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RESEARCH ARTICLE

EMPAGLIFLOZIN MITIGATES OXIDATIVE STRESS AND LIVER ENZYMES ELEVATION IN A DEXAMETHASONE –INDUCED HEPATIC STEATOSIS RAT MODEL

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Abstract

Empagliflozin, a sodium-glucose co-transporter 2 (SGLT-2) inhibitor, is recognized as an oral hypoglycemic agent with potential hepatoprotective effect. While Empagliflozin shows hepatoprotective potential in metabolic NAFLD models, its specific efficacy against glucocorticoid-induced oxidative stress and liver injury remains insufficiently characterized. The present study aimed to investigate the impact of Empagliflozin (EMPA) on malondialdehyde (MDA) and liver enzymes in rats with Dexamethasone (DEX)–induced hepatic steatosis. Twenty-five male albino rats were divided into five groups (5 rats in each group): normal control group did not receive any medication; two DEX-induced groups one received 8 mg/kg/day and the other received 16 mg/kg/day for six days consecutively; another group received (EMPA 10 mg/kg/day + DEX 8 mg/kg /day) EMPA for six consecutive days prior to DEX with another six days during DEX administration without interruption; and the last group underwent the same process but with DEX16 mg/kg (EMPA 10 mg/kg/day + DEX 16 mg/kg /day). Blood samples were collected before the rats were sacrificed. Results revealed that the levels of the oxidative stress biomarker (MDA) were significantly elevated in DEX-treated groups compared with the control group. At a dose of 8 mg/kg DEX, the MDA level was 1.12 nmol/ml ($P = 0.017$), representing a 154% increase compared with the control. At a dose of 16 mg/kg DEX, the MDA level further increased to 1.44 nmol/ml ($P < 0.001$), corresponding to a 227% increase relative to the control group. EMPA 10mg/kg (group IV) reduced MDA level by 55.3%, which was statistically significant ($P = 0.033$), and group V reduced MDA level by 70.8% ($P < 0.001$), compared to groups II and III, respectively. Group five rats pretreated with EMPA led to a substantial statistically significant reduction in serum ALT ($P < 0.001$), with a decline by 57.8%, and serum AST declined by 54.6% ($P < 0.001$), serum ALP by 33.5% ($P = 0.003$), and serum LDH by 47.5% ($P < 0.001$), compared to the DEX 16 mg/kg group (group III). In conclusion, Empagliflozin significantly ameliorated DEX-induced oxidative stress in albino rats and showed hepatoprotective effect through reduction of Dexamethasone-elevated liver enzymes and malondialdehyde. Further experimentation is required to explore the molecular mechanisms.

Keywords: Empagliflozin; Dexamethasone; Hepatic steatosis; Liver enzymes; Oxidative stress.

1. Introduction

In the absence of excessive alcohol consumption or other pathological causes, nonalcoholic fatty liver disease (NAFLD), which is defined as excessive lipid accumulation in hepatocytes (> 5% wet weight) and the formation of lipid droplets in the cytoplasm of hepatocytes has emerged as the leading cause of chronic liver disease worldwide [1]. The growing prevalence of NAFLD is a significant public health challenge, particularly among individuals with type 2 diabetes mellitus (T2DM) and obesity. Current estimates indicate that NAFLD affects approximately 30% of the general population and 65-70% of those with T2DM, with rates even higher in obese individuals [2].

The pathophysiology of NAFLD is complicated and includes insulin resistance, oxidative stress, lipid

peroxidation, mitochondrial dysfunction, and hepatic enzymes leakage into the circulation [3],[4].

Hepatic steatosis (fatty liver), known as non-alcoholic fatty liver (NAFL), is a kind of early-stage NAFLD that is characterized by increased intrahepatic lipid buildup, and in a more serious condition involving inflammation and hepatocyte destruction called (nonalcoholic steatohepatitis, NASH), that develops as the illness worsens and progresses, and can result in liver fibrosis, cirrhosis and hepatocellular carcinoma [5],[6].

Many drugs can induce liver injury, particularly hepatic steatosis, with different clinical, biochemical, and pathological presentations. Glucocorticoids (GCs) are one such type of these drugs [7].

Dexamethasone (DEX) is a potent glucocorticoid with minimal mineralocorticoid properties. It has a high affinity for glucocorticoid receptors and is a highly potent immunosuppressant, decongestant, and anti-inflammatory medication. High dosages of DEX are frequently used for extended periods in the treatment of several autoimmune diseases. However, despite its widespread use, DEX is associated with several metabolic adverse effects, including diabetes, hepatic steatosis, hyperglycemia, and lipid metabolism dysregulation, which restrict its potential applications [8],[9],[10].

A slight acceleration of very low-density lipoprotein production and release into the circulation, as well as inhibition of β-oxidation of fatty acids, stimulation of de novo lipogenesis, increasing the release of free fatty acids from adipose stores, and stimulation of their uptake by the liver are mechanisms by which DEX increases hepatic lipid accumulation [10].

Empagliflozin (EMPA), a sodium-glucose co-transporter 2 (SGLT-2) inhibitor, acts by inhibiting the reabsorption of glucose in the proximal tubular system in the kidneys. It is regarded as an oral hypoglycemic medication that reduces insulin resistance, decreases glucose absorption, inhibits de novo hepatic lipogenesis, and all of which improve lipid metabolism. Several studies have shown its additional hepatoprotective effects as well as its advantages on the cardiovascular and renal outcomes [11],[12]. In several animal model studies of NAFLD, SGLT2i treatment has been found to prevent steatosis, inflammation, and fibrosis in such models [13].

Despite increasing evidence of the hepato-protective effects of Empagliflozin in metabolic and diet-induced models of non-alcoholic fatty liver disease, its potential protective role in glucocorticoid-induced hepatic steatosis remains poorly understood. In particular, the influence of Empagliflozin on oxidative stress and liver injury biomarkers in dexamethasone-induced hepatic steatosis has not yet been fully elucidated.

The aim of this study was to investigate the impact of Empagliflozin on MDA and liver enzymes in a Dexamethasone–induced hepatic steatosis rat model.

2. Materials & Methods

2.1 Study design

The type of study design was an experimental study including quantitative and qualitative variables.

2.2 Study Duration and Setting

The experiments were carried out in the pharmacology laboratory (animal house) at the Faculty of Pharmacy – University of Aden, from January to April 2024.

2.3 Sample size

Twenty-five healthy male albino rats weighing 150–212 g were used in this study and randomly divided into five groups (n = 5 per group). The sample size was estimated using the resource equation method, which is commonly recommended for exploratory animal experiments when prior data for formal power analysis are limited. According to this method: E = N−G, where E represents the error degrees of freedom, N is the total number of animals, and G is the number of experimental groups.

In the present study: E = 25−5 = 20. An E value between 10 and 20 is considered appropriate for animal experiments. Therefore, 25 animals were considered sufficient for this experiment [14].

2.4 Materials

2.4.1 Chemicals

The chemicals used in the experiment were 10% formalin (Isochem – Laboratories- India), Paraffin (Numaligarh Refinery Limited – India), Ketamine (Rotixmedica – Germany), Hematoxylin and eosin Kit (Benz microscopic optic – Ireland) and Carboxymethyl cellulose (CMC) of extra-pure and medium-viscosity (Loba Cheme PVT. LTD -India).

2.4.2 Drugs

The drugs for the experiment were Jardiglose® (Empagliflozin) 10 mg tablets (Zein Pharma-Syria) was received as a gift from Himam Hadramout for importing medicine and medical appliances, and Dexampro® (Dexamethasone) 8 mg/2ml ampoule (Mepro Pharmaceuticals – India).

2.5 Instruments and Equipment

The instruments used were Electronic balance (Spanish - LABORCOM), Sensitive Electronic balance (Spanish – P SELECTA), Centrifuge (Spanish – P SELECTA), Screen master plus - Biochemical system international SrI (Italy- IVD), Eliza (USA - Star Fax 4700).

2.6 Treatment of Animals

Albino rats were housed in cages under standard laboratory conditions (temperature-controlled environment (20 - 25°C) with a 12:12-hour cycle for light and dark, with a relative humidity of 55 - 60%). They were handled according to the animal ethics guide. Standard diet and tap water ad libitum were available without charge. In addition, they were adapted to this condition for one week before starting the procedure to alleviate the stress caused by environmental changes. The accommodation period was in the pharmacology lab at the Faculty of Pharmacy - Aden University.

2.7 Methods

2.7.1 Drugs/sample preparation

2.7.1.1 CMC solution preparation

Five hundred milligrams of extra-pure and medium-viscosity CMC powder were slowly dissolved into 100 ml of distilled water with vigorous and prolonged mixing and allowed to stand for 24 hours for complete dissolution [15].

2.7.1.2 Empagliflozin preparation

Empagliflozin was prepared by accurately weighing 10 tablets, which were then finely crushed using a mortar and pestle. The resulting powder was dissolved in 100 mL of a 0.5% carboxymethyl cellulose (CMC) solution to achieve a final EMPA concentration of 1 mg/ml, ensuring thorough mixing. The prepared suspension was used immediately to maintain stability and prevent degradation [16],[17].

2.7.2 Experimentation

A total of 25 healthy male rats were randomly divided into five groups consisting of five rats in each group, as follows:

Group I (Control): rats received no medication throughout the experimental period and were considered normal controls.

Group II (DEX 8 mg/kg): rats received DEX alone at a dose of 8 mg/kg/day intraperitoneally for 6 consecutive days to induce metabolic changes and were considered a steatosis model, as described by [18].

Group III (DEX 16 mg/kg): rats received DEX alone at a dose of 16 mg/kg/ day intraperitoneally for 6 consecutive days to induce metabolic changes and were considered another steatosis model.

Group IV (EMPA 10 mg + DEX 8 mg/kg): rats received EMPA 10 mg/kg/day by oral gavage for 6 consecutive days before DEX administration and for another 6 consecutive days during DEX administration without interruption [19].

Group V (EMPA 10 mg + DEX 16 mg/kg): rats received EMPA 10 mg/kg/ day by oral gavage for 6 consecutive days before DEX administration and another 6 consecutive days during DEX administration without interruption.

At the end of the study, the animals were fasted overnight and then subjected to anesthesia with ketamine (50 mg/kg). Then, venous blood samples were drawn via a capillary tube from the orbital-sinus capillary vein. Blood was placed into test tubes, allowed to clot for 20 minutes, and then centrifuged at (4000 rpm) for 20 minutes to separate the serum, which was stored at -20°C until requested for the analysis of liver enzymes (ALT, AST, ALP, LDH), and the oxidative stress biomarker (MAD). Rats were sacrificed by cervical dislocation after anesthesia.

2.7.3 Experimental methods

2.7.3.1 Spectrophotometer Test

2.7.3.1.1 Serum Enzymatic Activity

Alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) were measured following the steps of the instruction manual supplied by Screen Master Plus-Biochemical System International Srl(Italy-IVD) supplied by AGAPPE Lab by using a spectrophotometer, and the tests were done at Al-Markazia Lab. The unit of measurement for enzyme activity is the international unit per liter (IU/L).

2.7.3.2 Eliza Test

2.7.3.2.1 Determination of oxidative stress markers in the serum of rats

Malondialdehyde (MDA) was measured by using the Rat MDA ELISA kit supplied by the Bioassay Technology Laboratory BT LAB ELISA kits (India), by following the steps of the instruction manual. The unit of measurement is nanomoles per milliliter (nmol/ml).

2.8 Statistical Analysis

Data were checked and then entered into the Statistical Package for Social Sciences (SPSS) software version 25 (IBM SPSS Inc., Chicago, Ill, USA). All results are presented as the mean ± SD. Treatment group means were compared using one - way ANOVA followed by Tukey's post-hoc test for pairwise comparisons. $P \leq 0.05$ was considered statistically significant for all tests.

2.9 Ethical Consideration

This study was conducted in accordance with the ARRIVE 2.0 guidelines for reporting animal research and approved by the Research Ethics Committee of the Faculty of Medicine and Health Sciences, University of Aden (REC-158-2023). All procedures involving animals were performed according to institutional and

international guidelines for the care and use of laboratory animals to ensure their welfare and minimize pain or distress [20].

3. Results

3.1 Effect of Empagliflozin on Dexamethasone-Induced Oxidative Stress Biomarker (MDA) in Rats

The mean levels of MDA were significantly elevated in the Dexamethasone-induced groups. At a dose of 8 mg/kg Dexamethasone, the level was 1.12 nmol/ml (P = 0.017), indicating 154% elevation, whereas at a dose of 16 mg/kg Dexamethasone, the MDA level rose to 1.44 nmol/ml (P < 0.001), which reflects a 227% increase compared to the control group. Moreover, group IV (0.50 nmol/ml) showed a reduced MDA level by 55.3%, which was statistically significant (P = 0.033), compared with group II. Similarly, the clear decreased level in group V (0.42 nmol/ml) in comparison with group III was reduced by 70.8% and was highly statistically significant (P < 0.001), as shown in (Table 3.1).

Table 3.1 Effect of Empagliflozin on Dexamethasone-Induced Serum MDA (n=5).

NO.	Groups	MDA (nmol/ml) mean ± SD	P-value
I	Control	0.44 ± 0.2	
II	DEX 8 mg/kg	1.12 ± 0.4	0.017**
III	DEX 16 mg/kg	1.44 ± 0.4	< 0.001***
IV	EMPA 10 mg/kg + DEX 8 mg/kg	0.50 ± 0.2	0.033 #
V	EMPA 10 mg/kg + DEX16 mg/kg	0.42 ± 0.2	< 0.001###

Note: Data are expressed as mean ± SD (n= 5/group). *** P <0.001 vs Group I, ** P < 0.05 vs Group I , ### P <0.001 vs Group III, #P <0.05 vs Group II [One-Way Analysis of Variance (ANOVA)Test].

3.2 Effect of Empagliflozin on Dexamethasone-Induced Liver Enzymes Activity in Rats

At the end of the experiment, blood samples were collected from all rats across the different groups to assess serum levels of ALT, AST, ALP, and LDH between groups. Compared to Dexamethasone-only groups, administration of Empagliflozin resulted in notable alterations in liver enzymes activities.

3.2.1 Effect of Empagliflozin on Dexamethasone-Induced Serum ALT

The mean serum ALT level was highly significantly elevated in Dexamethasone 16 mg/kg group (116.60 U/L) (P < 0.001) compared to the control group, while the Dexamethasone 8 mg/kg group showed an elevation (71.20 U/L) that was statistically insignificant (P = 0.059). Dexamethasone 16 mg/kg–induced increment in ALT was 223.8%, and that by Dexamethasone 8 mg/kg was 97.7%, respectively, as compared to the control.

Group five rats pretreated with Empagliflozin led to a substantial statistically significant reduction of serum ALT (P < 0.001) with a decline by 57.8% compared to the Dexamethasone 16 mg/kg group. On the other hand, Empagliflozin with Dexamethasone 8 mg/kg did not show a significant difference **(**Table 3.2**).**

Table 3.2 Effect of Empagliflozin on Dexamethasone-Induced Serum ALT (n=5).

NO.	Groups	ALT (IU/L) mean ± SD	*P*-value
I	Control	36.00 ± 6.0	
II	DEX 8 mg/kg	71.20 ± 11.9	0.059
III	DEX 16 mg/kg	116.60 ± 38.3	< 0.001***
IV	EMPA10 mg/kg + DEX 8 mg/kg	52.40 ± 11.6	0.542
V	EMPA10 mg/kg +DEX16 mg/kg	49.20 ± 6.3	< 0.001###

Note: Data are expressed as mean ± SD (n = 5/group). ***P < 0.001 vs Group I , ### P < 0.001 vs Group III [One-Way Analysis of Variance (ANOVA)Test].

3.2.2 Effect of Empagliflozin on Dexamethasone-Induced Serum AST

The levels of serum AST have shown higher elevated values in Dexamethasone-Induced groups (71.40 IU/L, 112.40 IU/L) compared to the control group, with elevated percentages of 116.3% and 240%, respectively, for groups II and III. These elevations were highly statistically significant (P < 0.001 and P < 0.001, respectively).

In contrast, serum AST levels for Empagliflozin-pretreated groups (48.20 IU/L,51.00 IU/L) were lower than Dexamethasone-Induced groups II and III by 32.5% and 54.6% for groups IV and V, respectively. This reduction was statistically significant in group IV (P = 0.042) and also in group V (P < 0.001). Notably, Empagliflozin had a greater effect on serum AST with higher doses of Dexamethasone (Table 3.3).

Table 3.3 Effect of Empagliflozin on Dexamethasone-Induced Serum AST (n=5).

NO.	Groups	AST (IU/L) mean ± SD	*P*-value
I	Control	33.00 ± 3.7	
II	DEX 8 mg/kg	71.40 ± 7.3	< 0.001***
III	DEX 16 mg/kg	112.40 ±19.2	< 0.001***
IV	EMPA 10 mg/kg +DEX 8 mg/kg	48.20 ± 15.6	0.042 #
V	EMPA 10 mg/kg +DEX16 mg/kg	51.00 ± 5.2	< 0.001###

Note: Data are expressed as mean ± SD (n = 5/group). ***P < 0.001 vs Group I ,# P <0.05 vs Group II, ### P < 0.001 vs Group III [One-Way Analysis of Variance (ANOVA)Test].

3.2.3 Effect of Empagliflozin on Dexamethasone-Induced Serum ALP

Serum ALP levels were markedly and highly significantly elevated in the Dexamethasone-induced groups at doses of 8 mg/kg and 16 mg/kg, recording 333.20 ± 43.2 IU/L and 408.00 ± 86.1 IU/L for groups II and III, respectively (P < 0.001 vs. control). These

elevations corresponded to increases of 235.2% in group II and 310.4% in group III relative to the control group.

In contrast, groups treated with Empagliflozin (10 mg/kg) showed a clear reduction in ALP levels compared with the corresponding Dexamethasone-induced groups. Group IV produced a substantial statistically significant decline of 51.4% (161.80 IU/L; $P < 0.001$) compared to group II, whereas group V showed a statistically significant reduction of 33.5% (271.20 IU/L; $P = 0.003$) as compared to group III (Table 3.4).

Table 3.4 Effect of Empagliflozin on Dexamethasone-Induced Serum ALP (n=5).

NO.	Groups	ALP (IU/L) mean ± SD	*P*-value
I	Control	99.40 ± 8.1	
II	DEX 8 mg/kg	333.20 ±43.2	< 0.001***
III	DEX 16 mg/kg	408.00 ±86.1	< 0.001***
IV	EMPA 10 mg/kg +DEX 8 mg/kg	161.80 ±57.3	< 0.001$^{\#\#\#}$
V	EMPA 10 mg/kg +DEX16 mg/kg	271.20 ± 6.9	< 0.003$^{\#\#}$

Note: Data are expressed as mean ± SD (n = 5/group). ***$P < 0.001$ vs Group I ,$^{\#\#\#}$ $P < 0.001$ vs Group II, $^{\#\#}$ $P < 0.01$ vs Group III [One-Way Analysis of Variance (ANOVA)Test].

3.2.4 Effect of Empagliflozin on Dexamethasone-Induced Serum LDH

LDH serum levels were significantly elevated (398.00 IU/L; $P = 0.001$ and 666.00 IU/L; $P < 0.001$, respectively) in group II and III compared to group I (193.60 IU/L). These elevations corresponded to increases of 105.5% in group II and 244% in group III relative to the control group. On the other hand, Empagliflozin pretreatment revealed a statistically significant reduction in LDH levels compared with the corresponding Dexamethasone-induced groups. Group IV recorded 241.40 IU/L, representing a 39.3% decrease compared with group II ($P = 0.007$), whereas group V showed a 47.5% reduction, with LDH levels of 349.40 IU/L compared with group III ($P < 0.001$) (Table 3.5).

Table 3.5 Effect of Empagliflozin on Dexamethasone-Induced Serum LDH (n=5).

NO.	Groups	LDH (IU/L) mean ± SD	*P*-value
I	Control	193.60 ± 9.8	
II	DEX 8 mg/kg	398.00 ± 11.5	0.001**
III	DEX 16 mg/kg	666.00 ± 106.3	< 0.001***
IV	EMPA 10 mg/kg +DEX 8 mg/kg	241.40 ± 35.8	0.007$^{\#\#}$
V	EMPA 10 mg/kg +DEX16 mg/kg	349.40 ± 86.5	< 0.001$^{\#\#\#}$

Note: Data are expressed as mean ± SD (n = 5/group). ***$P < 0.001$ vs Group I ,** $P < 0.001$ vs Group I, $^{\#\#\#}$ $P < 0.001$ vs Group III $^{\#\#}$ $P < 0.01$ vs Group II [One-Way Analysis of Variance (ANOVA)Test].

4. Discussion

The present study evaluated the hepatoprotective impact of Empagliflozin against Dexamethasone-induced hepatotoxicity in albino rats by assessing changes in liver enzymes and oxidative stress. The findings demonstrate that Dexamethasone administration resulted in significant liver injury, as evidenced by marked elevations in liver enzyme activities, while Empagliflozin pretreatment effectively ameliorated these biochemical disturbances. These results are in line with [12], [21]–[23].

Oxidative stress is associated with major health complications, including liver dysfunction. Dexamethasone, particularly at high doses, is known to promote hepatic lipid accumulation, insulin resistance, and oxidative stress through glucocorticoid receptor-mediated metabolic dysregulation, which contributes to mitochondrial dysfunction and hepatocellular membrane instability, leading to enzymes leakage into the bloodstream [4]. In the present study, the levels of MDA were significantly elevated in the Dexamethasone-induced groups. These elevations in MDA were dose-dependent, in which 8 mg/kg Dexamethasone induced a significant elevation ($P = 0.017$), indicating 154% elevation, while at a dose of 16 mg/kg of Dexamethasone, the elevation was highly significant ($P < 0.001$) with a 227% increase compared to the control group. These results are indicative of the presence of oxidative stress in our model and are in line with [19], [24], [25].

Rats treated with Empagliflozin showed reductions in the elevated MDA levels, which were significant ($P = 0.033$) in the case of 8 mg/kg Dexamethasone used, while the reduction was highly significant ($P < 0.001$) in the administration of 16 mg/kg Dexamethasone. The results may reflect a dose-dependent attenuation of oxidative stress, which agrees with [12], [26]–[28].

It has been reported that Dexamethasone administration for a long period or in high doses is associated with deleterious effects and can cause hepatotoxic injury, including steatosis, hepatocellular injury, and derangement in liver enzymes [19],[29],[30]. The results of the present study showed that the rats model received Dexamethasone at the doses of 8 mg/kg and16 mg/kg exhibited obvious liver injury, as evidenced by significantly elevated levels of liver enzymes (ALT, AST, ALP, LDH). These biomarkers are regarded as important indicators to evaluate hepatic integrity and function [31],[32].

ALT is an enzyme primarily found in the cytoplasm of liver cells, where it catalyzes the reversible transfer of amino groups from alanine to α-ketoglutarate to produce glutamate and pyruvate. The activity of ALT in hepatocytes is approximately three thousand times higher than that in serum. When liver injury occurs, ALT

is released from injured hepatocytes, leading to a significant increase in serum ALT levels [33]. Although ALT is also present in adipose tissues, brain, colon, intestines, muscles, and prostate, its concentration in these organs is much lower than that in the liver [34]. This is why ALT is widely regarded as a primary, specific, and reliable blood-based biomarker of hepatocellular damage [23], and as reported by [22] observing the alteration in ALT following Empagliflozin treatment proved to be a significantly more robust predictor of therapeutic response than other hepatic indicators.

The findings of this study demonstrated that Dexamethasone at a dose of 16 mg/kg (Group III) resulted in a highly significant elevation of serum ALT levels [29], which was three times higher compared to the control group ($P < 0.001$). Conversely, the lower dose of Dexamethasone 8 mg/kg (Group II) resulted in a statistically insignificant elevation of ALT ($P = 0.059$), highlighting the dose-dependent nature of Dexamethasone-induced liver toxicity [25]. These magnitudes of ALT, which are less than five times the baseline level of the control, indicate a mild liver injury that is commonly associated with chronic liver diseases such as NAFLD. This result is in agreement with [35], [36].

A noteworthy finding in the present study is the significant hepatoprotective effect of Empagliflozin (10 mg/kg) against Dexamethasone-induced liver injury, as groups that received Empagliflozin showed a clear reduction in ALT levels in both groups. However, this reduction was substantial and statistically significant only with Dexamethasone 16 mg/kg compared to the Dexamethasone-only group III ($P < 0.001$). This observation suggests that Empagliflozin (10 mg/kg) is capable of counteracting hepatic steatosis and has the ability to mitigate it. This finding is aligned with [21],[12],[37],[27].

Aspartate aminotransferase (AST) is another transaminase enzyme that is found in various tissues; in the liver, it is mainly located in the mitochondria (80%), and the rest is cytosolic (20%) [38]. Although it is not a specific indicator for hepatocellular damage, it is commonly used alongside ALT as a complement for the diagnosis and monitoring of liver injury [32].

The current study confirmed the hepatotoxic effect of Dexamethasone administration, evidenced by a substantial increase in serum AST levels in the Dexamethasone-induced groups (II and III) compared to the control group ($P < 0.001$). This observation is consistent with the findings of [19],[29] and demonstrates a dose-dependent effect, as reported by [25]. Notably, the higher dose of Dexamethasone (16 mg/kg) resulted in a 240% increment over the control and exceeded three-folds the baseline. whereas the lower dose of Dexamethasone (8 mg/kg) increased by two-folds with an elevation of 116.3%; these levels of serum AST are indicative of a mild hepatic injury associated with NAFLD, consistent with prior reports by [36],[35].

In contrast to the Dexamethasone-only groups, the results of the present study showed that Empagliflozin administration (10 mg/kg) before and during Dexamethasone administration demonstrated a significant reduction in the elevated AST levels by 32.5% and 54.6% for groups IV (EMPA+DEX 8 mg/kg) and V (EMPA+DEX 16 mg/kg) compared to the induction groups, respectively. A particularly notable observation is the greater magnitude of protection afforded by Empagliflozin at the high dose of Dexamethasone in Group V, as it was substantially greater than the reduction observed with the lower dose in Group IV. Furthermore, the statistical significance was much stronger in Group V ($P < 0.001$) than in Group IV ($P = 0.042$). This suggests that EMPA's protective effect is not merely a constant effect but may be amplified under more severe toxic challenges affecting the liver. This strong hepatoprotective effect of Empagliflozin aligns with a growing body of evidence highlighting the extra-glycemic benefits of Empagliflozin in the area of NAFLD, particularly in the condition of hepatic steatosis. These results are compatible with those obtained by [21],[37],[12],[27].

Another remarkable biomarker called Alkaline phosphatases (ALPs), which are a group of isoenzymes that catalyze the hydrolysis of extracellular organic phosphate esters. Serum ALP is a multi-source biomarker; Although there are various non-hepatic factors and sources can lead to an increase in serum ALP activity, it is primarily used as an indicator of liver disease. In the liver, ALP is located in the cytoplasm of hepatocytes and their canalicular membrane. Subsequent to liver damage, its activity is elevated due to the de novo synthesis and elution from hepatocytes and biliary epithelial membranes [39],[40].

The results of the current study indicate a highly significant elevation ($P < 0.001$) in serum ALP levels in the Dexamethasone-induced groups (Groups II and III) compared to the control group. Specifically, Group III with 16 mg/kg of Dexamethasone (408.00 ± 86.1 IU/L) showed an increase exceeding 300% relative to the control group (99.40 ± 8.1 IU/L). These results are supported by research from [30],[19],[29] which also reported that Dexamethasone administration causes a substantial elevation in liver enzymes, including ALP. Whereas the experimental groups that received Empagliflozin experienced a significant hepatoprotective effect against Dexamethasone-induced hepatic steatosis. Empagliflozin (10 mg/kg) resulted in a statistically significant reduction in the elevated serum ALP levels. This result is consistent with [41],[21],[42].

Interestingly, the study reveals that the protective effect of Empagliflozin on serum ALP was more pronounced at the lower dose of Dexamethasone (8 mg/kg). This suggests a potential dose-dependent interaction between the two drugs, which warrants further investigation.

Lactate dehydrogenase (LDH) is a cytosolic enzyme present in almost all body tissues, which catalyzes the reversible conversion of lactate to pyruvate with the reduction of NAD^+ to NADH and vice versa. Its release into the systemic circulation is a valuable marker of cellular injury and membrane damage [43].The liver is rich in LDH and releases this enzyme due to hepatocellular damage, making increasing levels of serum LDH a sensitive biomarker and clinical predictor of the presence and severity of liver injury [44].

The present study demonstrated elevated levels of serum LDH observed in the Dexamethasone-induced groups (Groups II and III) that were more prominent with the higher dose of Dexamethasone (16 mg/kg), with a statistically significant magnitude (P =0.001 and P < 0.001, respectively), which exceeded the level of the control group by 244%. This finding is consistent with previous studies by [19],[25],[45] documenting the ability of Dexamethasone to induce hepatotoxic effects, particularly hepatic steatosis at higher doses. Conversely, Empagliflozin administration (10 mg/kg) with Dexamethasone resulted in a highly significant attenuation of serum LDH levels compared to the Dexamethasone-only groups. This protective effect was observed in both Group IV (EMPA + DEX 8 mg/kg) and Group V (EMPA + DEX 16 mg/kg). A notably greater protective effect was observed in the group that received the higher dose of Dexamethasone, as Group IV showed a 39.3% reduction in LDH compared to Group II, while Group V exhibited a 47.5% reduction compared to Group III in a dose-dependent manner. This reduction in LDH release indicates that Empagliflozin preserves hepatocyte membrane integrity and reduces the extent of cellular damage. This protective effect is in agreement with [46],[47].

Experimental models have demonstrated that Dexamethasone treatment induced hepatic steatosis and metabolic changes in animal liver tissue, as evidenced by increased fat accumulation and liver enlargement [48]. Consistent with our findings, Empagliflozin has been reported to reduce hepatic lipid accumulation, neuronal lipid accumulation, lipotoxic intermediates, and oxidative stress in rodent models, thereby improving liver enzyme levels, which supports its hepatoprotective effect under Dexamethasone-induced hepatic stress [49].

In conclusion, Empagliflozin significantly ameliorated Dexamethasone-induced oxidative stress in albino rats and showed a hepatoprotective effect through the reduction of Dexamethasone-elevated liver enzymes. Further research is required to investigate and explore the precise molecular mechanisms that stand behind the hepatoprotective effect of Empagliflozin.

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مقالة بحثية

إمباجليفلوزين يخفف من الإجهاد التأكسدي وارتفاع إنزيمات الكبد في نموذج الفئران المصابة بالتشحم الكبدي الناجم عن الديكساميثازون

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المُلخّص

إمباجليفلوزين، وهو مثبط لمستقبلات نقل الصوديوم والجلوكوز 2 (SGLT-2)، يُعرف كدواء خافض لسكر الدم عن طريق الفم مع تأثير محتمل لحماية الكبد. بينما يُظهر الإمباجليفلوزين إمكانات حامية للكبد في نماذج الكبد الدهني غير الكحولي (NAFLD) الأيضية، فإن فعاليته المحددة ضد الإجهاد التأكسدي وتلف الكبد الناجم عن الجلوكوكورتيكويدات لا تزال غير موصوفة بشكل كافٍ. هدفت الدراسة الحالية إلى التحقيق في تأثير عقار إمباجليفلوزين (إمبا) على إنزيمات الكبد ومالونديالديهايد (MDA) في نموذج الفئران المصابة بالتشحم الكبدي الناجم عن الديكساميثازون (ديكس). تم تقسيم خمسة وعشرون فأراً من ذكور فئران الألبينو إلى خمس مجموعات (5 فئران في كل مجموعة)؛ لم تتلق المجموعة الضابطة العادية أي دواء، وتم تقسيم مجموعتين مستحثتين بالديكساميثازون، حيث تلقت إحداهما 8 ملغ/كغ/يوم وتلقت الأخرى 16 ملغ/كغ/يوم لمدة ستة أيام متتالية؛ بينما تلقت المجموعة الرابعة (إمبا 10 ملغ/كغ/يوم + ديكس 8 ملغ/كغ/يوم) حيث عولجت بدواء إمبا لمدة ستة أيام متتالية قبل أخذ عقار ديكس وستة أيام أخرى خلال المعالجة بعقار ديكس دون انقطاع؛ والمجموعة الأخيرة خضعت لنفس العملية ولكن مع جرعة أكبر من عقار ديكس بلغت 16 ملغ من ديكس (إمبا 10 ملغ/كغ/يوم + ديكس 16 ملغ/كغ/يوم). تم جمع عينات الدم قبل أن يتم التضحية بها. أظهرت النتائج أن مستويات علامة الإجهاد التأكسدي (MDA) كانت مرتفعة بشكل كبير في المجموعات المستحثة بالديكساميثازون. حيث كانت النتيجة بجرعة 8 ملغ/كغ من ديكس، كان المستوى 1.12 نانومول/مل (P = 0.017) ، مما يشير إلى ارتفاع بنسبة 154% مقارنةً بالمجموعة الضابطة . بينما بجرعة 16 ملغ/كغ من ديكس، ارتفع مستوى MDA إلى 1.44 نانومول/مل بدلالة إحصائية بلغت (P < 0.001) ، مما يعكس زيادة بنسبة 227% مقارنة بمجموعة الضابطة، بينما المجموعات التي عولجت بدواء إمبا 10 ملغ/كغ (المجموعة الرابعة) أنخفض مستوى MDA بنسبة 55.3%، وهو ما كان ذا دلالة إحصائية (P = 0.033)، بينما أنخفض المستوى في المجموعة الخامسة بنسبة 70.8% (P <0.001)، مقارنة بالمجموعتين الثانية والثالثة على التوالي. بالإضافة إلى أن الفئران في المجموعة الخامسة التي تم معالجتها مسبقًا بـعقار إمبا أظهرت انخفاضاً كبيراً وذو دلالة إحصائية في مستوى ALT (P < 0.001) مع انخفاض بنسبة 57.8 %، وانخفض مستوى AST في المصل بنسبة 54.6% وبدلالة إحصائية بلغت (P < 0.001) ، وانخفض مستوى ALP في المصل بنسبة 33.5% (P = 0.003)، وانخفض مستوى LDH في المصل بنسبة 47.5 % (P < 0.001) مقارنةً بمجموعة ديكس 16 ملغ/كغ (المجموعة الثالثة). (في الختام، حسّن إمباجليفلوزين بشكل كبير الإجهاد التأكسدي الناجم عن الديكساميثازون في فئران الألبينو وأظهر تأثيرًا واقيًا للكبد من خلال تقليل إنزيمات الكبد المرتفعة بسبب الديكساميثازون. هناك حاجة إلى مزيد من الدراسات لاستكشاف الآليات الجزيئية.

الكلمات المفتاحية: إمباجليفلوزين؛ ديكساميثازون؛ تشحم الكبد؛ أنزيمات الكبد؛ الاجهاد التأكسدي.

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