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Mini Review

# Ursodeoxycholic Acid for the Management of Drug-induced Liver Injury: Role of Hepatoprotective and Anti-cholestatic Mechanisms

Fernando Bessone[1*], Geraldine L. Hillotte[2], Norberto Tamagnone[1], Daiana Arnedillo[1] and Marcelo G. Roma[2*]

[1]*Hospital Provincial del Centenario, Facultad de Ciencias Médicas, Servicio de Gastroenterología y Hepatología, Universidad Nacional de Rosario, Rosario, Argentina;* [2]*Instituto de Fisiología Experimental (IFISE-CONICET), Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Rosario, Argentina*

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## Abstract

Drug-induced liver injury (DILI) is a harmful reaction to medications, herbs, and dietary supplements that results in liver dysfunction. Based on the distinct clinical patterns of liver damage, DILI can be categorized into hepatocellular, cholestatic, and mixed types. Hepatocellular DILI is linked to inflammation, apoptosis, and necrosis, while cholestatic DILI is commonly associated with bile plugs and, in rare cases, ductopenia. Ursodeoxycholic acid (UDCA) is the therapeutic agent most widely used for the treatment of cholestatic hepatopathies of diverse etiologies and has been mainly used as a supportive treatment in cholestatic DILI. In this review, we presented a more structured and systematic framework for the potential application of this hepatoprotective agent across a broader range of DILI scenarios. A MEDLINE search of the literature from 1995 to the present retrieved 41 preliminary clinical studies suggesting that UDCA may offer curative and preventive benefits for hepatocellular DILI as well. This aligns with preclinical studies in rodents, showing beneficial effects of UDCA in experimental DILI irrespective of the clinical patterns of injury involved. This could be due to the broad range of potentially beneficial effects of UDCA, which may address the various types of liver damage with different causes and mechanisms seen in all forms of DILI. UDCA's beneficial properties include anticholestatic, antioxidant, anti-inflammatory, anti-apoptotic, anti-necrotic, mitochondrial protective, endoplasmic reticulum stress-relieving, and immunomodulatory effects. Controlled studies with systematic use of standardized causality assessments are eagerly awaited to properly validate the use of UDCA in DILI. Meanwhile, we hope this article helps clarify and systematize the use of this versatile and safe hepatoprotective medication for different types of liver toxicity.

**Keywords:** Drug-induced liver injury; Ursodeoxycholic acid; DILI; Hepatocellular DILI; Cholestatic DILI; Hepatotoxicity.

***Correspondence to:** Fernando Bessone, Servicio de Gastroenterología y Hepatología, Facultad de Ciencias Médicas, Universidad Nacional de Rosario, Urquiza 3101, Rosario 2000, Argentina. ORCID: https://orcid.org/0000-0002-8569-8123. Tel/Fax: +54-341-425926, E-mail: bessonefernando@gmail.com; Marcelo G. Roma, Instituto de Fisiología Experimental, Facultad de Ciencias Bioquímicas y Farmacéuticas, Universidad Nacional de Rosario, Suipacha 570, Rosario 2000, Argentina. ORCID: https://orcid.org/0000-0002-1660-9801. Tel: +54-341-4305799, Fax: +54-341-4399473, E-mail: mroma@fbioyf.unr.edu.ar.

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## Introduction

Drug-induced liver injury (DILI) is a relatively common adverse drug reaction caused by medications, herbs, and dietary supplements. DILI can be classified into hepatocellular, cholestatic, and mixed types, according to the specific liver enzyme abnormalities that occur. This classification reflects distinct histological injury patterns: hepatocellular DILI is associated with severe inflammation, necrosis, and apoptosis, while cholestatic DILI is typically linked to bile plugs and bile duct paucity.[1]

There is no definitive treatment for DILI, other than discontinuing the offending drug and avoiding re-exposure. However, if liver dysfunction persists, therapeutic interventions become necessary. Ursodeoxycholic acid (UDCA) is commonly used in such cases, either alone or in combination with other medications, such as glucocorticoids for severe immune-allergic reactions.[2]

A recent systematic review by Robles-Díaz *et al*.[3] reinforced the presumption that UDCA might have beneficial effects not only in treating but also in preventing DILI. However, firm conclusions were limited by the design shortcomings of the available studies. Surprisingly, despite UDCA being better known as an anti-cholestatic drug, no difference in beneficial response was observed between the "hepatocellular" and "cholestatic" types of DILI.[3] This surely reflects the multiple hepatoprotective mechanisms of UDCA, which extend beyond its anti-cholestatic effects, making the drug potentially advantageous in diverse DILI scenarios.

This article discusses the efficacy of UDCA across the entire spectrum of DILI. We examine how these findings align with the various mechanisms underlying UDCA's hepatoprotective effects, with particular focus on connecting them to the distinct pathomechanisms involved in DILI. This approach aimed to provide a more rational and systematic framework

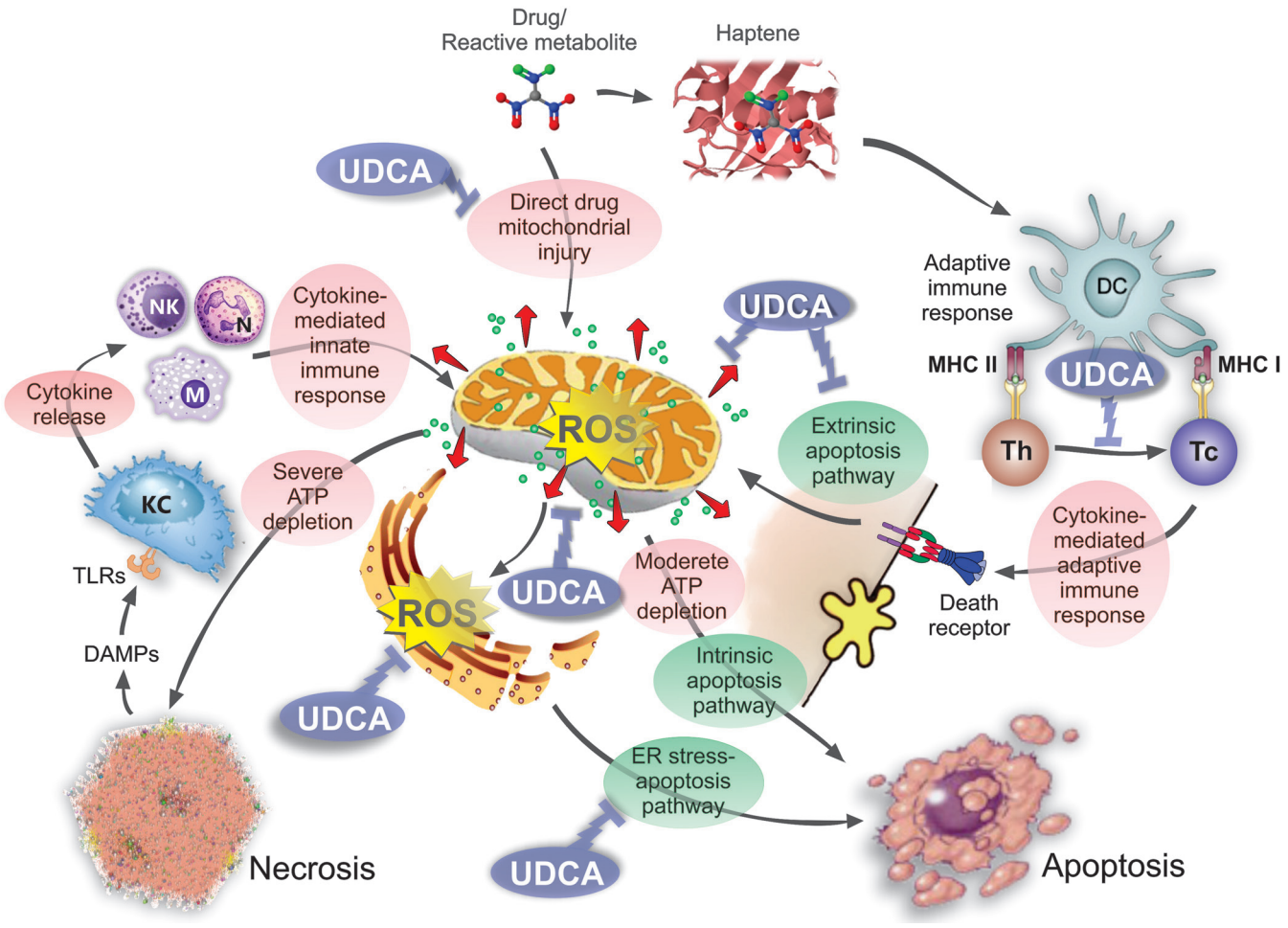


**Fig. 1. Pathomechanisms of "hepatocellular" DILI, and possible beneficial mechanisms of UDCA.** Hepatocytes can be injured by the original drug or its reactive metabolites through multiple mechanisms. These include direct injury or drug-induced immune-mediated attacks by both the innate and adaptive immune systems. Mitochondrial impairment can occur due to direct chemical insult from the drug or mitochondrial ROS generation secondary to the drug insult, leading to mitochondrial pore formation. This triggers the intrinsic (mitochondrial) pathways of cell death, resulting in apoptosis or necrosis depending on the level of ATP depletion. Alternatively, reactive drug metabolites can act as haptens, triggering the adaptive immune response by covalently binding to proteins. These hapten-protein complexes are presented by DCs to naïve Th and Tc lymphocytes in association with MHC class I or II molecules, respectively. This process converts naïve lymphocytes into drug-specific effector lymphocytes; thus, activated Tc cells can release or express in their plasma membrane cytokines that interact with death receptors on hepatocytes, triggering the extrinsic apoptosis pathway. Additionally, reactive drug metabolites or elevated ROS levels generated by nearby mitochondria can produce ER stress, which can further trigger pro-apoptotic signals to reinforce hepatocyte apoptosis. Loss of membrane integrity associated with necrosis leads to the release of DAMPs from various intracellular compartments. This triggers the innate immune-mediated response through TLR-mediated activation of KC, resulting in cytokine release. These cytokines recruit and activate N, NK cells, and macrophages, which contribute to hepatocyte death through different harmful mediators. UDCA interferes with these pathomechanisms at multiple levels due to its antioxidant, anti-inflammatory, anti-apoptotic, anti-necrotic, mitoprotective, ER-stress alleviating, and immunomodulatory mechanisms (for details, see text). Adapted with permission from elsewhere.[5] ROS, reactive oxygen species; DCs, dendritic cells; Th, T helper; Tc, T cytotoxic; ER, endoplasmic reticulum; DAMPs, damage-associated molecular patterns; TLR, toll-like receptor; KC, Kupffer cells; N, neutrophils; NK, natural killer; UDCA, ursodeoxycholic acid; DILI, drug-induced liver injury.

for the potential use of this hepatoprotective agent in different DILI scenarios.

## Mechanistic basis of the beneficial effects of UDCA in DILI

### *UDCA beneficial mechanisms in "hepatocellular" DILI*

Hepatocellular DILI often involves apoptosis and/or necrosis, associated with ischemic, toxic, or immune-mediated mechanisms of cell death.[1] These insults result in oxidative stress, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, and immune-mediated attack by both the innate and adaptive immune systems.[4] These pathomechanisms intertwine to produce several vicious cycles of liver injury (Fig. 1).[5]

Mitochondrial impairment due to direct drug-mediated chemical insult and subsequent mitochondrial reactive oxygen species (ROS) generation leads to mitochondrial pore formation and the release of mitochondrial pro-apoptotic factors that activate executor caspases. This triggers the so-called "intrinsic apoptosis pathway", which can result in necrosis rather than apoptosis when profound ATP depletion occurs due to massive mitochondrial impairment.[4] UDCA can efficiently counteract these pathomechanisms by acting as a mitotropic ROS scavenger and by inducing hepatocellular antioxidant enzymes through upregulation of the master redox-sensitive transcription factor, Nrf2.[6]

Alternatively, drug-reactive metabolites can act as haptens and trigger the adaptive immune response after covalent binding to proteins. These complexes can be presented by dendritic cells to naïve T helper and T cytotoxic lymphocytes in association with MHC class I or II molecules, respectively. This converts Tc cells into drug-specific effector lymphocytes, which can interact with death receptors on the surface of hepatocellular and cholangiocellular plasma membranes, triggering the so-called "extrinsic apoptosis pathway".[7] In turn, loss of membrane integrity associated with necrosis releases danger-associated molecular patterns from intracellular compartments. They trigger the innate immune response via Toll-like receptor-mediated Kupffer cell release of cytokines, which recruit and activate neutrophils, natural killers, and macrophages, attacking hepatocytes via various death mediators.[7] UDCA can limit this exacerbated immune response by activating the glucocorticoid receptor, which blocks activation of the pro-inflammatory transcription factors AP-1 and NF-κB. UDCA can also inhibit the mononuclear cell-mediated release of cytokines that trigger proliferation and activation of Tc and natural killer cells. Additionally, UDCA halts macrophage release of IL-8, a potent neutrophil chemoattractant. Finally, UDCA suppresses MHC I expression in hepatocytes, presumably via glucocorticoid receptor activation.[8]

Drug-reactive metabolites or mitochondrial ROS elevations can also affect the nearby ER, leading to ER stress. This triggers pro-apoptotic signals from the organelle that reinforce hepatocyte apoptosis.[9] Amide-UDCA conjugates act as chemical chaperones that mitigate ER stress.[8] Additionally, ER stress induces apoptosis via caspase 12 activation, and UDCA counteracts this activation.[10]

### *UDCA beneficial mechanisms in "cholestatic" DILI*

Etiological agents involved in "cholestatic" DILI include: 1) the drug itself or its reactive metabolites, and 2) the secondarily accumulated bile acids, which can lead to apoptosis or necrosis depending on their intracellular levels.[11] UDCA has unique protective properties that attenuate all these processes.

UDCA replaces cytotoxic endogenous bile acids with itself, resulting in a far less toxic hepatocellular and biliary bile-acid composition.[12] Additionally, UDCA improves the body's ability to clear both bile acids and the culprit drugs by modulating the expression of transporters in the liver, kidney, and intestine. UDCA reduces hepatocellular levels of these compounds by inhibiting their uptake and accelerating their reflux into sinusoidal blood to favor renal excretion.[12]

Accumulated cytotoxic bile acids can induce necrosis or apoptosis depending on the severity of cholestasis, and UDCA possesses numerous specific mechanisms of protection against this.[12]

UDCA increases plasma membrane resistance to bile-acid detergent damage by inserting itself into the lipid bilayers, and when inserted in its anion form after amidation, it repels negatively charged bile acids.[13]

Bile acids can trigger the intrinsic (mitochondrial-mediated), extrinsic (death-receptor-mediated), and ER-mediated apoptosis mechanisms. As stated above, UDCA has anti-apoptotic mechanisms to counteract all of them.[8]

The aforementioned antioxidant and anti-apoptotic mechanisms of UDCA in hepatocytes are also expected to apply to cholangiocytes. This is particularly important since cholangiocytes have low glutathione content, and therefore, are highly susceptible to pro-oxidizing drugs, especially the glutathione-depleting ones.

Similarly, the general mechanisms of UDCA's immunosuppressive and immunomodulatory effects discussed above would help attenuate the cellular immune response against biliary cells by inhibiting the release of cytokines from mononuclear cells.[14]

Finally, UDCA has unique properties that attenuate bile-acid cholangiocyte toxicity in obstructive DILI (Fig. 2): 1) UDCA stimulates the *multidrug-resistant protein 3* (Mrp3)-mediated phospholipid biliary excretion; phospholipids form mixed micelles with bile acids, thus lowering the biliary levels of highly toxic bile-acid monomers; 2) UDCA promotes ductular bicarbonate ($HCO_3^-$) excretion via *anion exchanger 2* (AE2), and this $HCO_3^-$-rich ductular choleresis both dilutes cytotoxic bile acids and forms the so-called "$HCO_3^-$ umbrella", an alkaline layer that helps maintain bile acids in their non-diffusible, anionic forms, thus preventing their passive diffusion into cholangiocytes as neutral lipophilic molecules. UDCA also undergoes extensive cholehepatic recycling following biliary excretion, inducing a $HCO_3^-$-rich hypercholeresis that further contributes to bile-acid dilution and neutralization.[5]

In summary, UDCA has antioxidant, anti-inflammatory, anti-apoptotic, anti-necrotic, mitoprotective, ER-stress-alleviating, immunomodulatory, and anticholestatic properties, making it a highly versatile tool to mitigate virtually all the wide range of injuries involved in DILI.

## UDCA in DILI treatment and prevention

### *Experimental evidence*

There is compelling evidence on the hepatoprotective role of UDCA in numerous experimental hepatopathies. The focus has primarily been on its well-known anticholestatic properties, particularly its ability to counteract bile salt cytotoxicity. UDCA has been shown to reduce proinflammatory cytokine release, oxidative stress, hepatocellular death, and hepatocellular levels of cytotoxic bile acids in rodents after hydrophobic bile acid administration.[15,16] This beneficial effect was reproduced in experimental models of extrahepatic and intrahepatic cholestatic injury induced by bile-duct ligation[17] and ANIT,[18] respectively. Although its role in experimental DILI is less explored, several studies have shown beneficial effects of UDCA in preclinical models. For example, in rodents, different UDCA formulations afforded hepatoprotection against hepatotoxicity induced by methotrexate,[19] amoxicillin-clavulanic acid,[20] tacrolimus,[21] gentamicin,[22] cyclosporine A,[23] carbon tetrachloride,[24] valproate-carbamazepine,[25] ethanol,[26] and isoniazid plus rifampicin.[27] UDCA's beneficial effects have been mainly attributed to its antioxidant, anti-inflammatory, and anti-apoptotic properties. This reinforces the concept that UDCA can be beneficial not only in cholestatic, but also in hepatocellular DILI.

### *Clinical evidence*

While most guidelines and recommendations on DILI management suggest potential benefits of UDCA in treating cholestatic forms of DILI (Table 1),[28–31] robust evidence from controlled studies supporting its systematic use is lacking. For example, the EASL DILI guidelines state that the efficacy of UDCA to reduce the severity of liver injury may not be substantiated, and that the evidence is inconclusive, being mainly derived from case series and individual case studies.[30] Bearing in mind these limitations, this anecdotal evidence suggests that UDCA, when used therapeutically, may improve liver function tests not only in idiosyncratic cholestatic DILI, but also in hepatocellular DILI. Furthermore, UDCA may serve as a preventive agent in DILI when given concomitantly with potentially hepatotoxic medications.[3]

A comprehensive search of Medline from 1995 to 2024

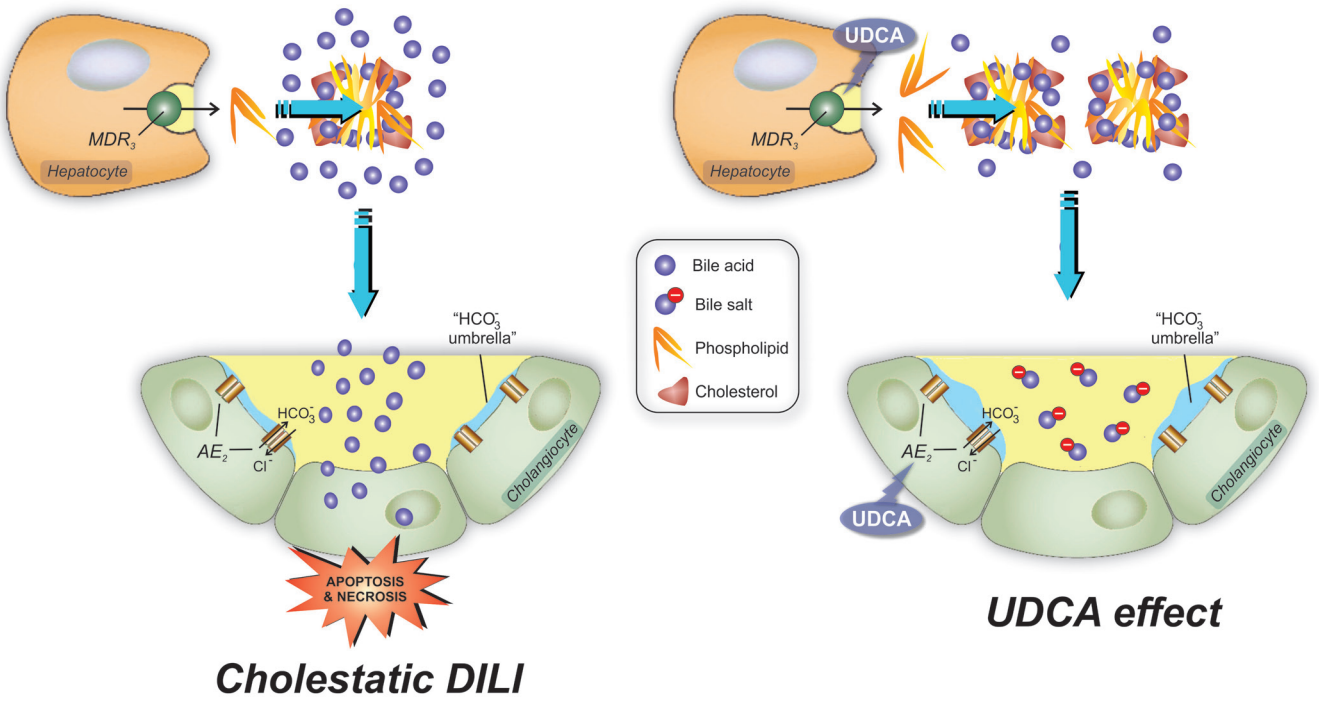


**Fig. 2. The mechanisms of protection of biliary cells against bile acid-induced damage are often impaired in "cholestatic" DILI.** Phospholipid excretion by MDR3 is hindered by several drugs or the cholestatic process itself. This limits the formation of mixed micelles with bile acids and cholesterol, resulting in an increased concentration of highly cytotoxic monomeric bile acids in bile. Additionally, the cholangiocellular $Cl^-/HCO_3^-$- antiporter, AE2, may also be impaired, leading to a dissipation of the so-called "$HCO_3^-$ umbrella". This $HCO_3^-$ layer maintains bile acids in their anionic, non-diffusible forms (bile salts), thus preventing them from damaging cholangiocytes. UDCA stimulates MDR3-mediated phospholipid excretion and AE2-mediated $HCO_3^-$ ductular excretion, thus mitigating the effect of cytotoxic bile acids on cholangiocytes. UDCA, ursodeoxycholic acid; DILI, drug-induced liver injury; AE2, anion exchanger 2; MDR3, multidrug-resistant protein 3.

yielded 41 publications on the favorable therapeutic and prophylactic responses to UDCA in DILI, encompassing 264 patients from 34 case reports and 9 clinical series (reviewed elsewhere until mid-2022,[14] and further expanded to include data up to 2024 here[32–42]).

DILI diagnosis was conducted by the original authors based on a comprehensive range of serological analyses, autoantibody measurements, imaging studies, biopsy findings, and/or the Roussel Uclaf Causality Assessment Method (RUCAM)[43] to exclude other potential causes. In cases where RUCAM was not used as the algorithm for causality assessment, the results were considered provisionally acceptable only if alternative causes were thoroughly excluded.

Demographics, clinical, and outcome features are depicted in Table 2. Doses of UDCA were reported either as mg/kg per day or total mg per day, depending on how they were reported in the original articles.

Reported benefits of UDCA were observed across cholestatic and mixed forms of DILI in 14 reported cases, predominantly affecting males. Clinical improvement occurred mostly in patients over 50 years old, with DILI being mainly associated with amoxicillin-clavulanate, flucloxacillin, bosentan, and anabolic steroids. Common initial symptoms included jaundice, itching, and abdominal discomfort. The therapy duration ranged from 16 to 120 days, and significant clinical and laboratory improvements typically occurred within seven

**Table 1. Statements on UDCA treatment in different DILI guidelines**

| Guidelines | Comments | Reference |
|---|---|---|
| APASL: Drug-induced liver injury: Liver consensus guidelines (2021) | "Case reports and series suggested UDCA may improve cholestatic liver injuries associated with certain antimicrobials and steroid-resistant immune checkpoints inhibitors combined with corticosteroids" | 28 |
| AASLD: Practice guidance on drug, herbal, and dietary supplement–induced liver injury (2023) | "Ursodeoxycholic acid may improve symptoms of pruritus and hasten DILI recovery" | 29 |
| EASL: Clinical Practice Guidelines: Drug-induced liver injury (2019) | "Chronic cholestasis following DILI is often treated with UDCA, However, the effects of UDCA in DILI are not well documented and contradicting results have been reported" | 30 |
| ALEH: Drug-induced liver injury: A management position paper (2021) | "Anecdotal small series suggests that UDCA treatment may be beneficial in some forms of drug-induced cholestasis" | 31 |

APSL, Asia Pacific Association for the Study of the Liver; AASLD, American Association for the Study of the Liver; EASL, European Association for the Study of the Liver; ALEH, Latin-American Association for the Study of the Liver; UDCA, ursodeoxycholic acid; DILI, drug-induced liver injury.

**Table 2. Summary of the clinical studies (1995–2024) showing beneficial effects of UDCA in DILI**

| Variable | Number of patients | % of total |
|---|---|---|
| Sex | | |
| Male | 118 | 44.5% |
| Female | 45 | 16.9% |
| NE | 101 | 38.4% |
| DILI pattern | | |
| Cholestatic | 90 | 34.1% |
| Hepatocelular | 128 | 48.5% |
| Mixed | 45 | 17.0% |
| NE | 1 | 0.4% |
| Duration of UDCA treatment | | |
| NE | 107 | 40.6% |
| <50 d | 46 | 17.4% |
| 51–100 d | 46 | 17.4% |
| >100 d | 65 | 24.6% |
| Outcome | | |
| Improvement | 232 | 87.9% |
| Resolution | 32 | 12.1% |
| Drug | | |
| Flutamide | 71 | 26.9% |
| Phenobarbital | 40 | 15.2% |
| Rifampicin, isoniazid and pyrazinamide | 27 | 10.2% |
| Vaproic acid | 22 | 8.3% |
| Glecaprevir/pibrentasvir | 21 | 8.0% |
| Methotrexate | 19 | 7.2% |
| Anabolic androgenic steroid | 18 | 6.8% |
| Tacrine | 16 | 6.1% |
| Amoxicillin/clavulanate | 6 | 2.3% |
| Flucloxacillin | 3 | 1.1% |
| Asiatic spark | 3 | 1.1% |
| Bosentan | 2 | 0.8% |
| Capmatinib | 2 | 0.8% |
| Ashwagandha root | 2 | 0.8% |
| Mesalazine | 1 | 0.4% |
| Terbinafine | 1 | 0.4% |
| Ibandronate | 1 | 0.4% |
| Methimazole | 1 | 0.4% |
| Pembrolizumab | 1 | 0.4% |
| Kratom | 1 | 0.4% |
| Nivolumab | 1 | 0.4% |
| Avacopan | 1 | 0.4% |
| L-carbocisteine | 1 | 0.4% |
| Leflunomide | 1 | 0.4% |
| Compound Congrong Yizhi | 1 | 0.4% |
| Cyproheptadine | 1 | 0.4% |
| Mean age | 42 years (range: 3 - 83) | |
| Average dose | | |
| Articles reported in mg/kg per day | 10.5 mg/kg per day | |
| Articles reported in mg per day | 520 mg per day | |
| Total of patients | 264 | |

DILI, drug-induced liver injury; NS, not specified; UDCA, ursodeoxycholic acid.

to twelve weeks of treatment initiation. UDCA doses ranged from 15 to 45 mg/kg per day, with no apparent correlation between higher UDCA doses and therapeutic efficacy. The highest dose used in the reported cases was 1,500 mg per day, with no adverse effects observed in the patients.[2]

The use of UDCA to treat hepatocellular types of DILI was reported in 12 case reports, involving predominantly women.[5] Eight out of 15 patients were over 50 years old. Asiatic spark was the more frequent culprit agent (three cases), while flutamide and ashwagandha root were the offending drugs in two cases. Terbinafine, ibandronate, amoxicillin-clavulanate, nivolumab, flucloxacillin, and antituberculous treatment with rifampicin, isoniazid, and pyrazinamide were each associated with a single case. Common signs and symptoms included right upper quadrant abdominal pain, asthenia, diarrhea, vomiting, jaundice, and itching. Histological studies in 9 patients revealed various conditions, including cholestatic hepatitis, granulomas, Stevens-Johnson syndrome, granulomatous hepatitis, bridging necrosis, vanishing bile duct syndrome, and autoimmune-like hepatitis. All patients showed complete or partial improvement in clinical and biochemical conditions between two weeks and five months after starting UDCA treatment, with doses ranging from 10 to 40 mg/kg per day.

Regarding the preventive use of UDCA, three series of patients and two case reports described beneficial effects of UDCA, including improved biochemical parameters or no increase in liver enzymes after prophylactic treatment, compared to patients receiving only the potentially toxic drug.[44,45] For instance, the protective effect of UDCA (13 mg/kg per day, 105 days) against tacrine-induced hepatotoxicity was investigated in 14 Alzheimer's patients, with their outcomes being compared to 100 patients receiving tacrine alone.[44] Normal serum ALT was recorded in 93% of patients co-treated with UDCA, compared to 69% in the control group. Furthermore, 25% of controls experienced an increase in ALT < 3 ULN, whereas no patients receiving UDCA showed a rise in transaminase levels. These findings suggest that UDCA protects against tacrine-induced moderate hepatotoxicity.

Similar prophylactic effects of UDCA were described by Kojima *et al*.,[45] who examined 181 patients with prostate cancer on flutamide therapy. Seventy of these patients received UDCA prophylactically, while the remaining 111 did not. In patients receiving UDCA, the incidence of hepatotoxicity was 11% (8/70), compared to 32% (36/111) in patients not receiving UDCA ($p < 0.05$).

In summary, the empirical use of UDCA in cholestatic DILI resulted in symptom alleviation and improvements in cholestatic biochemical parameters. Due to the lack of alternative agents to treat this clinical pattern, UDCA administration should be considered in clinical practice. Surprisingly, benefits have also been reported in hepatocellular DILI, suggesting broader hepatoprotective pathways. Due to these additional properties beyond its anticholestatic effects, UDCA may offer a unique therapeutic advantage in patients suffering from hepatocellular DILI.

However, there is not enough information to draw definitive conclusions regarding UDCA as a prophylactic agent to prevent transaminase elevations in high-risk clinical situations, such as therapy with recognized hepatotoxic medications. If confirmed, its prophylactic use might change the outlook for individuals who are potential candidates to develop severe DILI.

## New horizons to continue exploring UDCA in DILI

Although UDCA is not currently strongly recommended as a therapeutic option in DILI, most guidelines acknowledge its potential benefits, particularly in cholestatic-DILI patients (Table 1). Carefully designed randomized controlled trials are essential to properly demonstrate its effectiveness and maximize its application in clinical practice. Designing such trials is challenging due to the heterogeneity of DILI, stemming from its diverse etiologies and pathophysiological mechanisms. Utilizing biomarkers of DILI severity, such as microRNA-122, to monitor UDCA efficacy may help to objectively validate its therapeutic role and better establish its significance for both the prognosis and outcome of DILI. Similarly, optimal doses of UDCA for each DILI type and for its therapeutic and prophylactic use should be established.

## Conclusions

UDCA is a multifaceted drug with a plethora of hepatoprotective properties and a high safety profile in terms of adverse events. The lack of controlled studies and systematic RUCAM use in the reported cases should be considered major limitations of the data.[46] Therefore, caution is warranted when drawing conclusions until standardized causality assessment methods are applied, resulting in robust and consistent data. Meanwhile, circumstantial evidence suggests that UDCA may be beneficial for both cholestatic and hepatocellular DILI. It may also serve as a preventive agent for drugs or treatment regimens associated with a high hepatotoxic potential (*e.g.*, anti-tuberculosis drugs). We encourage clinicians to consider prescribing UDCA as a safe therapeutic tool for DILI patients.

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## Conflict of interest

FB has been an Editorial Board Member of the *Journal of Clinical and Translational Hepatology* since 2018. The other authors have no conflict of interests related to this publication.

## Author contributions

Conception (FB, MGR), drafting (FB, GLH, NT, DA, MGR), and revision (FB, MGR). All authors approved the final version and publication of the manuscript.

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