UDC 616-002.5:577.15 doi: https://doi.org/10.15407/ubj96.03.048

EMBELIN MITIGATES HEPATOTOXICITY INDUCED BY ISONIAZID AND RIFAMPICIN IN RATS

O. F. MOSA

Public Health Department, College of Al-Lieth Health Science,
Umm Al Qura University, Makkah, Saudi Arabia;
e-mail: drosama2030@gmail.com

Received: 09 March 2024; **Revised:** 29 April 2024; **Accepted:** 31 May 2024

Isoniazid and rifampicin are reliable drugs against tuberculosis, but while effective, their use is associated with the risk of drug-induced liver damage. Embelin, a natural parabenzoquinone derived from the Embelia ribes plant, has gained attention for its potential therapeutic properties, antioxidant and organ-protective effects. The study aimed to assess the hepatoprotective properties of embelin against liver damage induced by isoniazid and rifampicin in rats. Wistar rats were used, and liver damage was induced by administration of isoniazid (100 mg/kg) and rifampicin (100 mg/kg). Embelin was given at doses of 50, 75, and 100 mg/kg for 21 days. All the drugs were given orally. Serum levels of the oxidative stress markers, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) activity measured by enzymatic assay kits (Elabscience, China), and the levels of tumour necrosis factor-α (TNF-α), interleukins IL-1β and IL-6 measured by ELISA kits (Randox, UK) were estimated. Embelin administration at varying doses effectively restored AST, ALT, ALP, SOD and catalase activity and notably decreased MDA and nitric oxide concentration as well as expression of inflammatory cytokines TNF-α, IL-1β and IL-6 in the serum of animals with drug-induced liver damage. These findings underscore embelin's hepatoprotective effects, likely attributed to its radical scavenging properties and ability to suppress cytokine production.

K e y w o r d s: embelin, isoniazid, rifampicin, hepatoprotection, antioxidant effect, cytokine suppression.

Drug-induced liver damage refers to harm caused to the liver by the use of medications, illicit substances, or herbal supplements. Various drugs can lead to liver injury, ranging from mild abnormalities to severe conditions like hepatitis or fulminant liver failure. Common culprits include acetaminophen, certain antibiotics, statins, and herbal supplements. Symptoms may include jaundice, abdominal pain, and elevated liver enzymes. Early detection is crucial, and discontinuation of the offending drug is the primary treatment [1]. Monitoring liver function, supportive care, and, in severe cases, liver transplantation may be necessary. However, drug-induced liver damage symptoms may include jaundice, abdominal pain, nausea, vomiting, and fatigue. Prompt identification and discontinuation of the offending drug are essential to prevent further damage. In severe cases, liver transplantation may be necessary. Individual susceptibility to drug-induced liver damage can vary, and certain factors, such as pre-existing liver disease or genetic predisposition, may increase the risk. Monitoring liver function through regular blood tests is crucial for patients on potentially hepatotoxic medications [2].

Isoniazid (INH) and rifampicin are reliable drugs against tuberculosis (TB). While effective, their use is associated with the risk of drug-induced liver damage. The molecular mechanisms underlying this hepatotoxicity involve complex interactions between the drugs and liver cells. Isoniazid, when metabolized in the liver, forms reactive metabolites that can cause oxidative stress. These reactive species can initiate lipid peroxidation, damaging cellular membranes and leading to hepatocellular injury [3]. Additionally, isoniazid may deplete cellular antioxidants, further exacerbating oxidative damage. Rifampicin, on the other hand, induces the expression of cytochrome P450 enzymes in the liver, which play a role in drug metabolism. This induction can lead to increased production of reactive metabolites and the generation of free radicals, contributing to oxidative stress and liver cell damage. Moreover, rifampicin may interfere with mitochondrial function, leading

to energy depletion and cellular dysfunction. The combination of isoniazid and rifampicin may synergistically amplify these hepatotoxic effects. Genetic factors influencing drug metabolism and detoxification pathways can also contribute to individual variability in susceptibility to liver damage [4].

While modern medicine lacks specific hepatoprotective drugs, herbal medicines have shown promise in preventing liver damage. *Schisandra chinensis*, *Silybum marianum*, and *Curcuma longa* are herbs of antioxidant and anti-inflammatory properties that can support liver health [5]. These herbs may help mitigate oxidative stress, reduce inflammation, and promote liver regeneration [6, 7]. Research suggests that herbal compounds like silymarin in milk thistle can enhance liver function. Embelin, a natural compound derived from the *Embelia ribes* plant, has gained attention for its potential therapeutic properties, including antioxidant and organ-protective effects. The molecular mechanisms underlying its antioxidant effects involve intricate interactions at the cellular level [8, 9].

Embelin is known to act as an inhibitor of the X-linked inhibitor of apoptosis protein (XIAP), a regulator of apoptosis (programmed cell death). By inhibiting XIAP, embelin promotes apoptosis in damaged cells, preventing their survival and propagation. This selective elimination of compromised cells contributes to the reduction of oxidative stress, a key factor in various pathological conditions. Moreover, embelin has been shown to modulate multiple signalling pathways involved in oxidative stress, including the nuclear factor-κB (NF-κB) pathway. Despite, NF-κB regulates genes expression involved in inflammation, and embelin's inhibitory effects on NF-κB reverse its inflammatory and oxidative effects [10]. In terms of organ protection, embelin has demonstrated efficacy in safeguarding various organs from damage. Its antioxidant and anti-inflammatory actions contribute to protection against organ injuries induced by oxidative stress [11]. While the antioxidant and organ-protective properties of embelin are promising, further research is necessary to fully elucidate its mechanisms and establish its therapeutic potential in various medical conditions.

Our aim is to evaluate the protective impact of embelin on the liver damage caused by isoniazid and rifampicin in Wistar rats. Leveraging embelin's recognized antioxidant and organ-protective traits, an exploration will be conducted into its capacity to alleviate liver injuries induced by the anti-tuberculosis drugs isoniazid and rifampicin. This research is anticipated to offer valuable insights into the potential therapeutic use of embelin in averting drug-induced harm to the liver.

Materials and Methods

Experimental lab animals. Our study was conducted on thirty-six Wistar rats with a weight range (180-200 g) of either sex, housed in polypropylene cages under standard conditions (12 h light/dark cycles, 28±2°C) with free access to pellet food and drinking water. Prior to experimental procedure, the animal protocol was properly approved by the Institutional Animal Ethics Committee of Alexandria Medical Research Institute (MRI), Egypt.

Animal group and dosing. Embelin was used in the dose of 50, 75 and 100 mg/kg of body weight according to Patel and Gohil [12] and Silymarin (100 mg/kg) were administered for 21 days. Whereas, Isoniazid and Rifampicin were used in fixed manner doses (100 mg/kg) [13] and only administered on first day. Studied animals were divided into six groups with six animals in each as in Table.

After 21 days of pharmacological treatments, blood was taken using a retro-orbital puncture for estimation of biochemical parameters.

Biochemical kits, chemicals and analysis. Blood samples were collected into Eppendorf tubes and centrifuged for 10 min at 7000 rpm using micro-centrifuge to separate the serum. Serum levels of glutamic oxaloacetic transaminase (SGOT/AST), glutamic-pyruvic transaminase (SGPT/ALT), alkaline phosphatase (ALP) were estimated using enzy-

Table. Animal groups and dosing technique used

Groups	Doses used
I	Nil (Normal control)
II	Isoniazid (100 mg/kg) + rifampicin (100 mg/kg)
III	Isoniazid (100 mg/kg) + rifampicin (100 mg/kg) + silymarin (100 mg/kg)
IV	Isoniazid (100 mg/kg) + rifampicin (100 mg/kg) + embelin (50 mg/kg)
V	Isoniazid (100 mg/kg) + rifampicin (100 mg/kg) + embelin (75 mg/kg)
VI	Isoniazid (100 mg/kg) + rifampicin (100 mg/kg) + embelin (100 mg/kg)

matic assay kits (Elabscience, China). Other chemicals (embelin, isoniazid, rifampicin, and silymarin) were purchased from Merck-Sigma Aldrich, Germany with high analytical grades.

Superoxide dismutase (SOD). SOD activity in serum was determined by Masayasu et al. method [14]. However, liberation of superoxide anions was done by pyrogallol autoxidation, then detected by nitro blue tetrazolium (NBT) formazan color appearance and finally, the amount of superoxide anions scavenged by SOD were quantified. The serum was centrifuged to 10 000 rpm for 15 min at 4°C. 0.5 ml of Tris cacodylic buffer, 0.1 ml of 16% triton x-100 and 0.25 ml NBT were added to 0.25 ml of supernatant. The reaction was initiated by adding 0.01 ml diluted pyrogallol, incubated for 5 min at 37°C, then the reaction was stopped by adding 0.3 ml of 2 M formic acid. The intensity of the formazan color was measured spectrophotometrically at wavelength 430 nm. The enzymatic activity of SOD was expressed as µg/gm of tissue.

Catalase activity. Catalase activity was measured by Sinha method [15]. 0.1ml of serum was mixed with 1.0 ml of 0.01 M phosphate buffer (pH 7.4), incubated for 1 min with 0.4 ml of 0.2 M H_2O_2 at 37°C. The reaction was halted by adding 2 ml of 5% potassium dichromate diluted with glacial acetic acid in a 1:3 ratio. Further, the samples were incubated in a boiling water bath for 15 min and later centrifuged at 5000 rpm for 15 min. The supernatant was considered for quantification of H_2O_2 amounts to calculate catalase activity at 570 nm. One unit represents 1 µmole of H_2O_2 consumed/min/mg protein.

Assay of oxidative stress index. Malondialdehyde (MDA), an indicator of lipid peroxidation degree in the liver was measured by Ohkawa method [16]. While, The nitrate levels were determined by Griess reaction [17].

Assay of inflammatory index. Serum levels of tumour necrosis factor-α (TNF-α), interleukin 1 beta (IL-1β) and interleukin 6 (IL-6) were measured by using ELISA kits from (Randox, United Kingdom).

Determination of total bilirubin. The determination of total bilirubin (TB) was performed according to enzyme assay kit from (Elabscience, China).

Statistical analysis. The results were expressed as mean ± SEM. Statistical analysis was performed using a software package SPSS version 28 (SPSS Inc., Chicago, IL), using one-way ANOVA followed by Dunnett's test. *P* values < 0.05, < 0.01, < 0.001 were considered significant.

Results

Effect of embelin administration on marker enzyme levels. Rats treated with isoniazid and rifampicin experienced significant liver damage, as indicated by elevated levels of specific enzymes such as ALT, AST, and ALP. However, in the current study, groups IV to VI, which were administered varying doses of embelin (50, 75, and 100 mg/kg), exhibited noticeable restoration of enzyme levels (AST, ALP, and ALT) (Fig. 1, 2, 3). Moreover, pre-treatment with silymarin also showed significant protection against liver damage induced by isoniazid and rifampicin.

Effect of embelin administration on superoxide dismutase and catalase activity. The administration of isoniazid and rifampicin in animals resulted

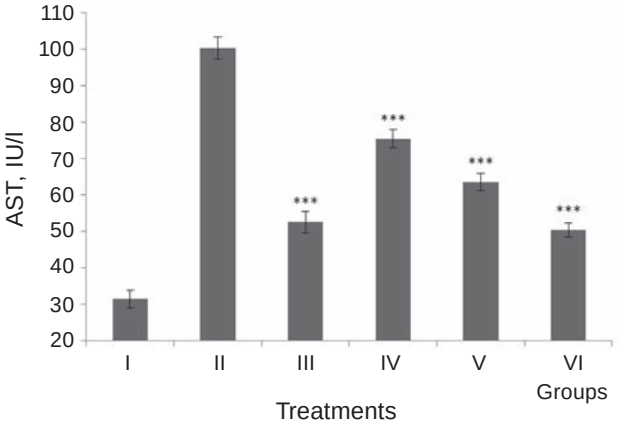

Fig. 1. Effect of embelin administration on AST levels in the blood serum of isoniazid-rifampicin treated rats

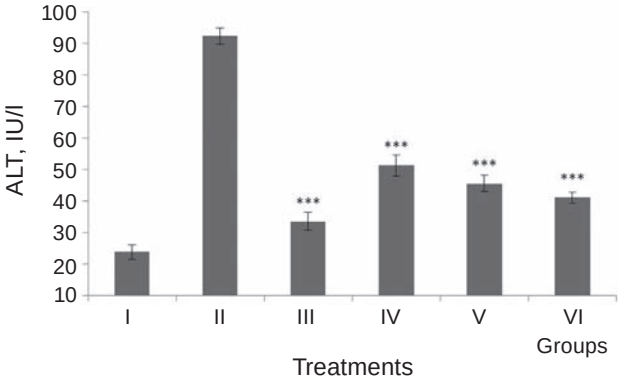

Fig. 2. Effect of embelin administration on ALT levels in the blood serum of isoniazid-rifampicin treated rats

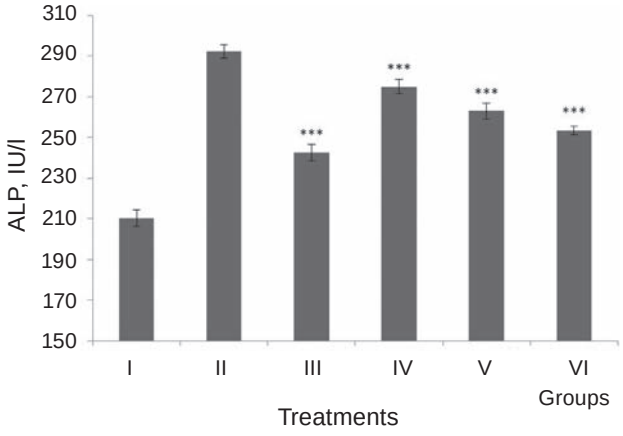

Fig. 3. Effect of embelin administration on ALP levels in the blood serum of isoniazid-rifampicin treated rats

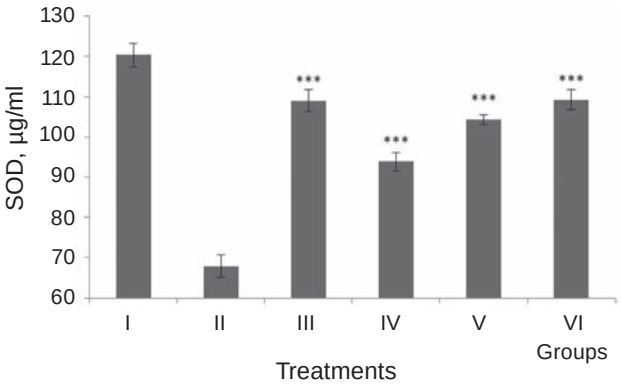

Fig. 4. Effect of embelin administration on SOD levels in the blood serum of isoniazid-rifampicin treated rats

in a reduction in SOD levels. However, treatment with embelin at various doses (50, 75, and 100 mg/kg) significantly increased SOD levels compared to the toxic control group (Group II) ($P < 0.001$). Additionally, the administration of embelin (50, 75, and 100 mg/kg) in animals notably elevated catalase levels ($P < 0.001$; Fig. 4, 5).

Effect of embelin administration on cytokine levels. TNF-α, IL-1β, and IL-6 are vital cytokines expressed during inflammation. In the current study, rats treated with isoniazid-rifampicin showed elevated levels of these serum cytokines (Fig. 6, 7, 8). Silymarin treatment (Group III) helped normalize the levels of TNF-α, IL-1β, and IL-6. Administration of embelin at doses of 50, 75, and 100 mg/kg (Group III, IV, and V) resulted in reduced levels of these cytokines. The most significant effect was observed in animals of Group VI.

Effect of embelin administration on lipid peroxidation and nitrate formation. Lipid peroxidation and nitrate formation are crucial indicators of biological stress. A biochemical examination focused on the liver (for lipid peroxidation) and serum (for nitrate formation) revealed heightened biological stress due to isoniazid-rifampicin treatment (Group II). However, embelin treatment (Group IV-VI) significantly decreased lipid peroxidation, demonstrated by reduced MDA production (Fig. 9). Isoniazid-rifampicin treatment resulted in elevated nitrate formation (Group II), but embelin administration (Fig. 10) effectively reversed these increased levels,

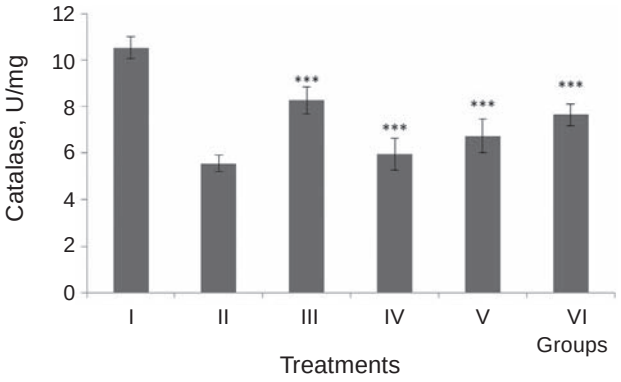

Fig. 5. Effect of embelin administration on catalase levels in the blood serum of isoniazid-rifampicin treated rats

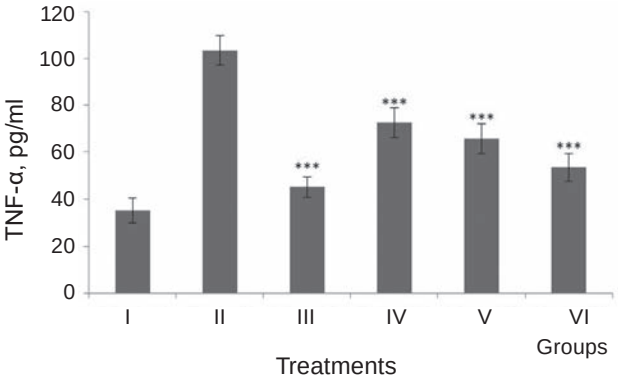

Fig. 6. Effect of embelin administration on TNF-α levels in the blood serum of isoniazid-rifampicin treated rats

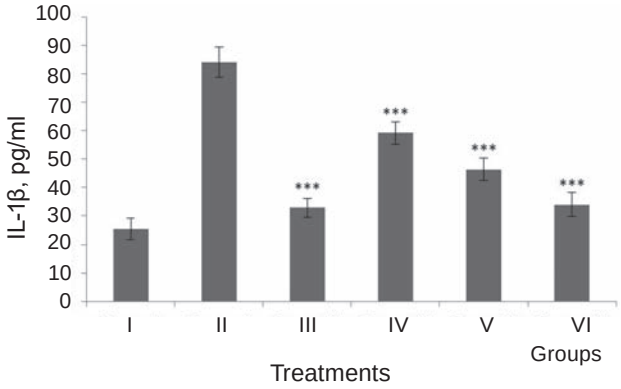

Fig. 7. Effect of embelin administration on IL-1β levels in the blood serum of isoniazid-rifampicin treated rats

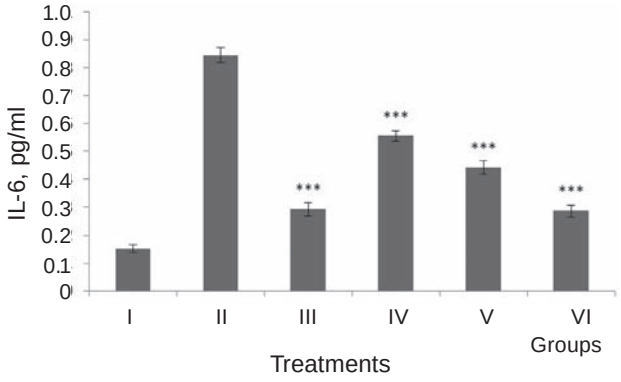

Fig. 8. Effect of embelin administration on IL-6 levels in the blood serum of isoniazid-rifampicin treated rats

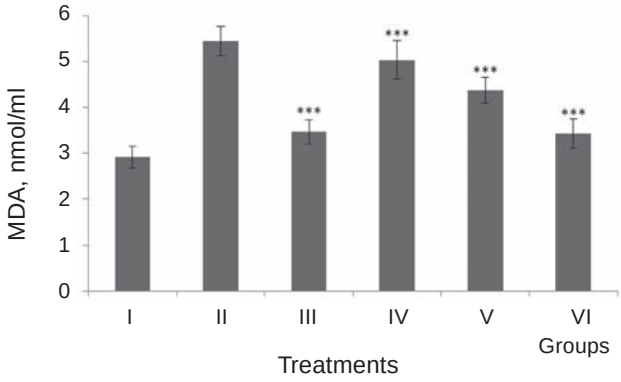

Fig. 9. Effect of embelin administration on MDA levels in the blood serum of isoniazid-rifampicin treated rats

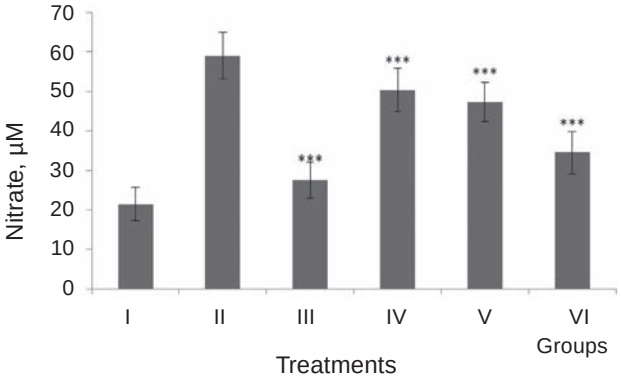

Fig. 10. Effect of embelin administration on Nitrate levels in the blood serum of isoniazid-rifampicin treated rats

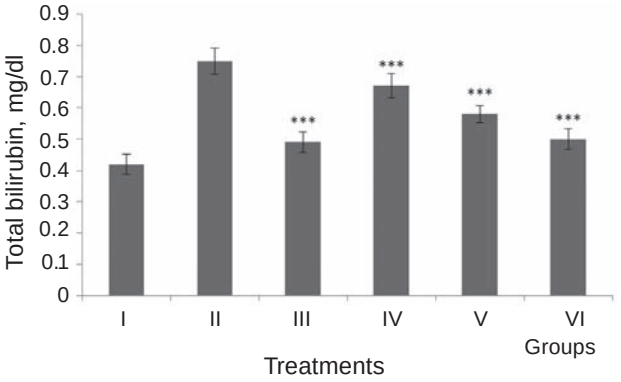

Fig. 11. Effect of embelin administration on total bilirubin in the blood serum of isoniazid-rifampicin treated rats

showing a notable trend toward restoring values close to normal, particularly observed in Group VI.

Effect of embelin administration on bilirubin level. In animals treated with isoniazid-rifampicin (Group II), there was an increase in bilirubin levels. However, when embelin was administered (Group IV-VI), a significant reduction in bilirubin level was observed. The rise in bilirubin levels induced by isoniazid-rifampicin was effectively mitigated by embelin treatment (Fig. 11). The administration of embelin led to a notable decrease in bilirubin peroxidation, suggesting a potential protective effect.

Discussion

Isoniazid, a key anti-mycobacterial agent globally used in tuberculosis treatment, undergoes biotransformation leading to metabolites linked to liver toxicity. The metabolic products form covalent adducts with liver macromolecules, resulting in hepatotoxic effects. The liver injury is attributed to the development of covalent bonds between these metabolites and numerous lysine residues present in hepatic proteins. This covalent interaction disrupts normal cellular functions, contributing to the observed liver toxicity associated with isoniazid [18]. Furthermore, the auto-oxidation of isoniazid is linked to the generation of free radicals. During this process, isoniazid undergoes spontaneous oxidation, leading to the release of reactive oxygen species. These free radicals can induce oxidative stress and contribute to cellular damage, particularly in the liver. The association of isoniazid with free radical production highlights another potential mechanism underlying its role in oxidative stress and hepatotoxicity [19]. Rifampicin is a crucial anti-tubercular agent widely employed in tuberculosis treatment. However, multiple reports indicate that the co-administration of rifampicin with isoniazid can contribute to the development of liver-related issues. The combined use of these medications is known to exacerbate the risk of hepatotoxicity. The precise mechanisms involve complex interactions between the drugs and the liver, potentially leading to liver cell damage [20].

Treatment strategies aimed at managing and reversing hepatotoxicity often involve the use of radical scavengers and antioxidants. These antioxidants, typically natural compounds, exhibit the ability to counteract oxidative stress within the cell. Their effectiveness in providing a protective shield for the liver is assessed, making them valuable candidates for hepatoprotective interventions. The evaluation of antioxidants for their potential in safeguarding liver health is a critical aspect of therapeutic considerations. Silymarin, a flavonoid complex extracted from milk thistle (Silybum marianum), exhibits potent hepatoprotective effects through several molecular mechanisms. Primarily, it scavenges free radicals, reducing oxidative stress-induced liver damage. Silymarin also modulates inflammatory pathways by inhibiting NF-κB activation and cytokine production, thus attenuating liver inflammation. Additionally, it enhances liver regeneration by stimulating DNA and RNA synthesis, promoting hepatocyte proliferation, and inhibiting fibrogenesis by interfering with the activation of hepatic stellate cells. Furthermore, silymarin chelates metal ions, preventing metal-induced liver injury [21]. These compounds play a crucial role in neutralizing harmful free radicals, mitigating cellular damage, and contributing to the restoration of normal liver function. The present study aimed to investigate the ameliorative effects of embelin on hepatocellular damage induced by isoniazid and rifampicin in rats. The objective was to assess whether the administration of embelin could mitigate the detrimental impact of these anti-tuberculosis drugs on liver cells. The study focused on understanding the potential protective role of embelin in countering hepatotoxicity caused by isoniazid and rifampicin.

The primary goal of this study was to assess the ameliorative impact of embelin on hepatocellular damage induced by isoniazid and rifampicin in rats. The experimental design involved administering embelin to animals at doses of 50, 75, and 100 mg/kg. Notably, embelin administration led to a restoration of enzyme levels (AST, ALP, and ALT) in animals from groups IV to VI. Additionally, the administration of embelin at varying doses resulted in a significant increase in the levels of important antioxidants such as SOD, catalase, and bilirubin. Moreover, there was a substantial decrease in lipid peroxidation levels, bringing them closer to normal. Serum ALP and bilirubin levels, indicative of liver cell function, demonstrated a close association [22]. Elevated levels typically signify biliary pressure, but in this study, embelin administration caused a noteworthy reduction in both ALP and bilirubin.

Eukaryotes have evolved a robust defence system to safeguard cells against damage caused by free radicals. Enzymes such as SOD and catalase play a crucial role in preventing harm from free radicals [23]. However, isoniazid and rifampicin can compromise liver function by inducing the production of free radicals, potentially disrupting enzyme activity and causing hepatic damage. Treatment with embelin results in a significant increase in the levels of these enzymes, indicating its ability to effectively neutralize reactive oxygen species. The elevated production of lipid peroxides signifies cellular damage, correlating with increased free radical generation that harms cell morphology and is associated with oxidative stress-induced damage.

IL-1β serves as a potent stimulator for effector cells expressing the interleukin-1 receptor, notably monocytes and neutrophils [24]. The activation of

IL-1β occurs through the proteolytic cleavage pathway, leading to caspase-1 activation. Regardless of the intracellular pathways involved, inflammasome activation predominantly results in caspase-1 recruitment and the conversion of pro-IL-1β to IL-1β. The latter interacts with IL-1R, potentially influencing liver function. It may play a role in reducing the inflammatory translocation of IL-1R-expressing cells to the liver, thus mitigating tissue inflammation. The administration of embelin to experimental animals resulted in a decrease in IL-1β levels, suggesting a potential role in modulating inflammatory processes.

IL-6 functions as a versatile mediator with diverse activities in the body. It plays a pivotal role as a key activator of the acute phase during inflammation and aids in preventing infections in the liver. Additionally, IL-6 is crucial for regulating hepatocytes and serves as a potent activator for these liver cells [25]. However, prolonged activation of the IL-6 signalling pathway can be detrimental to hepatic tissues, potentially contributing to the development of liver cancer. The hepatic inflammatory response induced by isoniazid-rifampicin treatment involves increased levels of initial responders like IL-6 and subsequent responders such as ROS. IL-6, being a pro-inflammatory cytokine, stimulates neutrophil influx, prostaglandin production, and the involvement of B and T-lymphocytes. In the current study, the elevated IL-6 level was effectively suppressed by embelin, highlighting its potential in dampening the inflammatory response.

Elevated levels of reactive oxygen species (ROS) can inflict cellular damage by oxidizing macromolecules like lipids, peptides, and DNA. ROS-induced lipid peroxidation, in particular, compromises the functionality and stability of cell membranes, enhancing susceptibility to ion permeability and disrupting membrane structure and cellular activities [23]. In the current investigation, the administration of embelin led to a reduction in the levels of malondialdehyde (MDA), a marker indicative of lipid peroxidation. Notably, embelin is characterized as both an antioxidant and an anti-inflammatory agent. Embelin is characterized as both an antioxidant and an anti-inflammatory agent. As an antioxidant, embelin scavenges free radicals, reducing oxidative stress and protecting cells from damage. Additionally, it modulates key signalling pathways involved in inflammation, such as NF-κB and MAPK pathways, thereby inhibiting the production of pro-inflammatory mediators like cytokines and prostaglandins. Embelin also targets specific enzymes like cyclooxygenase and lipoxygenase, further suppressing inflammatory responses. Moreover, it regulates the expression of enzymes, enhancing cellular antioxidant defences [11]. Therefore, it is plausible that the hepatoprotective effect of embelin is associated with its antioxidant properties.

The body consistently produces nitric oxide ($NO^{\bullet}$), playing a pivotal role in regulating cellular metabolism. Excessive $NO^{\bullet}$ production, however, can contribute to various disorders including inflammation and cancer [26]. Under aerobic conditions, $NO^{\bullet}$ is reactive and typically reacts with oxygen to produce stable products like nitrate and nitrite, forming intermediates such as NO_2, N_2O_4, and N_3O_4. These free radicals induce changes in the functional activity of cellular components. Embelin has the potential to inhibit the formation of intermediate molecules, thereby protecting cellular organelles. Subsequently, the embelin scavenging capability of nitrate suggests a dosage-dependent effect [27].

The liver serves as a crucial metabolic organ, overseeing essential processes such as calorie generation, detoxification, enzyme production, and drug biotransformation. Liver injury is associated with harmful alterations that can advance towards the development of cirrhosis. The findings of the current studies support the positive impact of administering embelin to experimental animals.

Conclusion. The outcomes of the current study underscore the protective capacity of embelin in mitigating the adverse impacts induced by isoniazid-rifampicin on rats. These promising findings may contribute significantly to the advancement of hepatoprotective bioactives. The observed positive effects of embelin in countering the detrimental effects of the anti-tuberculosis drugs on the liver highlight its potential therapeutic value in protecting hepatic function. Such insights not only enhance our understanding of embelin's hepatoprotective properties but also open avenues for the development of novel bioactive compounds that could potentially alleviate drug-induced liver damage.

Conflct of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

ЕМБЕЛІН ЗМЕНШУЄ ГЕПАТОТОКСИЧНІСТЬ, ІНДУКОВАНУ ІЗОНІАЗИДОМ ТА РИФАМПІЦИНОМ У ЩУРІВ

O. F. Mosa

Public Health Department, College of Al-Lieth Health Science, Umm Al Qura University, Makkah, Saudi Arabia;
e-mail: drosama2030@gmail.com

Ізоніазид і рифампіцин є ефективними протитуберкульозними препаратами, але їх застосування пов'язане з ризиком медикаментозного ураження печінки. Ембелін, природний парабензохінон, що отримують з рослини ембелії ребристої, привернув увагу через свої потенційні терапевтичні, антиоксидантні та органопротекторні властивості. Метою роботи було оцінити гепатопротекторні властивості ембеліну на тлі ураження печінки, індукованого ізоніазидом та рифампіцином. Дослідження проводили на щурах лінії Вістар, ураження печінки індукували введенням ізоніазиду (100 мг/кг) та рифампіцину (100 мг/кг). Ембелін вводили в дозах 50, 75 і 100 мг/кг протягом 21 дня. Всі препарати вводили перорально. У сироватці крові визначали рівні маркерів оксидативного стресу, активність аспартатамінотрансферази (АСТ), аланінамінотрансферази (АЛТ), лужної фосфатази (ЛФ) з використанням наборів для імуноензимного аналізу (Elabscience, Китай). Рівні фактора некрозу пухлин-α (ФНП-α), інтерлейкінів IL-1β та IL-6 визначали з використанням наборів для імуноензимного аналізу (Randox, Великобританія). Показано, що ембелін у різних дозах ефективно відновлював активність АСТ, АЛТ, лужної фосфатази, СОД і каталази та помітно знижував концентрації МДА, оксиду азоту, а також експресію прозапальних цитокінів IL-1β та IL-6, ФНП-α у сироватці крові тварин із медикаментозним ураженням печінки. Зроблено висновок, що гепатопротекторна дія ембеліну, ймовірно, пов'язана з його властивостями нейтралізувати радикали та пригнічувати експресію цитокінів.

Ключові слова: ембелін, ізоніазид, рифампіцин, гепатопротекторна дія, антиоксидантна дія, пригнічення цитокінів.

References

1. Bessone F, Dirchwolf M, Rodil MA, Razori MV, Roma MG. Review article: drug-induced liver injury in the context of nonalcoholic fatty liver disease - a physiopathological and clinical integrated view. *Aliment Pharmacol Ther.* 2018; 48(9): 892-913.
2. Marquez L, Raheja R, Chan-Liston M, Marcinak J, Estilo A, Pineda Salgado L, Jiang J, Chang C, Beninger P. Industry Review of Best Practices for Risk Management of Drug-Induced Liver Injury from Development to Real-World Use. *Drug Saf.* 2024; 47(1): 1-22.
3. Lu J, Metushi I, Uetrecht J, Einhorn S, Mann DA, Hanzlik RP, Paul B. Watkins1, LeCluyse EL. Investigation of isoniazid DILI mechanisms in human induced pluripotent stem cell derived hepatocytes. *Drug Metab Rev.* 2014; 45: 177.
4. Brewer CT. Rifampicin and Isoniazid Induced Liver Injury via the Pregnane X Receptor. *FASEB J.* 2017; 31(S1): lb486-lb486.
5. Ganeshpurkar A, Saluja AK. The Pharmacological Potential of Rutin. *Saudi Pharm J.* 2017; 25(2): 149-164.
6. Thabrew MI, Hughes RD, McFarlane IG. Screening of hepatoprotective plant components using a HepG2 cell cytotoxicity assay. *J Pharm Pharmacol.* 1997; 49(11): 1132-1135.
7. Ryle PR, Chakraborty J, Thomson AD. Biochemical mode of action of a hepatoprotective drug: observations on (+)-catechin. *Pharmacol Biochem Behav.* 1983; 18(Suppl 1): 473-478.
8. Joshi R, Kamat JP, Mukherjee T. Free radical scavenging reactions and antioxidant activity of embelin: biochemical and pulse radiolytic studies. *Chem Biol Interact.* 2007; 167(2): 125-134.
9. Gupta R, Sharma AK, Sharma MC, Gupta RS. Antioxidant activity and protection of pancreatic β-cells by embelin in streptozotocin-induced diabetes. *J Diabetes.* 2012; 4(3): 248-256.
10. Prabhu KS, Siveen KS, Kuttikrishnan S, Iskandarani A, Tsakou M, Achkar IW, Therachiyil L, Krishnankutty R, ParrayчA, Kulinski M, Merhi M, Dermime S, Mohammad RM, Uddin S. Targeting of X-linked inhibitor of apoptosis protein and PI3-kinase/AKT signaling by embelin suppresses growth of leukemic cells. *PLoS One.* 2017; 12(7): e0180895.

11. Kumaraswamy HM, Krishna V, Sharath R, Satyanarayan ND, Meghana P, Jain RSK, Prashanth N, Raja Naika H. Potential role of embelin in the prevention of Freund's adjuvant induced inflammation and ROS. *3 Biotech*. 2022; 12(1): 10.
12. Patel RS, Gohil P. Effect of Embelin in middle cerebral artery occlusion-induced focal cerebral ischemia in rats. *Oxid Antioxid Med Sci*. 2014; 3(2): 135-139.
13. Sabina EP, Peter SJ, S P, Geetha A. A comparison of hepatoprotective activity of Bacoside to Silymarin treatment against a combined Isoniazid and Rifampin-induced hepatotoxicity in female Wistar rats. *J Histotechnol*. 2019; 42(3): 128-136.
14. Masayasu M, Hiroshi Y. A simplified assay method of superoxide dismutase activity for clinical use. *Clin Chim Acta*. 1979; 92(3): 337-342.
15. Sinha AK. Colorimetric assay of catalase. *Anal Biochem*. 1972; 47(2): 389-394.
16. Ohkawa H, Ohishi N, Yagi K. Reaction of linoleic acid hydroperoxide with thiobarbituric acid. *J Lipid Res.* 1978; 19(8): 1053-1057.
17. Moshage H, Kok B, Huizenga JR, Jansen PL. Nitrite and nitrate determinations in plasma: a critical evaluation. *Clin Chem*. 1995; 41(6): 892-896.
18. Zhuang X, Li L, Liu T, Zhang R, Yang P, Wang X, Dai L. Mechanisms of isoniazid and rifampicin-induced liver injury and the effects of natural medicinal ingredients: A review. *Front Pharmacol*. 2022; 13: 1037814.
19. Mani S, Tyagi S, Pal KV, Jaiswal H, Jain A, Gulati A, et al. Drug-Induced Oxidative Stress and Cellular Toxicity. In: Free Radical Biology and Environmental Toxicity. Springer; 2022: 73-113.
20. Garcia-Cortes M, Robles-Diaz M, Stephens C, Ortega-Alonso A, Lucena MI, Andrade RJ. Drug induced liver injury: an update. *Arch Toxicol.* 2020; 94(10): 3381-3407.
21. Akakpo JY, Ramachandran A, Jaeschke H. Novel strategies for the treatment of acetaminophen hepatotoxicity. *Expert Opin Drug Metab Toxicol.* 2020; 16(11): 1039-1050.
22. Jewad AM, Jihad IA. Role of heart failure in variation of serum ALT, AST, ALP, bilirubin and electrolytes. *Biochem Cell Arch*. 2021; 21(2):3415-3421.
23. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. *Arch Toxicol.* 2023; 97(10): 2499-2574.
24. Cavalli G, Colafrancesco S, Emmi G, Imazio M, Lopalco G, Maggio MC, Sota J, Dinarello CA. Interleukin 1α: a comprehensive review on the role of IL-1α in the pathogenesis and treatment of autoimmune and inflammatory diseases. *Autoimmun Rev.* 2021; 20(3): 102763.
25. Niculet E, Chioncel V, Elisei AM, Miulescu M, Buzia OD, Nwabudike LC, Craescu M, Draganescu M, Bujoreanu F, Marinescu E, Arbune M, Radaschin DS, Bobeica C, Nechita A, Tatu A. Multifactorial expression of IL-6 with update on COVID-19 and the therapeutic strategies of its blockade (Review). *Exp Ther Med.* 2021; 21(3): 263.
26. Gantner BN, LaFond KM, Bonini MG. Nitric oxide in cellular adaptation and disease. *Redox Biol*. 2020; 34: 101550.
27. Joshi R, Kamat JP, Mukherjee T. Free radical scavenging reactions and antioxidant activity of embelin: biochemical and pulse radiolytic studies. *Chem Biol Interact*. 2007; 167(2): 125-134.