DOI: https://doi.org/10.31351/vol34iss4pp224-230

Cilnidipine Alleviates Alpha-Naphthyl Isothiocyanate -Induced Cholestasis in Rats

Thamer Abdulla Mohammed [*,1] and Munaf H. Zalzala[2]

[1]Ministry of Health, State Company for Drugs and Medical Appliances, Baghdad, Iraq.
[2]Department of Pharmacology and Toxicology, College of Pharmacy, University of Baghdad, Baghdad, Iraq
***Corresponding author**

Received 22/7/2024, Accepted 19 /11/2024, Published 20/12/2025

Abstract

Cholestasis is defined as a reduction or stagnation in bile secretion and flow. Inflammation results from blocked bile that leaks into the bloodstream and accumulates in the organs. It was postulated that cilnidipine would mitigate the liver damage linked to cholestasis by its confirmed farnesoid x receptor (FXR) activation. Hence, this study aimed to examine the impact and potential anticholestatic capabilities of cilnidipine in the rat's model of cholestasis produced by α-naphthyl isothiocyanate (ANIT), which is a widely used model that resembles human cholestasis. The white albino rats used in this investigation were separated into three distinct groups, with eight in each group. Negative control (Group I), in this group, rats get a single dose of corn oil orally (1ml/kg) 48 hours before euthanized; Positive control (Group II), in this group, rats get a single dosage of Alpha-naphthyl isothiocyanate (ANIT) (100mg/kg) orally 48 hours before euthanized; Treatment group (Group III), in this group, rats get orally (cilnidipine 10 mg/kg/day) for seven successive days, on the fifth day, rats received a single oral dose of ANIT (100mg/kg) 48 hours before euthanized. The results demonstrated that cilnidipine pretreatment decreased the levels of alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), total bile acids (TBA), direct bilirubin (DBIL), and total bilirubin (TBIL). Additionally, cilnidipine therapy also resulted in a decrease in oxidative stress and inflammatory mediators. In conclusion, the results show that cilnidipine reduces cholestasis in rats, which is induced by ANIT.

Keywords: ANIT, Cholestasis, Cilnidipine, Protective Effects, UDC

Introduction

Bile acids (BAs), derived from cholesterol, are amphipathic molecules that enhance lipid absorption while simultaneously interacting with the aqueous environment. The biological roles of BAs have been extensively investigated throughout the last few decades [(1)]. BAs are endogenous molecules that regulate energyhomeostasis, activate nuclear receptors, and govern cell proliferation and inflammation in the liver [(2,3)].Cholestasis is a gradual decrease of bile flow that can lead to liver damage. It comprises both intrahepatic and extrahepatic cholestasis [(4)]. Without appropriate care, this illness will eventually result in cirrhosis and liver failure. Because of the severe consequences, patients and society worldwide are always burdened greatly [(5)]. Clinically, a broad spectrum of liver diseases have a cholestatic phenotype, which includes hepatocyte and cholangiocyte molecular abnormalities [(6)].Since ursodeoxycholic acid (UDCA) is now the sole medication for cholestasis that the FDA has licensed, the finding of novel therapeutic medicines is necessary because of the limited effectiveness of UDCA in treating some types of cholestasis [(7)].Also, UDCA and other bile acids have been found to affect a variety of liver cell functions, such as biotransformation, through cytochrome P450 (CYP) enzymes at both the transcriptional and post-transcriptional levels, according to recent experimental evidence. The CYP3A subfamily has been demonstrated to be induced by UDCA in particular [(8–11)]. CYP3A is critically important for drug metabolism and is involved in the pre-systemic extraction of over 50% of all currently available drugs [(12)].

Hepatocyte proliferation and tumor growth were induced in hepatitis B virus transgenic mice by a diet that was enriched in UDCA [(13)]. Nevertheless, the prevailing opinion among hepatologists is that UDCA should be administered with extreme caution, or even contraindicated, in patients who are suspected of having cholangiopathies with a predominant obstructive component, such as the late stages of primary sclerosing cholangitis (PSC), primary biliary cirrhosis (PBC), or biliary atresia. Additionally, it has been contended that the limited therapeutic efficacy of UDCA, or even the detrimental effects of UDCA in late-stage PBC and

PSC, may be partially attributed to its deleterious effects [14,15]. Similarly, the therapeutic use of UDCA in biliary atresia has been limited to the type-III condition (ductules exceeding 50 μm) [16]. In view of the above, there is a need for new drugs to treat such diseases. Cholesterol can be broken down into bile acids in two different ways in the liver: the acidic, which is also called the alternative pathway, uses mitochondrial (CYP27A1), and the classic, which is also called the neutral pathway, uses (CYP7A1) [17].The FXR is a member of the nuclear receptor superfamily and functions as a sensor of bile acids. Consequently, FXR might be a valuable therapeutic target for managing cholestasis [18]. By stimulating the small heterodimer partner (SHP), FXR indirectly suppresses the transcription of the CYP7A1 gene. Furthermore, FXR stimulates fibroblast growth factor 19 (FGF19) in the gut, which in turn inhibits CYP7A1 in the liver through its action on fibroblast growth factor receptor 4 (FGFR4) [19].Calcium channel blockers (CCBs) are a structurally and functionally heterogeneous group of drugs that play a vital role in treating angina pectoris and hypertension [20]. A newly developed CCB, cilnidipine acts as an antihypertensive and blocks both L- and N-type calcium channels [21]. It was recently demonstrated that cilnidipine functions as an FXR agonist [22]. The use of α-naphthyl isothiocyanate (ANIT) is a standard method for inducing intrahepatic cholestasis in rodents. ANIT-induced cholestasis is distinguished by elevation of serum bile acids and transaminases, hepatobiliary cell necrosis, and inflammatory cell infiltration, followed by blockage and proliferation of bile ducts [23–25]. Injury to biliary epithelial cells by ANIT results in intrahepatic cholestasis [26]. Hepatobiliary barrier function analysis revealed dynamic variations in tight junction (TJ) permeability after ANIT induction [27].

Materials and Methods

Materials

Alpha-naphthyl isothiocyanate (ANIT) was purchased from Sigma Aldrich St Louis USA, assay rat's Elisa kits for serum Interleukin 1 Beta (IL1β), serum Gamma-Glutamyl transferase 1 (GGT1), tissue Malondialdehyde (MDA), serum Tumor Necrosis Factor Alpha (TNFα) were obtained from Cloud-Clone Corp. China. On the other hand, total bile acids (TBA), total bilirubin (TBIL), alkaline phosphatase (ALP), and direct bilirubin (DBIL) were measured by colorimetric analysis. Animals, Drug Treatments, and Experimental Protocol: Twenty-four (24) male albino rats weighing approximately 150-200 gm were acquired from the College of Pharmacy Animal House/University of Baghdad. After an acclimation period of one week, the animals were placed in standard laboratory conditions with a 25 ± 2 °C temperature and a dark-light-cycle of 12:12 hours.The rats were separated into three distinct groups, with eight rats in each group. Negative control (Group I), in this group rats, got 1ml/kg of corn oil orally 48 hours before being euthanized; Positive control (Group II), in this group, rats received a single dosage of Alpha-naphthyl isothiocyanate (ANIT) (100mg/kg) [28] orally 48 hours before euthanized; Treatment group (Group III), in this group, rats were administered (cilnidipine 10 mg/kg) [29] orally for seven successive days, on the fifth day, rats received a single oral dose of ANIT (100mg/kg) 48 hours before being euthanized. At the end of our work, rats were euthanized using diethyl ether and cervical dislocation. Blood was collected in tubes with coagulation activator gel and centrifuged for 10 minutes at 3000 rpm to extract the serum, which was subsequently kept at −80°C. An electric homogenizer was used to homogenize a tiny portion of liver tissue on ice with cold phosphate buffer saline PBS (1: 10, w/v). This was done after the liver tissue had been washed for a short period of time. Homogenates were then centrifuged for 15 minutes at a temperature of 4 °C and a speed of 14000 rpm. The supernatant that was obtained was stored at a temperature of -20 °C to conduct additional analysis on malondialdehyde (MDA).Another piece of liver tissue was preserved in 10% buffered formalin for hematoxylin-eosin staining [30]. A histopathologist scored the severity of liver histopathological changes, as shown in Table 1.*Statistical analysis:* The data are reported as the mean value plus or minus the standard deviation. The statistical significance was assessed using one-way analysis of variance (ANOVA) in GraphPad Prism version 9.5.1, employing Post Hoc Tukey tests to compare groups. Significance was attributed to p-values less than 0.05.

Results and Discussion

Effect of cilnidipine on Liver biochemical and inflammatory parameters: As demonstrated in Figure. 1-panel a-d, the serum levels for ALP, bile acid, DBIL, and TBIL were significantly higher in the ANIT group (Group II) than in the control group (Group I). Compared to the ANIT-treated rats (Group II), pretreatment with cilnidipine (Group III) produced a substantial decrease in these biochemical parameters. In the Figure. 2a, the serum level for GGT was notably elevated in the ANIT group compared to the control and cilnidipine pretreatment groups. The liver tissue homogenate level of MDA was measured, as depicted in Figure. 2b. Compared to the control (Group I), the tissue level of the oxidative stress marker MDA was significantly elevated in both the ANIT-treated (Group II) and cilnidipine-treated rats (Group III). However, its level was reduced considerably in the cilnidipine-

treated rats (Group III) compared to the ANIT-treated (Group II).

To assess cholestatic liver damage, levels of inflammation-related markers such as IL-1β and TNF-α were evaluated, as illustrated in Figure 2 pane c and d, respectively. The tissue levels of IL-1β and TNF-α were notably elevated in the ANIT-treated (Group II) and cilnidipine-treated rats (Group III). However, their levels still significantly decreased in the cilnidipine-treated rats (Group III) compared with the ANIT-treated (Group II).*Effect of cilnidipine on liver histopathology:* The degree of liver tissue damage was dramatically reduced in the cilnidipine pretreatment group compared to the ANIT-treated group (Group II), as shown in Figure. 3. The ANIT produces focal necrotic damage with inflammatory cell infiltration to the bile duct with a score (++). The pretreatment with cilnidipine returned the tissue section to normal with mild dilatation of the sinusoid with a score (-/+).

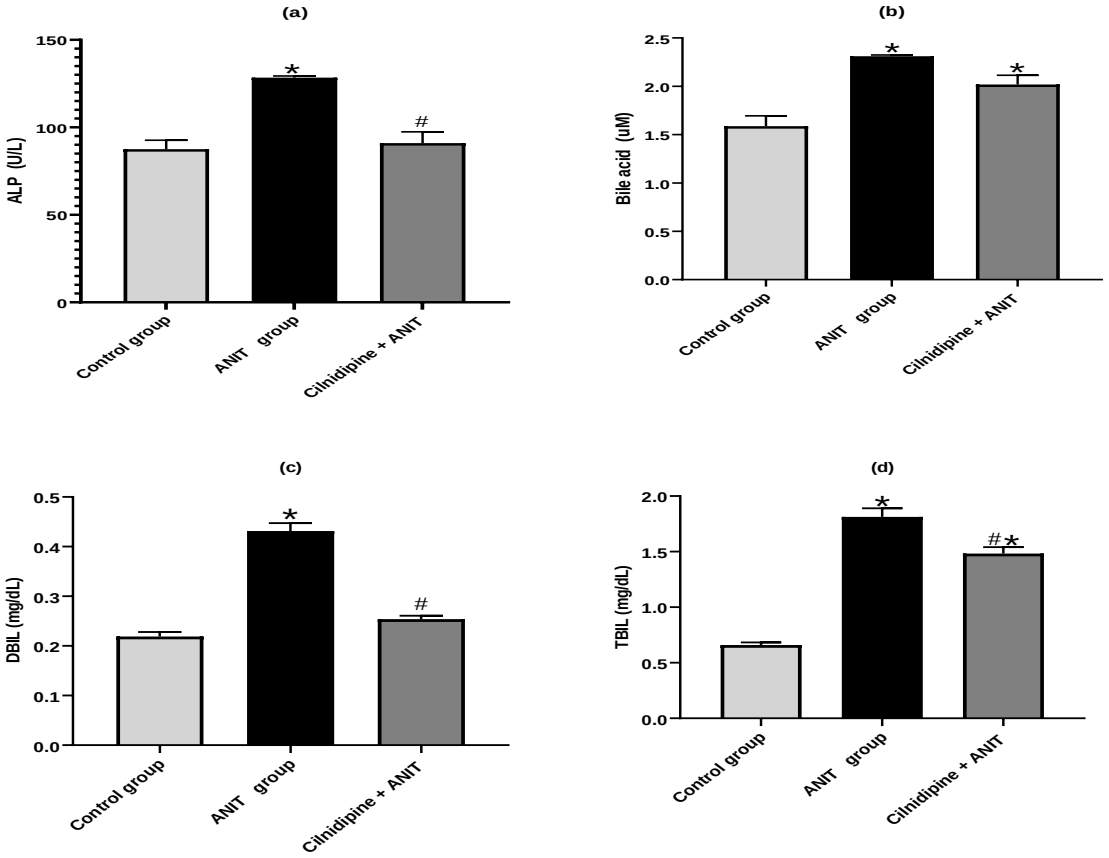
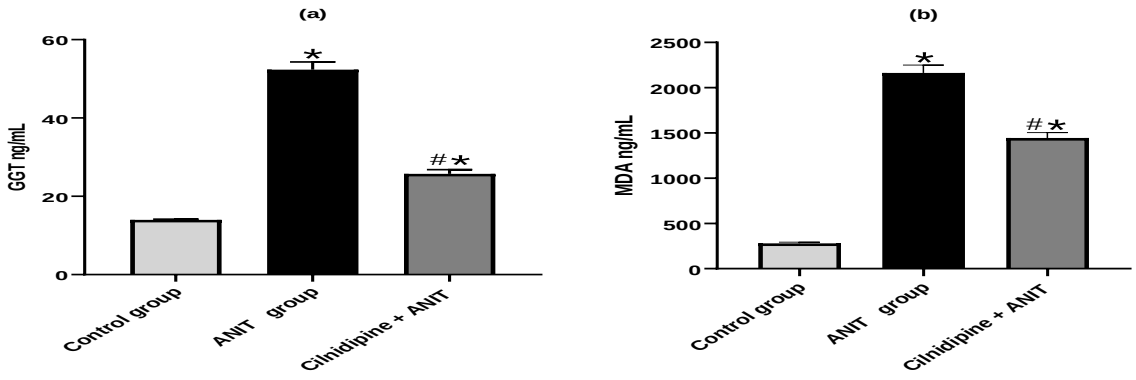


Figure 1. The effect of cilnidipine on serum levels of ALP (a), Bile acid (b), DBIL (c), and TBIL (d) in rats with cholestatic liver damage produced by ANIT. Each value is represented as mean ± SD; *P<0.05 vs. control group; #P < 0.05 vs. ANIT-treated rats.



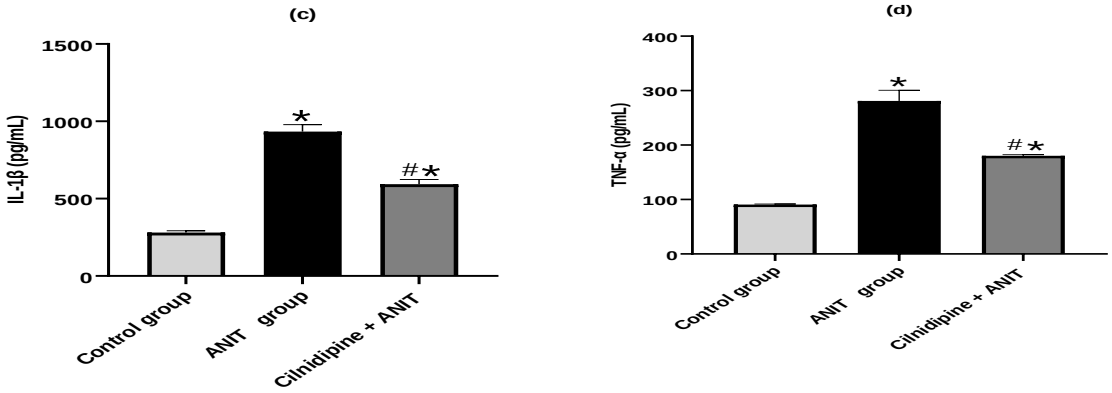


Figure 2. The effect of cilnidipine on serum levels of GGT (a), tissue MAD (b), serum levels of IL-1β (c), and serum levels of TNF-α (d) in rats with cholestatic liver damage produced by ANIT. Each value is represented as mean ± SD; *P<0.05 vs. control group; #P < 0.05 vs. ANIT-treated rats.

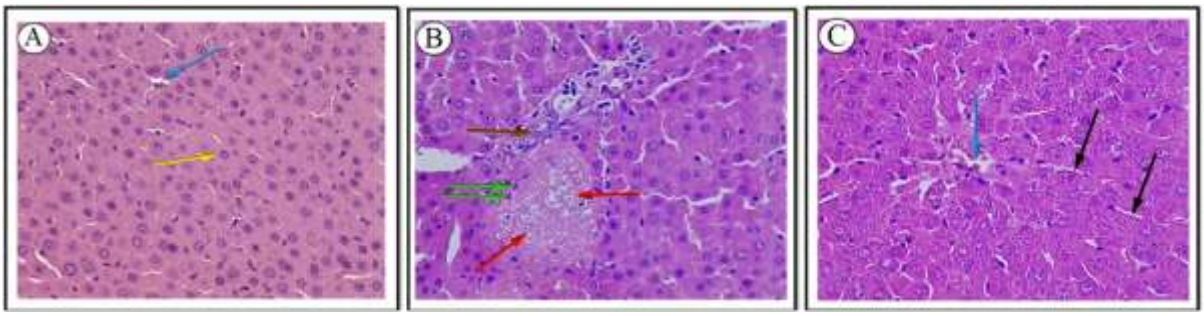


Figure 3. Histopathological changes (H & E) (X40). Section of the liver in the control, Group I (A) showed a normal histological structure appearance, which consisted of a central vein (marked by a blue arrow) with threads of hepatocyte cells (marked by a yellow arrow); its score is (0). In the ANIT-treated, Group II (B), the section showed a focal necrotic area (marked by red arrow); proliferation of bile ducts also presents (marked by brown arrow) with inflammatory cells infiltration (marked by the green arrow), its score is (++). The section of the cilnidipine-treated, Group III (C) has a normal histological structure appearance with mild dilatation of the sinusoid (marked by the black arrow). The central vein (marked with a blue arrow) has a score of (-/+).

Table 1. Histopathological changes score

Score	Histopathological changes
Score (-)	No pathological lesion
Score (-/+)	Very mild changes
Score (+)	Histopathological changes in < 20% of the field
Score (++)	Histopathological changes in 20 - 60% of the field
Score (+++)	Histopathological changes in > 60% of the field

Cholestasis, a condition characterized by impaired bile flow [31]. ANIT (alpha-naphthyl isothiocyanate) is widely used to induce cholestasis in experimental models [32]. The significant elevation of inflammatory markers and oxidative stress indicators in the ANIT-treated group (Group II), as demonstrated in this study, underscores the severity of liver injury induced by this compound [33–35].Cilnidipine is a calcium channel blocker that specifically targets L/N-type calcium channels. It has been shown to possess unique pharmacological properties that extend beyond its antihypertensive effects (21). The results of this study suggest that cilnidipine's hepatoprotective effects may be due to its ability to modulate oxidative and inflammatory pathways. Cholestatic indicators (GGT and ALP activity), total bilirubin concentration, and DBIL are significantly higher in patients with cholestasis [36,37].The significant reduction in serum ALP, bile acids, DBIL, TBIL, and GGT levels in cilnidipine-pretreated rats (Group III) compared to ANIT-treated rats (Group II) indicates an amelioration of cholestatic liver damage and improved liver function, which is consistent with earlier research findings [38]. Bile acids (BAs) affect oxidative stress pathways and play a role in the development of cholestatic liver injury, while bilirubin acts as a potent antioxidant [39,40]. Studies conducted in vitro have shown that hepatocytes are killed by bile acids through a process that is dependent on reactive oxygen species (ROS). Additionally, cholestasis triggers an inflammatory reaction that leads to a

buildup of neutrophils in the liver [41].Malondialdehyde (MDA) is a byproduct of polyunsaturated fatty acid peroxidation. MDA has been a biomarker for oxidative stress in several diseases [42]. Moreover, the decreased levels of MDA, a key indicator of oxidative stress [43], in cilnidipine-pretreated rats (Group III) when compared to Group II suggest that cilnidipine mitigates oxidative damage in hepatic tissues. This antioxidative effect is particularly noteworthy, as oxidative stress is a critical mediator of liver injury in cholestasis. Cilnidipine's ability to reduce oxidative stress markers may involve mechanisms such as inhibiting reactive oxygen species (ROS) production and enhancing antioxidant defenses. In addition to its proposed antioxidative properties, cilnidipine's anti-inflammatory effects likely contribute to its protective role in cholestatic liver injury. By reducing the levels of inflammatory markers, cilnidipine may help attenuate the inflammatory response triggered by cholestasis, thereby preventing further hepatic damage.Activation of FXR has been shown to reduce bile acid toxicity, inflammation, and fibrosis in the liver [44]. The protective effects of cilnidipine observed in this study may be partially mediated through the modulation of FXR activity. By influencing FXR pathways, cilnidipine could enhance bile acid detoxification and efflux, thereby reducing cholestatic liver injury and promoting liver health [45].The study's findings align with previous research highlighting the potential therapeutic benefits of cilnidipine in various models of liver injury [46,47]. However, while the results are promising, further investigations are warranted to elucidate the precise molecular mechanisms underlying cilnidipine's hepatoprotective effects, including its interaction with FXR. Additionally, translating these findings to clinical settings will require comprehensive studies to evaluate the efficacy and safety of cilnidipine in human subjects with cholestatic liver diseases.

Conclusion

This study demonstrated that cilnidipine protects rats from cholestatic liver injury by reducing inflammatory and oxidative stress markers and improving liver function biomarkers compared to ANIT-treated rats.

Acknowledgement

I extend my thanks to the University of Baghdad—College of Pharmacy for allowing me to work on the modern laboratory equipment that has recently been installed.

Conflicts of Interest

There is no conflict of interest.

Funding

None

Ethics Statements

The University of Baghdad/ College of Pharmacy Animal Research Local Ethics Committee accepted this study with Approval Number RECAUBCP on 20/4/2023.

Author Contribution

Conception and Design of the study by Dr. Munaf H. Zalzala. The animal experiment work and manuscript writing by Thamer Abdulla Mohammed.

References

1. Houten SM, Watanabe M, Auwerx J. Endocrine functions of bile acids. EMBO J. 2006;25(7):1419–25.
2. Li T, Chiang JYL. Bile acid signaling in liver metabolism and diseases. J Lipids. 2012;2012.
3. Chiang JYL. Bile acid metabolism and signaling. Compr Physiol. 2013;3(3):1191.
4. Chen Z, Ma X, Zhao Y, Wang J, Zhang Y, Li J, et al. Yinchenhao decoction in the treatment of cholestasis: A systematic review and meta-analysis. J Ethnopharmacol. 2015;168:208–16.
5. Ma X, Zhao Y, Zhu Y, Chen Z, Wang J, Li R, et al. Paeonia lactiflora Pall. protects against ANIT-induced cholestasis by activating Nrf2 via PI3K/Akt signaling pathway. Drug Des Devel Ther. 2015;5061–74.
6. Mariotti V, Cadamuro M, Spirli C, Fiorotto R, Strazzabosco M, Fabris L. Animal models of cholestasis: An update on inflammatory cholangiopathies. Biochim Biophys Acta (BBA)-Molecular Basis Dis. 2019;1865(5):954–64.
7. Hirschfield GM, Heathcote EJ, Gershwin ME. Pathogenesis of cholestatic liver disease and therapeutic approaches. Gastroenterology. 2010;139(5):1481–96.
8. Paolini M, Pozzetti L, Piazza F, Cantelli-Forti G, Roda A. Bile acid structure and selective modulation of murine hepatic cytochrome P450–linked enzymes. Hepatology. 1999;30(3):730–9.
9. Paolini M, Pozzetti L, Montagnani M, Potenza G, Sabatini L, Antelli A, et al. Ursodeoxycholic acid (UDCA) prevents DCA effects on male mouse liver via up-regulation of CXP and preservation of BSEP activities. Hepatology. 2002;36(2):305–14.
10. Schuetz EG, Strom S, Yasuda K, Lecureur V, Assem M, Brimer C, et al. Disrupted bile acid homeostasis reveals an unexpected interaction among nuclear hormone receptors, transporters, and cytochrome P450. J Biol Chem. 2001;276(42):39411–8.
11. Bodin K, Bretillon L, Aden Y, Bertilsson L, Broomé U, Einarsson C, et al. Antiepileptic drugs increase plasma levels of 4β-

hydroxycholesterolin humans: Evidence for involvement of cytochrome P450 3A4. J Biol Chem. 2001;276(42):38685–9.
12. Thummel KE, Wilkinson GR. In vitro and in vivo drug interactions involving human CYP3A. Annu Rev Pharmacol Toxicol. 1998;38(1):389–430.
13. Barone M, Maiorano E, Ladisa R, Cuomo R, Pece A, Berloco P, et al. Influence of ursodeoxycholate-enriched diet on liver tumor growth in HBV transgenic mice. Hepatology. 2003;37(4):880–6.
14. Corpechot C, Carrat F, Bahr A, Chrétien Y, Poupon R-E, Poupon R. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology. 2005;128(2):297–303.
15. Lindor KD, Kowdley K V, Luketic VAC, Harrison ME, McCashland T, Befeler AS, et al. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. Hepatology. 2009;50(3):808–14.
16. Mohanty MK, Gupta SD, Bhatnagar V. Surgical outcome in relation to duct size at the porta hepatis and the use of cholagogues in patients with biliary atresia. Trop Gastroenterol. 2010;31(3):184–9.
17. Chiang JYL. Regulation of bile acid synthesis: pathways, nuclear receptors, and mechanisms. J Hepatol. 2004;40(3):539–51.
18. Yang F, Tang X, Ding L, Zhou Y, Yang Q, Gong J, et al. Curcumin protects ANIT-induced cholestasis through signaling pathway of FXR-regulated bile acid and inflammation. Sci Rep. 2016;6(1):33052.
19. Chiang JYL, Ferrell JM. Bile acid biology, pathophysiology, and therapeutics. Clin liver Dis. 2020;15(3):91.
20. Eisenberg MJ, Brox A, Bestawros AN. Calcium channel blockers: an update. Am J Med. 2004;116(1):35–43.
21. Chandra KS, Ramesh G. The fourth-generation Calcium channel blocker: Cilnidipine. Indian Heart J. 2013;65(6):691–5.
22. Hsu C-W, Zhao J, Huang R, Hsieh J-H, Hamm J, Chang X, et al. Quantitative high-throughput profiling of environmental chemicals and drugs that modulate farnesoid X receptor. Sci Rep. 2014;4(1):6437.
23. Amin K, Ip C, Sato B, Le T, Green CE, Tyson CA, et al. Characterization of ANIT-induced toxicity using precision-cut rat and dog liver slices cultured in a dynamic organ roller system. Toxicol Pathol. 2006;34(6):776–84.
24. FAIOLA B, PETERSON RA, KIMBROUGH CL, JORDAN HL, CULLEN JM. Faiola, B., Peterson, RA, Kimbrough, CL, Jordan, HL, Cullen, JM (2010). Acute ANIT Toxicity in Male IL-10 Knockout and Wild-type Mice. Toxicol Pathol 38, 745-55.(Original. Toxicol Pathol. 2010;38(6).
25. 2Desmet VJ, Krstulović B, Van Damme B. Histochemical study of rat liver in alpha-naphthyl isothiocyanate (ANIT) induced cholestasis. Am J Pathol. 1968;52(2):401.
26. Tanaka Y, Aleksunes LM, Cui YJ, Klaassen CD. ANIT-induced intrahepatic cholestasis alters hepatobiliary transporter expression via Nrf2-dependent and independent signaling. Toxicol Sci. 2009;108(2):247–57.
27. Yang T, Mei H, Xu D, Zhou W, Zhu X, Sun L, et al. Early indications of ANIT-induced cholestatic liver injury: Alteration of hepatocyte polarization and bile acid homeostasis. Food Chem Toxicol. 2017;110:1–12.
28. Atshan DA, Zalzala MH. Papaverine attenuates the progression of alpha naphthylisothiocyanate induce cholestasis in rats. Curr Res Pharmacol Drug Discov. 2024;6:100177.
29. Varagic J, Susic D, Frohlich ED. Cilnidipine improves spontaneously hypertensive rat coronary hemodynamics without altering cardiovascular mass and collagen. J Hypertens. 2002;20(2):317–22.
30. Nafeer SA, Zalzala M. Possible Amelioration of the Severity of Nutritional Steatohepatitis by Guggulsterone in Mice: guggulsterone and steatohepatitis in mice. Iraqi J Pharm Sci (P-ISSN 1683-3597 E-ISSN 2521-3512). 2019;28(1):17–23.
31. Pieters A, Gijbels E, Cogliati B, Annaert P, Devisscher L, Vinken M. Biomarkers of cholestasis. Biomark Med. 2021;15(6):437–54.
32. Atshan DA, Zalzala MH. POSSIBLE PROTECTIVE EFFECT OF NICARDIPINE ON ANIT INDUCE CHOLESTASIS IN RAT. Farmacia. 2024;72(1).
33. Levitt MD, Hapak SM, Levitt DG. Alkaline phosphatase pathophysiology with emphasis on the seldom-discussed role of defective elimination in unexplained elevations of serum ALP–a case report and literature review. Clin Exp Gastroenterol. 2022;41–9.
34. Ommati MM, Niknahad H, Najibi A, Arjmand A, Alidaee S, Mazloomi S, et al. Cholestasis-associated pulmonary inflammation, oxidative stress, and tissue fibrosis: The protective role of the biogenic amine agmatine. Pharmacology. 2023;108(4):379–93.
35. Li Y, Yu H, Xu Z, Shi S, Wang D, Shi X, et al. Melatonin ameliorates ANIT-induced cholestasis by activating Nrf2 through a PI3K/Akt-dependent pathway in rats. Mol Med Rep. 2019;19(2):1185–93.
36. Zajic S, Damnjanovic Z, Stojanovic M, Visnjic M, Dencic S, Ilic D, et al. Biochemical markers in patients with extrahepatic cholestasis. Acta Medica Median. 2007;47(1):5–12.

37. Luo M, Wang L, Yao H, Wen Y, Cao D, Shen W, et al. Diagnostic and prognostic value of blood inflammation and biochemical indicators for intrahepatic cholestasis of pregnancy in Chinese pregnant women. Sci Rep. 2022;12(1):20833.

38. Mao H, Jin D, Lu M. Hepatoprotective Effect of S-ademetionine in the treatment of Intrahepatic Cholestasis through Farnesoid X Receptor Mechanism in Rats. J Biomol Res Ther. 2019;8:176.

39. Muchova L, Vanova K, Zelenka J, Lenicek M, Petr T, Vejrazka M, et al. Bile acids decrease intracellular bilirubin levels in the cholestatic liver: implications for bile acid-mediated oxidative stress. J Cell Mol Med. 2011;15(5):1156–65.

40. Jurate K, Rimantas Z, Jolanta S, Vladas G, Limas K. Sensitivity and specificity of biochemical tests for diagnosis of intrahepatic cholestasis of pregnancy. Ann Hepatol. 2017;16(4):569–73.

41. Copple BL, Jaeschke H, Klaassen CD. Oxidative stress and the pathogenesis of cholestasis. In: Seminars in liver disease. © Thieme Medical Publishers; 2010. p. 195–204.

42. Cordiano R, Di Gioacchino M, Mangifesta R, Panzera C, Gangemi S, Minciullo PL. Malondialdehyde as a potential oxidative stress marker for allergy-oriented diseases: an update. Molecules. 2023;28(16):5979.

43. Atshan DA, Zalzala MH. Possible Protective Effect of Low Dose of Papaverine on ANIT Induce Cholestasis in Rat. Iraqi J Pharm Sci (P-ISSN 1683-3597 E-ISSN 2521-3512). 2023;32(Suppl.):118–26.

44. Al-Khfajy WS, Kathem SH, Aboddy AA, Hatem SF, Zalzala MH, Arif IS. Farnesoid X receptor is an exciting new perspective target for treatment of diverse pathological disorders: Review. J Pharm Sci Res. 2018;10(9):2292–6.

45. Fuchs CD, Sroda N, Scharnagl H, Gupta R, Minto W, Stojakovic T, et al. Non-steroidal FXR agonist cilofexor improves cholestatic liver injury in the Mdr2-/-mouse model of sclerosing cholangitis. JHEP Reports. 2023;5(11):100874.

46. Abe M, Maruyama N, Suzuki H, Inoshita A, Yoshida Y, Okada K, et al. L/N-type calcium channel blocker cilnidipine reduces plasma aldosterone, albuminuria, and urinary liver-type fatty acid binding protein in patients with chronic kidney disease. Heart Vessels. 2013;28:480–9.

47. Fouda A, Youssef AR, Sharaf Eldin O. Comparative study of amlodipine vs. cilnidipine for the prevention of hepatic ischemia-reperfusion injury in rat model. Fundam Clin Pharmacol. 2018;32(2):163–73.

السلندبين يخفف من الركود الصفراوي المستحدث بمادة الفا- نافثيل ازوثايوسيانايد في الجرذان

ثامر عبد الله محمد*[١،] ومناف هاشم زلزله[٢]

[١]وزارة الصحة والبيئة، الشركة العامة للأدوية والمستلزمات الطبية، بغداد، العراق

[٢] فرع الادوية والسموم، كلية الصيدلة، جامعة بغداد، بغداد، العراق.

الخلاصة

يتم تعريف الركود الصفراوي على أنه انخفاض أو ركود في إفراز الصفراء وتدفقها مما يسبب التهابات نتيجة الصفراء المتسربة الى مجرى الدم والتي تتجمع بعدد من أعضاء الجسم . تم أفتراض أن السلندبين ممكن أن يخفف ألاعراض المتعلقة بالركود الصفراوي من خلال تحفيز مستقبل FXR حيث تم إختبار التأثير العلاجي للسلندبين على الجرذان التي قمنا بأصابتها بالركود الصفراوي بواسطة مادة الفا- نافثيل ازوثايوسيانايد والذي يعتبر نموذج شائع محاكي للركود الصفراوي عند الانسان. تم تقسيم الجرذان المستخدمة في هذه الدراسة إلى ٣ مجموعات، كل مجموعة تحوي ثمانية جرذان كما يلي: المجموعة الأولى وهي مجموعة السيطرة حيث تم إعطائها عن الطريق الفم جرعة واحدة من زيت الذرة (١ مل / كجم) قبل ٤٨ ساعة من التضحية بالمجموعة؛ أما المجموعة الثانية فتم إعطائها عن الطريق الفم جرعة واحدة من مادة الفا- نافثيل ازوثايوسيانايد (١٠٠ ملغ/كغم) قبل ٤٨ ساعة من التضحية بالمجموعة؛ أما المجموعة الثالثة فتم إعطائها عن الطريق الفم (١٠ مجم / كجم) من مادة السلندبين لمدة ٧ أيام متتالية وفي اليوم الخامس تم إعطاء المجموعة جرعه واحدة عن طريق الفم (١٠٠ ملغ/كغم) من مادة الفا- نافثيل ازوثايوسيانايد وتم التضحية بالمجموعة بعد ٤٨ ساعة.أظهرت نتائج هذه الدراسة أن المعالجة بمادة السلندبين تؤدي الى تقليل مستوياتALP ، GGT، إجمالي حامض الصفراء، إجمالي البليروبين، البلروبين المباشر، وأيظاً الى تقليل مؤشرات جهد الاكسدة والالتهاب.لذلك نستنتج مما سبق من نتائج أن السيلينيديبين يخفف من ركود الصفراء في الجرذان ، والذي يسببه الفا- نافثيل ازوثايوسيانايد.

الكلمات المفتاحية : ANIT، الركود الصفراوي، السلندبين، التأثيرات الوقائية، UDCA