusoids (S), Inflammatory cell infiltration (Black arrow), fatty degeneration (blue arrow), disintegrated hepatic lobule structure (yellow arrow). (c) Lisinopril treated group showing near normal hepatocytes (H) with less enlargement nuclei (N), radial arrangement of hepatocytes (H), separated by dilated congested blood sinusoids (S), The inflammatory infiltration was also reduced. 3.270±0.1085**

DISCUSSION: The current study demonstrated that ferrous sulfate leads to functional disorders and tissue damage in the liver. Our findings indicate that treatment with lisinopril attenuates hepatotoxicity induced by iron overload. Thus, maybe an adjuvant therapy to combat co-morbidities associated with iron accumulation.

Excess iron content in the cell is toxic because it participates in redox reactions and forms free radicals, promoting tissue injury induced by oxidative stress [12]. The liver is the major site for storing iron [23]. Therefore, it is considered the key organ to be adversely affected by iron overload toxicity [10]. Accumulating evidence showed that Angiotensin II is implicated in the progression of hepatic injury through induction of oxidative stress [15, 16]. Thus, ACE is may have antioxidant properties to target oxidative stress in the liver [24]. Based on the aforementioned background, the current study aimed to verify the potential protective effect of lisinopril against hepatotoxicity induced by ferrous sulfate in rats. The present study showed that ferrous sulphate increased liver weight coupled with a reduction in body growth. This result is consistent with other studies of iron overload [22, 25, 26]. The result is that iron deposition in the liver causes hepatocellular injury and liver function disturbance. Thus, stimulating hepatocyte inflammation and consequently leading to liver weight gain [25]. It is noteworthy that the liver coefficient was significantly decreased in lisinopril-treated animals, indicating that the adverse effects of iron overload can be ameliorated by lisinopril. Liver function tests are an indicator of the disease progress [5]. The activity of serum ALT and AST are the main biochemical marker for liver function [27], which indicates hepatocyte integrity loss [28]. Ferrous sulfate induces reactive free radicals formation that alters cell membrane permeability due to oxidation of polyunsaturated fatty acid (PUFA) in cellular membranes, which causes the leakage of liver enzymes into the serum [27]. Ferrous sulfate led to increased enzymatic activities of serum AST and ALT in agreement with other experimental studies of iron overload [5, 11, 20]. Importantly, our results showed that lisinopril significantly attenuated the release of ALT and AST enzymes into the blood. This finding indicates improvement of hepatocyte physiological function17. Which may be due to the inhibition of angiotensin II-induced hepatic injury [15]. In this regard, the membrane protective effect of lisinopril has already been reported [29].

Lipid peroxidation usually produces several cytotoxic products, such as MDA [30], which forms a covalent adduct with phospholipids, proteins, and DNA. Greater formation of these MDA macromolecules adducts might be a potential mechanism in iron-induced hepatotoxicity.

Therefore, inhibition of lipid peroxidation is considered one of the major strategies for treating hepatic damage under iron overload conditions [31].

From the results obtained, lisinopril attenuated the hepatic peroxidative damage induced by ferrous sulfate, as evidenced by lower levels of MDA in the lisinopril treated group; this result may be attributed to the antioxidative effect of Lisinopril due to its ability to scavenge free radical [19]. The Protecting effect of lisinopril against lipid peroxidation-induced oxidative stress has already been reported. Mohammed *et al.* (2015) reported lisinopril's ability to correct oxidative stress biomarkers in acetaminophen-induced hepatotoxicity in rats [29]. In addition, the study by saber *et al.* (2018) demonstrated the effects of lisinoprilin in reducing lipid peroxidation in liver fibrosis [17]. Histopathological examination is regarded as the gold standard in assessing tissue injury [32]. Our findings for histopathological observation were consistent with other studies showing different models of iron overload [5, 10, 23]. The liver sections of iron overloaded rats showed swelling, cytoplasmic vacuolation, apoptosis, enlarged nuclei, and hepatocytes' fatty degeneration, which is considered one of the most detrimental results of oxidative damage to lipids hepatic parenchyma [33]. In addition, the hepatic lobule structure appeared disintegrated in the iron overload group when compared with the control group. Ferrous sulfate-induced hepatocytes damage can be explained by the formation of highly reactive radicals and the oxidative stress induced by iron overload. As a result edhydroperoxides can cause cytotoxicity through peroxidation of membrane phospholipids by lipid hydroperoxides, the basis for cellular damage [34]. In addition, iron overload can damage the mitochondrial inner membrane and open the mitochondrial pores through oxidative stress mechanism, which leads to ATP depletion and release of the pro-apoptotic protein, cytochrome C. Hence, promoting hepatic cell injury and apoptosis [11].

Other remarkable pathological characteristics of ferrous sulfate-induced liver injury were irregularly dilated central vein, portal triad, and hepatic sinusoids. In addition, there was inflammatory cell infiltration near the central vein, between hepatocytes, and in the portal triad. Our findings agreed with Li *et al.* (2017), who showed that injection of iron can cause inflammatory infiltration through various mechanisms [35]. Iron overload increases hepatic inflammatory infiltration and the expression of pro-inflammatory cytokines, such as interleukin-6 (IL-6), IL-1b, and tumor necrosis factor-a (TNF-a) 35 through generating free radical triggers macrophage-mediated innate immune responses. In addition, recent studies have reported that iron overload reduces HNF4a/miR-122 pathway in hepatocytes, which contributes to hepatic inflammation [35].

Lisinopril co-administration resulted in a reduction of the magnitude of the ferrous sulfate-induced histological changes as evidenced by significant decreases in fatty degeneration, less enlargement and fragmentation of hepatocytes nuclei, reduction in the apoptosis of the hepatic cells, preserved hepatic lobule structure.

In agreement with our results, lisinopril treated group showed nearly normal architecture and normal hepatocytes in treating liver injury induced by acetaminophen [29]. In addition, the study by Saber *et al.* (2018) showed that lisinopril-treated rats showed restoration of lobular architecture in CCl_4 induced hepatic fibrosis [17]. The reduction in parenchymal damage can be attributed, as mentioned earlier, to the antioxidant capacity of lisinopril related to inhibition of angiotensin II, besides its ability to scavenge •OH free radicals [19], which in turn reduces the oxidative stress induced by ferrous sulfate and contributes to the protection of membrane lipids from free radicals and Eventually, attenuates the histopathological changes and helps to restore the normal hepatic histoarchitecture. The decrease of hepatic MDA content in the lisinopril treated group justifies the hypothec stated above.

In this study, other observation includes a major reduction in inflammatory cell infiltration near the central vein and between hepatocytes with a mild reduction in inflammatory cells infiltration in the portal triad of lisinopril-treatedrats. Several studies have shown in several models that ACE inhibitors reduce the number of infiltrating cells through various mechanisms [18, 17]. It may be primarily due to the inhibitory effect of lisinoprilon Ang II, which functions as an inflammatory cell recruitment agent

by inducing the release of pro-inflammatory cytokines and activating nuclear factor-kappa B (NF-κB) 36, which results in inflammatory cell infiltration [18].

Nevertheless, the hepatic veins were still dilated including the central vein, hepatic sinusoids and portal triad of the livers of lisinopril treated rats, which may be explained by lisinopril stimulating effect onbradykin in signalling [37]. Bradykinin in turn causes vascular vasodilation through releasing nitric oxide (NO), hyperpolarizing factor (EDHF) [38] and epoxyeicosatrienoic acids (EETs) in the endothelial cell. Bradykinin has also shown anti-inflammatory and anti-ROS activity which may be an additional mechanism of lisinopril against iron overload-induced hepatic injury [39].

CONCLUSION: The current study showed that lisinopril significantly decreased the liver coefficient, restored abnormal hepatic function and improved the pathological alterations of the liver induced by ferrous sulfate, which may be a consequence of the reduction of oxidative stress induced-lipid peroxidation. These findings provide a novel pharmacological effect of lisinopril against iron-induced liver impairment.

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CONFLICTS OF INTEREST: The authors have no conflicts of interest regarding this investigation.

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