Hepat Mon. January-December 2025; 25(1): e165095 https://doi.org/10.5812/hepatmon-165095

Published Online: 2025 October 18 **Research Article**

Comparison of the Safety and Efficacy of Newly-Developed Generic Ursodeoxycholic Acid (Cholicray®) and Ursophar® as Standard Drug in Patients with Non-alcoholic Fatty Liver Disease: A Phase IIa Double-Blind Randomized Controlled Clinical Trial

Mohammad Heiat [1], Mohammad Mahmudian [1], Sobhan Eisazadeh [2], Ramin Radmanesh [3], Mostafa Eslamimahmoudabadi [2], Mohamad Ali Abyazi [1,*]

[1] Baqiyatallah Research Center for Gastroenterology, Clinical Research Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran
[2] Student Research Committee, Baqiyatallah University of Medical Sciences, Tehran, Iran
[3] Department of Pharmacoeconomy and Pharmaceutical Management, Faculty of Pharmacy, Tehran Medical Sciences, Islamic Azad University, Tehran, Iran

[*] ***Corresponding Author:*** Baqiyatallah Research Center for Gastroenterology, Clinical Research Institute, Baqiyatallah University of Medical Sciences, Tehran, Iran. Email: yashar862@gmail.com

Received: 4 August, 2025; **Revised:** 13 September, 2025; **Accepted:** 19 September, 2025

Abstract

Background: Ursodeoxycholic acid (UDCA) is a complementary treatment used to improve liver enzyme tests and reduce the risk of gallstone formation.

Objectives: This study aimed to compare the safety and efficacy of two UDCA formulations: Cholicray® (a newly-developed generic drug, manufactured by Reyhaneh Pharmaceutical Co.) and Ursophar® (a standard drug, manufactured by Koushan Pharmed Co.), in patients with non-alcoholic fatty liver disease (NAFLD), which is one of the most prevalent chronic liver disorders.

Methods: In this randomized, double-blind, phase IIa clinical trial, a total of 73 patients with ultrasound-confirmed grade II NAFLD who presented to Baqiyatallah Clinic were enrolled after obtaining informed consent. Patients were randomly allocated in blocks to receive either Cholicray® or Ursophar®. By the end of the study, 55 patients (28 in the Cholicray® group and 27 in the Ursophar® group) completed the full 3-month treatment course and were included in the final analysis. Changes in liver enzymes, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), as well as any adverse events (dermatological, gastrointestinal, ocular, renal, pulmonary, neurological systems), were recorded and compared before and after treatment.

Results: The findings indicated that both Cholicray® and Ursophar® reduced the levels of liver enzyme markers. The reduction in ALT levels was statistically significant in both groups (P = 0.001 and P = 0.004 for Ursophar® and Cholicray®, respectively). Additionally, there were no statistically significant differences in mean changes and adverse effects reported before and after treatment between the groups.

Conclusions: The results of this study demonstrated that Cholicray®, similar to the standard treatment Ursophar®, has beneficial effects on liver enzyme biomarkers (LEBs) and does not induce significant adverse effects. However, our results are preliminary and require validation through larger, more comprehensive studies.

Keywords: UDCA, Non-alcoholic Fatty Liver Disease (NAFLD), Ursodeoxycholic Acid, Cholicray®, Ursophar®, Clinical Trial

1. Background

Chronic liver diseases, particularly non-alcoholic fatty liver disease (NAFLD), have emerged as a major public health challenge worldwide over the recent decade. Epidemiological studies have estimated a significant increase in the global prevalence of NAFLD among the adult population, from 25.26% in 1990 - 2006 to 38.00% in 2016 - 2019 (1). In Iran, research suggests that approximately 30 - 40% of adults may have some degree of NAFLD (2), often associated with increasing age, obesity, type 2 diabetes, and metabolic syndrome.

The pathophysiology of NAFLD is complex and multifactorial. Key mechanisms include insulin resistance, increased peripheral lipolysis, oxidative stress, chronic inflammation, mitochondrial

How to Cite: Heiat M, Mahmudian M, Eisazadeh S, Radmanesh R, Eslamimahmoudabadi M, et al. Comparison of the Safety and Efficacy of Newly-Developed Generic Ursodeoxycholic Acid (Cholicray®) and Ursophar® as Standard Drug in Patients with Non-alcoholic Fatty Liver Disease: A Phase IIa Double-Blind Randomized Controlled Clinical Trial. Hepat Mon. 2025; 25 (1): e165095. https://doi.org/10.5812/hepatmon-165095.

dysfunction, and hepatotoxicity induced by bile acids (3-8). The accumulation of hydrophobic bile acids, such as deoxycholic and lithocholic acid, within liver tissue is considered a major contributor to hepatocellular injury and chronic inflammation in these patients (9).

Among therapeutic options, ursodeoxycholic acid (UDCA), a hydrophilic bile acid, exerts hepatoprotective effects through various mechanisms. These include shifting the bile acid composition toward less toxic forms (10), reducing cholesterol absorption (11, 12), stabilizing hepatocyte membranes (13), inhibiting apoptosis (14), and modulating inflammatory signaling pathways such as NF-κB (15). Additionally, UDCA enhances bile flow and has an established role in treating cholestatic liver diseases such as primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) (16).

Numerous pieces of evidence have demonstrated the efficacy of UDCA in improving liver biochemical markers [e.g., alanine aminotransferase (ALT), aspartate aminotransferase (AST), GGT, alkaline phosphatase (ALP)], reducing fibrosis, and increasing transplant-free survival in patients with PBC and NAFLD. Studies have shown that using this drug significantly reduces liver enzymes and improves liver enzyme markers in patients with NAFLD. Clinical studies indicate that daily UDCA administration, alongside lifestyle modification, leads to significant reductions in the Fatty Liver Index (FLI), triglyceride levels, LDL cholesterol, and histological liver abnormalities (17-20).

In Iran, Ursophar® (produced by Koushan Pharmed) has long served as the reference brand for UDCA. However, the recent introduction of Cholicray® (manufactured by Reyhaneh Pharmaceutical Company) as a generic formulation necessitates rigorous evaluation of its efficacy, safety, and tolerability in comparison with the standard. The use of domestically produced generics may help reduce treatment costs for both patients and the healthcare system.

2. Objectives

This study was designed as a proof-of-concept, randomized, double-blind, controlled clinical, phase IIa trial to compare the safety and efficacy of Cholicray® versus Ursophar® in patients with grade II NAFLD. This study aimed to determine whether the new formulation provides comparable therapeutic benefits and safety profiles, thereby offering clinically relevant data to inform treatment decisions.

3. Methods

3.1. Study Design and Targeted Endpoints

This study was conducted as a proof-of-concept phase IIa, randomized, double-blind clinical trial, designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 guideline (21). This setting was chosen to assess the relative efficacy and safety of a newly developed generic medicine compared to an established standard treatment. The primary endpoint of this study was the change in serum ALT level from baseline to the end of treatment. Secondary endpoints included changes in other hepatic biochemical markers (AST and ALP) and the incidence of adverse events as indicators of safety.

3.2. Inclusion and Exclusion Criteria

Participants were eligible for enrollment if they were over 18 years old, provided informed consent, and had ultrasound-confirmed grade II NAFLD at Baqiyatallah Clinic. Since the ultrasonographic assessment of liver steatosis is inherently approximate and relies on the comparative echogenicity of tissues, to ensure a homogeneous patient randomized control trial (RCT) with reliable grading, we selected the intermediate grade II, which represents a moderate level of steatosis that is less prone to inter-observer variability. Exclusion criteria included the inability to complete follow-up, withdrawal of consent, irregular medication use, the onset or worsening of acute symptoms, or the treating physician's decision to discontinue the medication due to clinical concerns.

3.3. Study Population, Randomization, Blinding, and Concealment

In this double-blind phase IIa trial, the sample size was determined based on the study design and primary evaluation objectives. According to standard guidelines indicating that phase II trials typically enroll between 50 to 100 participants in total (22-25), we initially planned for 62 patients (31 per group). However,

accounting for potential attrition (dropout rate) and adding an additional 15 - 20% to ensure adequate power, we screened 82 participants to meet the study's recruitment targets. This approach ensured sufficient data collection for preliminary assessments of safety and early efficacy signals, consistent with similar phase IIa trials. Upon enrollment, 73 eligible patients with ultrasound-confirmed grade II NAFLD were randomized into two intervention groups using a block randomization method, following written informed consent. The study was double-blind, with both participants and researchers blinded to treatment allocation. Medications were packaged in random numeric identical coded containers to ensure concealment.

3.4. Intervention and Assessments

Participants were randomized into two treatment groups. The first group received Cholicray® as the newly-developed generic drug, at a dose of 13 - 15 mg/kg/day for 3 months, while the second group received Ursophar® as the standard drug, at an equivalent dose of 13 - 15 mg/kg/day for the same duration. Liver enzyme tests, including ALP, ALT, and AST, were evaluated before and after treatment. Additionally, the occurrence of adverse events across various organ systems (dermatological, gastrointestinal, ocular, renal, pulmonary, neurological systems) was monitored and recorded.

3.5. Statistical Analysis

Data analysis was conducted on a per-protocol basis. Data from the 55 patients who completed the study were entered into SPSS software (version 23). Descriptive statistics (means ± SD and frequencies) and analytical comparisons of drug effects as well as side effects were reported. Categorical variables were analyzed using McNemar's test or Fisher's exact test, while continuous variables were assessed by calculating the mean changes before and after the intervention within each group. After evaluating the normality of data distribution, the proper statistical approaches were utilized to analyze variables. A P-value < 0.05 was considered as the threshold to determine statistical significance.

3.6. Ethical Considerations and Registration

The study protocol was designed and implemented in accordance with the SPIRIT 2025 guideline. Ethical approval was obtained from the National Committee for Ethics in Biomedical Research (ethics code: IR.BMSU.BAQ.REC.1401.127). The trial was also registered in the Iranian Registry of Clinical Trials (IRCT) under the registration code IRCT20210914052480N3.

3.7. Participant Insurance and Transparency Measures

The study was covered under civil liability insurance, ensuring that all participants, regardless of group allocation, were insured. Participants were also provided with detailed information about their rights and the nature of their involvement in clinical research. Methodological details, including block randomization procedures, blinding protocol, detailed inclusion and exclusion criteria, adverse event monitoring, and data documentation protocols, were outlined in the study protocol. To ensure transparency and scientific reproducibility, all stages, from study design to statistical analysis, were conducted in accordance with a predefined statistical analysis plan (SAP) and documented in the trial master file (TMF).

4. Results

4.1. Demographic Characteristics, Baseline Comorbidities, and Study Flow Diagram

In this phase IIa clinical trial conducted on 73 patients with non-alcoholic and cholestatic fatty liver disease, the efficacy and potential side effects of Cholicray® were evaluated in comparison to Ursophar®. Of the total participants, 18 individuals discontinued the study due to reasons such as exacerbation of side effects or unwillingness to continue. The remaining 55 patients (31 males and 24 females) continued the trial, with 27 patients receiving Cholicray® and 28 patients receiving Ursophar®. Demographic characteristics and baseline comorbidities of participants have been summarized in Table 1. Additionally, Figure 1 illustrates the flow diagram of the overall study design.

4.2. Baseline in Completers and Non-completers

In the evaluation of biochemical parameters, baseline levels of liver enzyme biomarkers (LEBs), including AST, ALT, and ALP, were compared between the

Table 1. Demographic Characteristics and Baseline Comorbidities of Completer Participants [a]

Variables	Groups		P-Value
	Ursophar®	Cholicray®	
Gender			0.816
Male	16 (57.14)	15 (55.55)	
Female	12 (42.85)	12 (44.44)	
Ulcerative colitis	2 (7.14)	0	0.491
Hypertension	4 (14.28)	7 (25.92)	0.329
Gallstones	5 (17.85)	4 (14.81)	1.000
Cardiovascular disease	1 (3.57)	1 (3.7)	1.000
Hypercholesterolemia	1 (3.57)	3 (11.11)	0.352
IBD	0	1 (3.7)	0.491
Anemia	2 (7.14)	0	0.491
LFTs	2 (7.14)	2 (7.40)	1.000
Polyp	1 (3.57)	1 (3.7)	1.000
Diabetes mellitus	3 (10.74)	5 (18.51)	0.469
Asthma	0	2 (7.40)	0.236
Allergy	1 (3.57)	2 (7.40)	0.611
Hepatitis	1 (3.57)	0	1.000
Migraine	0	1 (3.7)	0.491
Depression	0	1 (3.7)	0.491
Liver cirrhosis	0	2 (7.40)	0.236
Hypothyroidism	1 (3.57)	0	1.000
Sinusitis	1 (3.57)	0	1.000
Osteoarthritis	0	1 (3.7)	0.491

Abbreviations: IBD, inflammatory bowel disease; LFTs, abnormal liver function tests.
[a] Values are expressed as No. (%).

Cholicray® and Ursophar® groups (completers plus non-completers). Statistical analysis revealed no significant differences in the baseline values of these markers between the two groups ($P > 0.05$). Therefore, the initial biochemical status of patients with respect to these enzymes was comparable in both groups (Table 2).

A comparative analysis of the available baseline LEBs (ALT, AST, and ALP) was conducted between the 7 non-completer and the 55 completer participants. Statistical analysis revealed no significant differences in these baseline characteristics between the two groups (Table 3).

4.3. Liver Enzyme Biomarkers

The impact of Ursophar® and Cholicray® on LEBs in the study participants demonstrated that both medications led to reductions in key liver enzymes such as AST, ALT, and ALP in both groups. However, the comparison of pre- and post-treatment values revealed that Ursophar® and Cholicray® caused a statistically significant reduction in ALT levels ($P = 0.001$ and $P = 0.004$ for them, respectively). However, no significant change was observed between the two study groups (Table 4).

4.4. Comparison of Potential Adverse Effects Before and After Drug Administration in Study Participants

In accordance with the predefined objectives of this study, the safety profile of the generic formulation Cholicray® was systematically evaluated in comparison with the reference drug Ursophar®, both prior to and following administration. Adverse events were assessed across key physiological systems, including dermatological, gastrointestinal, visual, renal, and neurological domains, each of which was independently monitored throughout the study period. Comparative analysis of the incidence of adverse effects between the two treatment groups revealed no

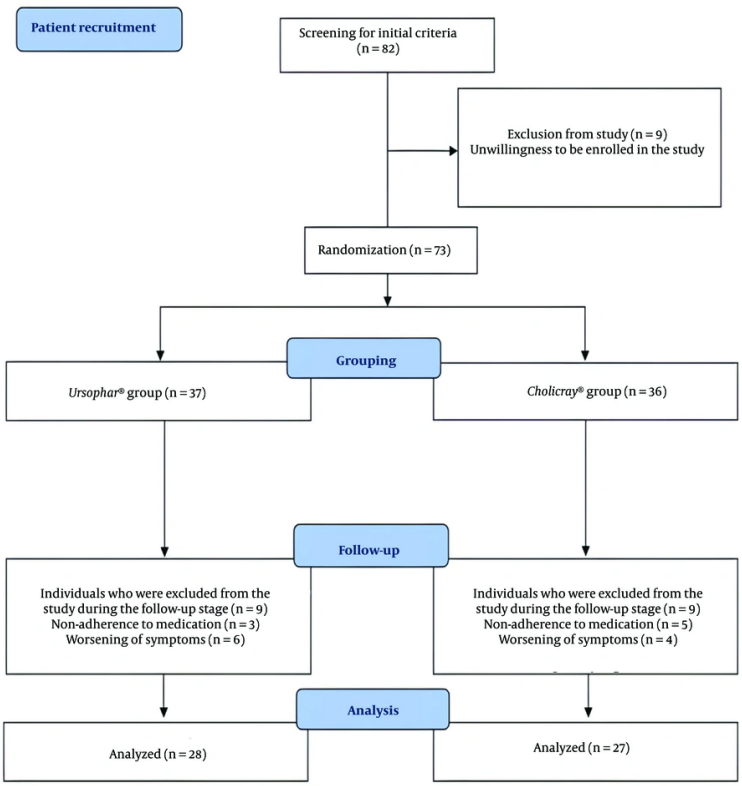

Figure 1. The flow diagram of overall study design

Table 2. Comparison of Baseline Levels of Liver Enzymes Between the Cholicray® and Ursophar® Groups (Completers Plus Non-completers)

LEB; Groups	(Completers N), (Non-completers N)	Mean ± SD	P-Value
Before-AST (IU/L)			0.908
Ursophar® (n = 31)	(28), (3)	38.01 ± 20.107	
Cholicray® (n = 31)	(27), (4)	38.60 ± 19.778	
Before-ALT (IU/L)			0.729
Ursophar® (n = 31)	(28), (3)	43.02 ± 21.020	
Cholicray® (n = 31)	(27), (4)	45.06 ± 25.088	
Before-ALP (IU/L)			0.065
Ursophar® (n = 31)	(28), (3)	211.13 ± 76.925	
Cholicray® (n = 31)	(27), (4)	178.81 ± 56.863	

Abbreviations: LEB, liver enzyme biomarkers; Before-AST, aspartate aminotransferase before intervention; Before-ALT, alanine aminotransferase before intervention; Before-ALP, alkaline phosphatase before intervention.

statistically significant differences in any of the evaluated systems. The most frequently reported events were mild. Importantly, all adverse events were self-limiting and comparable between groups. These findings are detailed in Tables 5 through 10.

5. Discussion

Table 3. A Comparative Analysis of the Available Baseline Liver Enzyme Biomarkers Between Non-completer and the Completer Participants

LEB; Study Groups; Completers (C) vs. Not-Completers (NC)	No.	Mean ± SD	P-Value
Before-AST (IU/L)			0.661
C	55	37.91 ± 20.876	
NC	7	41.43 ± 6.554	
Before-ALT (IU/L)			0.963
C	55	43.99 ± 24.282	
NC	7	44.43 ± 7.764	
Before-ALP (IU/L)			0.328
C	55	198.06 ± 71.738	
NC	7	170.71 ± 36.909	

Abbreviations: LEB, liver enzyme biomarkers; Before-AST, aspartate aminotransferase before intervention; Before-ALT, alanine aminotransferase before intervention; Before-ALP, alkaline phosphatase before intervention.

Table 4. The Impact of Ursophar® and Cholicray® on Liver Enzyme Biomarkers

LEB; Groups	Mean ± SD		P-Value	Mean Change ± SD	P-Value	Mean Difference (CI 95%)
	Before Intervention	After Intervention				
AST (IU/L)					0.764	0.993 (-6.89, 8.88)
Ursophar® (n = 28)	37.51 ± 21.004	33.43 ± 21.137	0.136	-4.082 ± 14.166		
Cholicray® (n = 27)	38.31 ± 21.135	35.23 ± 22.833	0.258	-3.089 ± 15.005		
ALT (IU/L)					0.970	-1.326 (-12.86, 10.20)
Ursophar® (n = 28)	42.95 ± 22.038	29.25 ± 20.132	0.001	-13.696 ± 17.045		
Cholicray® (n = 27)	45.07 ± 26.793	30.05 ± 20.008	0.004	-15.022 ± 24.998		
ALP (IU/L)					0.793	6.67 (-14.26, 27.60)
Ursophar® (n =28)	212.50 ± 80.877	197.43 ± 61.005	0.070	-15.076 ± 41.195		
Cholicray® (n = 27)	183.07 ± 58.635	174.67 ± 52.626	0.055	-8.407 ± 35.920		

Abbreviations: LEB, liver enzyme biomarkers; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

The present study demonstrates that Cholicray®, a locally manufactured generic formulation of UDCA, exhibits comparable safety and efficacy to the reference drug Ursophar® in patients with NAFLD. The decision to target patients with grade II NAFLD, rather than those with cholestatic liver diseases such as PBC or PSC, was based on scientific, methodological, and ethical considerations.

First, NAFLD has a significantly higher prevalence in the general population, both globally and in Iran, facilitating access to an adequate sample size and allowing for sufficient statistical power within a practical timeframe. In contrast, PBC and PSC are considered rare diseases, and conducting a large-scale clinical trial in these populations would require extended durations and specialized referral centers. Second, the efficacy of UDCA in treating PBC has already been well-established through multiple international trials and is recognized in clinical practice guidelines. In contrast, evidence supporting the use of UDCA in NAFLD and related metabolic liver disorders remains limited and heterogeneous, necessitating locally conducted, well-designed studies. From this standpoint, evaluating Cholicray® in an NAFLD population provides greater scientific value than replicating existing cholestatic studies.

Furthermore, assessing the safety profile of UDCA-based therapies in patients without advanced cholestatic pathology allows for a more accurate detection of subclinical or mild adverse effects. Some adverse effects, like itching, diarrhea, and visual disturbances, are known potential side effects of UDCA-based therapies, and their documentation helps

Table 5. Dermatological Adverse Effects Before and After Intervention

Variables	After Use		Total	P
	No	Yes		
Ursophar® (n = 28)				
Pruritus				0.289
Before use				
No	20	2	22	
Yes	6	0	6	
Xerosis				NC
Before use				
No	25	0	25	
Yes	3	0	3	
Urticaria				0.625
Before use				
No	24	3	27	
Yes	1	0	1	
Jaundice				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Rash and acne				NC
Before use				
No	27	0	27	
Yes	1	0	1	
Desquamation				NC
Before use				
No	27	0	27	
Yes	1	0	1	
Cholicray® (n = 27)				
Pruritus				0.625
Before use				
No	19	1	20	
Yes	3	4	7	
Xerosis				1
Before use				
No	25	1	26	
Yes	0	1	1	
Urticaria				1
Before use				
No	22	1	23	
Yes	2	2	4	
Jaundice				NC
Before use				
No	26	0	26	
Yes	1	0	1	
Rash and acne				0.625
Before use				
No	23	1	24	
Yes	3	0	3	
Desquamation				NC
Before use				
No	27	0	27	
Yes	0	0	0	

Abbreviation: NC, not calculated due to insufficient events.

physicians weigh benefits against risks, monitor patients appropriately, and manage symptoms.

However, our findings align with those of Nakano et al. (26), who reported no statistically significant differences in biochemical response between branded and generic UDCA formulations. Similarly, the safety profile of Cholicray® observed in our trial corresponds well with the Nakano et al. study. This study provides direct evidence of comparable safety between generic/formulated UDCA and standard branded UDCA in a controlled clinical setting (26).

Our results are also consistent with broader clinical evidence regarding UDCA's role in NAFLD. For instance, a meta-analysis of nine randomized controlled trials (up to September 2019, n = 1106 patients) found that UDCA significantly reduced ALT levels (P = 0.07), though changes in AST, GGT, and other biochemical markers were not statistically significant. Notably, patients over 50 years old, of European ancestry, or those undergoing therapy for more than six months experienced more pronounced benefits (18). Among the enzymes secreted by the liver, ALT has the highest specificity for hepatocellular injury, surpassing the other enzymes. The lack of changes in AST and ALP may reflect their lower sensitivity in such settings. In NAFLD, hepatocytes are primarily affected, making ALT a valuable marker for assessing liver status.

Table 6. Gastrointestinal Adverse Effects Before and After Intervention

Variables	After Use		Total	P
	No	Yes		
Ursophar® (n = 28)				
Gastroesophageal reflux				1
Before use				
No	25	0	25	
Yes	0	3	3	
Diarrhea				NC
Before use				
No	26	0	26	
Yes	2	0	2	
Constipation				1
Before use				
No	25	1	26	
Yes	2	0	2	
Abdominalgia				NC
Before use				
No	25	0	25	
Yes	3	0	0	
Bloating				0.125
Before use				
No	23	0	23	
Yes	4	1	5	
Nausea				1
Before use				
No	26	1	27	
Yes	1	0	1	
Dyspepsia				NC
Before use				
No	26	0	26	
Yes	0	0	0	
Cholicray® (n = 27)				
Gastroesophageal reflux				1
Before use				
No	24	1	25	
Yes	2	0	2	
Diarrhea				1
Before use				
No	25	1	26	
Yes	0	1	1	
Constipation				0.625
Before use				
No	22	1	23	
Yes	3	1	4	
Abdominalgia				NC
Before use				
No	25	0	25	
Yes	2	0	2	
Bloating				0.375
Before use				
No	21	1	22	
Yes	4	1	5	
Nausea				NC
Before use				
No	26	0	26	
Yes	1	0	0	
Dyspepsia				1
Before use				
No	24	1	25	
Yes	1	0	1	

Abbreviation: NC, not calculated due to insufficient events.

The observed reduction, though modest, is clinically relevant in the context of a proof-of-concept phase IIa trial, indicating potential efficacy. The modest ALT reduction might indeed stem from the short three-month treatment duration, which may not suffice for more pronounced effects; an insufficient dose relative to disease severity; or the limited sample size, which reduces power to detect smaller changes.

An open-label, multicenter international trial with 174 NAFLD patients, receiving 15 mg/kg/day of UDCA in combination with lifestyle modification, demonstrated significant reductions in liver enzymes, FLI, triglycerides, and LDL cholesterol after 6 months, although no improvement was observed in fibrosis scores (17). A recent study on the efficacy of UDCA in NAFLD followed patients for 3 months and measured outcomes based on clinical findings and serum ALT levels, demonstrating significant reductions in liver enzymes (27). A reduction in liver enzyme levels within three months, as seen in the present study, suggests that

Table 7. Visual Adverse Effects Before and After the Intervention

Variables	After Use		Total	P
	No	Yes		
Ursophar® (n = 28)				
Blurred vision				0.125
Before use				
No	23	0	23	
Yes	4	1	5	
Diplopia				NC
Before use				
No	27	0	27	
Yes	1	0	1	
Presbyopia				NC
Before use				
No	26	0	26	
Yes	2	0	2	
Ocular pruritus				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Redness				NC
Before use				
No	27	0	27	
Yes	1	0	1	
Cataract				NC
Before use				
No	27	0	27	
Yes	1	0	1	
Ophthalmalgia				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Xerophthalmia				
Before use				NC
No	28	0	28	
Yes	0	0	0	
Cholicray® (n = 27)				
Blurred vision				1
Before use				
No	23	1	24	
Yes	1	2	3	
Diplopia				1
Before use				
No	26	0	26	
Yes	0	1	1	
Presbyopia				NC
Before use				
No	27	0	27	
Yes	0	0	0	
Ocular pruritus				NC
Before use				
No	25	0	25	
Yes	2	0	2	
Redness				NC
Before use				
No	26	0	26	
Yes	1	0	1	
Cataract				NC
Before use				
No	26	0	26	
Yes	1	0	1	
Ophthalmalgia				1
Before use				
No	25	0	25	
Yes	1	1	2	
Xerophthalmia				1
Before use				
No	25	0	25	
Yes	1	1	2	

Abbreviation: NC, not calculated due to insufficient events.

the treatment is likely effective and impactful. However, from a clinical perspective, more invasive assessments like biopsy would provide stronger evidence of improvement, but as these were not feasible in the present and many other studies, the observed drop in hepatic enzymes serves as a practical proxy for treatment efficacy.

A 2018 systematic review of 1548 RCTs noted that approximately 85% of studies documented biochemical and histological improvements in the liver, while 15%

Table 8. Renal Adverse Effects Before and After Intervention

Variables	After Use		Total	P
	No	Yes		
Ursophar® (n = 28)				
Renal colic				NC
Before use				
No	26	0	26	
Yes	2	0	2	
Polyuria				0.625
Before use				
No	24	1	25	
Yes	3	0	3	
Nephrolithiasis				NC
Before use				
No	26	0	26	
Yes	2	0	2	
Urine discoloration				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Creatinine excretion				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Dysuria				1
Before use				
No	27	0	27	
Yes	0	1	1	
Cholicray® (n = 27)				
Renal colic				NC
Before use				
No	23	0	23	
Yes	4	0	4	
Polyuria				NC
Before use				
No	23	0	23	
Yes	4	0	4	
Nephrolithiasis				NC
Before use				
No	26	0	26	
Yes	1	0	1	
Urine discoloration				NC
Before use				
No	25	2	27	
Yes	0	0	0	
Creatinine excretion				NC
Before use				
No	26	1	27	
Yes	0	0	0	
Dysuria				NC
Before use				
No	26	0	26	
Yes	1	0	1	

Abbreviation: NC, not calculated due to insufficient events.

showed no benefit. The authors highlighted the farnesoid X receptor (FXR) pathway as a potential mechanistic target of UDCA action in these outcomes (19). Another systematic review noted that UDCA monotherapy improved liver enzymes in multiple studies with follow-up periods as short as 3 - 6 months (ALT: $P \leq 0.0001$, AST: $P = 0.0009$) (28).

In our study, both medications, Ursophar® and Cholicray®, demonstrated comparable effects in improving LEBs in patients with NAFLD. The reduction in liver enzymes without significant adverse events observed in both groups indicates that these two drugs exhibit efficacy in enhancing hepatic status. Although this phase IIa trial, due to its limited sample size, lacks the statistical power to draw definitive conclusions on efficacy, the results showed that the reduction in ALT levels was statistically significant in both groups. On the other hand, no statistically significant differences were observed in the mean changes before and after the intervention between the study groups.

Despite the relatively high attrition rate in the present study, the comparative analyses between completers and the subset of non-completers with available data revealed no significant differences in their baseline characteristics. This reduces concerns about the potential risk of bias related to attrition and strengthens the validity of the final findings. However,

Table 9. Pulmonary Adverse Effects Before and After Intervention

Variables	After Use		Total	P
	No	Yes		
Ursophar® (n = 28)				
Sputum				1
Before use				
No	25	2	27	
Yes	1	0	1	
Dyspnea				1
Before use				
No	25	2	27	
Yes	1	0	1	
Cough				1
Before use				
No	26	0	26	
Yes	0	2	2	
Rhinorrhea				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Chest pain				NC
Before use				
No	27	0	27	
Yes	1	0	1	
Seasonal allergy				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Wheezing				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Cholicray® (n = 27)				
Sputum				1
Before use				
No	23	1	24	
Yes	2	1	3	
Dyspnea				NC
Before use				
No	24	0	24	
Yes	3	0	3	
Cough				1
Before use				
No	25	0	25	
Yes	0	2	2	
Rhinorrhea				NC
Before use				
No	26	0	26	
Yes	1	0	1	
Chest pain				NC
Before use				
No	27	0	27	
Yes	0	0	0	
Seasonal allergy				NC
Before use				
No	26	0	26	
Yes	1	0	1	
Wheezing				NC
Before use				
No	27	0	27	
Yes	0	0	0	

Abbreviation: NC, not calculated due to insufficient events.

the results revealed the potential of generic medications as safe and cost-effective alternatives to branded drugs.

As a generic formulation, Cholicray® may enhance access to effective treatment options for NAFLD and reduce the economic burden on healthcare systems.

5.1. Conclusions

Cholicray® demonstrated a comparable generic formulation to Ursophar® in improving hepatic biochemical markers in NAFLD patients, with a similar safety profile. These findings suggest that this generic version can be considered a clinically equivalent alternative in controlled treatment settings for NAFLD.

While Cholicray® demonstrated comparable safety and efficacy to Ursophar® in improving hepatic biomarkers, the study has several limitations, including a relatively short duration (3 months), lack of histological endpoints, and a modest sample size. Therefore, the

findings should be considered preliminary and require confirmation in larger and longer-term studies with histological or imaging-based assessments.

Acknowledgements

The authors would like to thank the Clinical Research Development Unit of Baqiyatallah Hospital, Tehran, Iran, for their guidance and support.

Footnotes

Authors' Contribution: M. A. A., M. H., and R. R. conceptualized and designed the study, including the clinical trial protocol M. M., S. E., and M. E. contributed to patient recruitment, data collection, and monitoring of clinical trial participants at Baqiyatallah Clinic. M. H., S. E., M. M., M. E., R. R., and M. A. A. drafted the initial manuscript, including the introduction, methods, results, and discussion sections. M. H., M. M., S. E., R. R., M. E., and M. A. A. critically revised the manuscript for scientific accuracy, clarity, and intellectual content. M. H. performed the statistical analysis and interpretation of the study data. M. A. A. supervised the overall study, ensuring adherence to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2025 guideline. All authors reviewed and approved the final version of the manuscript.

Clinical Trial Registration Code: IRCT20210914052480N3 .

Conflict of Interests Statement: The fourth author, R.R., had been an employee of Reyhaneh Pharmaceutical Company and contributed to the study's conceptualization and initial design. However, he was not involved in the data collection, analysis, or interpretation of the results to minimize potential bias. All other authors declare no financial or non-financial conflicts of interest related to this work.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication. The data are not publicly available due to ethical restrictions and patient confidentiality requirements, as the study involves clinical trial data from human participants.

Ethical Approval: This study is approved under the ethical approval code of IR.BMSU.BAQ.REC.1401.127 .

Funding/Support: Grant number is 2206.

Informed Consent: Written informed consent was obtained from the participants.

References

1. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. *Hepatology*. 2023;**77**(4):1335-47. [PubMed ID: 36626630]. [PubMed Central ID: PMC10026948]. https://doi.org/10.1097/HEP.0000000000000004.
2. Moghaddasifar I, Lankarani KB, Moosazadeh M, Afshari M, Ghaemi A, Aliramezany M, et al. Prevalence of Non-alcoholic Fatty Liver Disease and Its Related Factors in Iran. *Int J Organ Transplant Med*. 2016;**7**(3):149-60. [PubMed ID: 27721961]. [PubMed Central ID: PMC5054138].
3. Di Ciaula A, Passarella S, Shanmugam H, Noviello M, Bonfrate L, Wang DQ, et al. Nonalcoholic Fatty Liver Disease (NAFLD). Mitochondria as Players and Targets of Therapies? *Int J Mol Sci*. 2021;**22**(10). [PubMed ID: 34065331]. [PubMed Central ID: PMC8160908]. https://doi.org/10.3390/ijms22105375.
4. Song C, Long X, He J, Huang Y. Recent evaluation about inflammatory mechanisms in nonalcoholic fatty liver disease. *Front Pharmacol*. 2023;**14**:1081334. [PubMed ID: 37007030]. [PubMed Central ID: PMC10061077]. https://doi.org/10.3389/fphar.2023.1081334.
5. Prasun P, Ginevic I, Oishi K. Mitochondrial dysfunction in nonalcoholic fatty liver disease and alcohol related liver disease. *Transl Gastroenterol Hepatol*. 2021;**6**:4. [PubMed ID: 33437892]. [PubMed Central ID: PMC7792990]. https://doi.org/10.21037/tgh-20-125.
6. Ramanathan R, Ali AH, Ibdah JA. Mitochondrial Dysfunction Plays Central Role in Nonalcoholic Fatty Liver Disease. *Int J Mol Sci*. 2022;**23**(13). [PubMed ID: 35806284]. [PubMed Central ID: PMC9267060]. https://doi.org/10.3390/ijms23137280.
7. Cruz-Ramon V, Chinchilla-Lopez P, Ramirez-Perez O, Mendez-Sanchez N. Bile Acids in Nonalcoholic Fatty Liver Disease: New Concepts and therapeutic advances. *Ann Hepatol*. 2017;**16**(Suppl. 1: s3-105):s58-67. [PubMed ID: 29080343]. https://doi.org/10.5604/01.3001.0010.5498.
8. Bugianesi E, Moscatiello S, Ciaravella MF, Marchesini G. Insulin resistance in nonalcoholic fatty liver disease. *Curr Pharm Des*. 2010;**16**(17):1941-51. [PubMed ID: 20370677]. https://doi.org/10.2174/138161210791208875.
9. Xue R, Su L, Lai S, Wang Y, Zhao D, Fan J, et al. Bile Acid Receptors and the Gut-Liver Axis in Nonalcoholic Fatty Liver Disease. *Cells*. 2021;**10**(11). [PubMed ID: 34831031]. [PubMed Central ID: PMC8616422]. https://doi.org/10.3390/cells10112806.
10. Bessone F, Hillotte GL, Tamagnone N, Arnedillo D, Roma MG. Ursodeoxycholic Acid for the Management of Drug-induced Liver Injury: Role of Hepatoprotective and Anti-cholestatic Mechanisms. *J Clin Transl Hepatol*. 2025;**13**(2):162-8. [PubMed ID: 39917470]. [PubMed Central ID: PMC11797819]. https://doi.org/10.14218/JCTH.2024.00325.

11. Guarino MP, Cocca S, Altomare A, Emerenziani S, Cicala M. Ursodeoxycholic acid therapy in gallbladder disease, a story not yet completed. *World J Gastroenterol*. 2013;**19**(31):5029-34. [PubMed ID: 23964136]. [PubMed Central ID: PMC3746374]. https://doi.org/10.3748/wjg.v19.i31.5029.
12. Roma MG, Toledo FD, Boaglio AC, Basiglio CL, Crocenzi FA, Sanchez Pozzi EJ. Ursodeoxycholic acid in cholestasis: linking action mechanisms to therapeutic applications. *Clin Sci (Lond)*. 2011;**121**(12):523-44. [PubMed ID: 21854363]. https://doi.org/10.1042/CS20110184.
13. Trauner M, Graziadei IW. Review article: mechanisms of action and therapeutic applications of ursodeoxycholic acid in chronic liver diseases. *Aliment Pharmacol Ther*. 1999;**13**(8):979-96. [PubMed ID: 10468672]. https://doi.org/10.1046/j.1365-2036.1999.00596.x.
14. Amaral JD, Viana RJ, Ramalho RM, Steer CJ, Rodrigues CM. Bile acids: regulation of apoptosis by ursodeoxycholic acid. *J Lipid Res*. 2009;**50**(9):1721-34. [PubMed ID: 19417220]. [PubMed Central ID: PMC2724780]. https://doi.org/10.1194/jlr.R900011-JLR200.
15. Peng CY, Liao YC, Yang YC, Hung YW, Huang LR, Peng YC. Ursodeoxycholic Acid Modulates the Interaction of miR-21 and Farnesoid X Receptor and NF-kappaB Signaling. *Biomedicines*. 2024;**12**(6). [PubMed ID: 38927442]. [PubMed Central ID: PMC11200433]. https://doi.org/10.3390/biomedicines12061236.
16. Floreani A, Gabbia D, De Martin S. Update on the Pharmacological Treatment of Primary Biliary Cholangitis. *Biomedicines*. 2022;**10**(8). [PubMed ID: 36009580]. [PubMed Central ID: PMC9405864]. https://doi.org/10.3390/biomedicines10082033.
17. Nadinskaia M, Maevskaya M, Ivashkin V, Kodzoeva K, Pirogova I, Chesnokov E, et al. Ursodeoxycholic acid as a means of preventing atherosclerosis, steatosis and liver fibrosis in patients with nonalcoholic fatty liver disease. *World J Gastroenterol*. 2021;**27**(10):959-75. [PubMed ID: 33776366]. [PubMed Central ID: PMC7968130]. https://doi.org/10.3748/wjg.v27.i10.959.
18. Zhang W, Tang Y, Huang J, Ren H, Yang Y, Yang Q, et al. Efficacy of Ursodeoxycholic Acid in Nonalcoholic Fatty Liver Disease: An Updated Meta-Analysis of Randomized Controlled Trials. *ResearchSquare*. 2019;**Preprint**. https://doi.org/10.21203/rs.2.15906/v1.
19. Mappala H. IDDF2019-ABS-0251 The efficacy of ursodeoxycholic acid in the treatment of non-alcoholic steatohepatitis: A 15-year systematic review. *Clinical Hepatology*. 2019. p. A152.2-A152.
20. Xiang Z, Chen YP, Ma KF, Ye YF, Zheng L, Yang YD, et al. The role of ursodeoxycholic acid in non-alcoholic steatohepatitis: a systematic review. *BMC Gastroenterol*. 2013;**13**:140. [PubMed ID: 24053454]. [PubMed Central ID: PMC3848865]. https://doi.org/10.1186/1471-230X-13-140.
21. Chan AW, Boutron I, Hopewell S, Moher D, Schulz KF, Collins GS, et al. SPIRIT 2025 Statement: Updated Guideline for Protocols of Randomized Trials. *JAMA*. 2025;**334**(5):435-43. [PubMed ID: 40294593]. https://doi.org/10.1001/jama.2025.4486.
22. Sola E, Pose E, Campion D, Piano S, Roux O, Simon-Talero M, et al. Endpoints and design of clinical trials in patients with decompensated cirrhosis: Position paper of the LiverHope Consortium. *J Hepatol*. 2021;**74**(1):200-19. [PubMed ID: 32896580]. https://doi.org/10.1016/j.jhep.2020.08.009.
23. Mann DL, Felker GM, Unger EF, Wittes JT, Bozkurt B, Malik FI, et al. Derisking Phase II Clinical Trials in Heart Failure: A Position Paper from JACC: Basic to Translational Science and the Heart Failure Collaboratory. *JACC Basic Transl Sci*. 2025;**10**(5):677-88. [PubMed ID: 40436529]. [PubMed Central ID: PMC12235394]. https://doi.org/10.1016/j.jacbts.2025.04.003.
24. Harrison SA, Ruane PJ, Freilich B, Neff G, Patil R, Behling C, et al. A randomized, double-blind, placebo-controlled phase IIa trial of efruxifermin for patients with compensated NASH cirrhosis. *JHEP Rep*. 2023;**5**(1):100563. [PubMed ID: 36644237]. [PubMed Central ID: PMC9832280]. https://doi.org/10.1016/j.jhepr.2022.100563.
25. Kim GA, Cho HC, Jeong SW, Kang BK, Kim M, Jung S, et al. A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of ALS-L1023 in Non-Alcoholic Fatty Liver Disease. *Pharmaceuticals (Basel)*. 2023;**16**(4). [PubMed ID: 37111380]. [PubMed Central ID: PMC10142612]. https://doi.org/10.3390/ph16040623.
26. Nakano LA, Cancado ELR, Chaves CE, Madeira MCV, Katayose JT, Nabeshima MA, et al. A randomized crossover trial to assess therapeutic efficacy and cost reduction of acid ursodeoxycholic manufactured by the university hospital for the treatment of primary biliary cholangitis. *BMC Gastroenterol*. 2020;**20**(1):253. [PubMed ID: 32758152]. [PubMed Central ID: PMC7406387]. https://doi.org/10.1186/s12876-020-01399-5.
27. Fouda A, Abdelaziz AE, Hussien M, Ali AA, Abdelkawy KS, Elbarbry F. A randomized controlled trial comparing the effects of Vitamin E, Ursodeoxycholic acid and Pentoxifylline on Egyptian non-alcoholic steatohepatitis patients. *Eur Rev Med Pharmacol Sci*. 2021;**25**(23):7449-59. [PubMed ID: 34919247]. https://doi.org/10.26355/eurrev_202112_27442.
28. Patel VS, Mahmood SF, Bhatt KH, Khemkar RM, Jariwala DR, Harris B, et al. Ursodeoxycholic Acid's Effectiveness in the Management of Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-analysis. *Euroasian J Hepatogastroenterol*. 2024;**14**(1):92-8. [PubMed ID: 39022193]. [PubMed Central ID: PMC11249908]. https://doi.org/10.5005/jp-journals-10018-1434.

Table 10. Neurological Adverse Effects Before and After Intervention

Variables	After Use		Total	P
	No	Yes		
Ursophar® (n = 28)				
Cephalalgia				1
Before use				
No	22	3	25	
Yes	2	1	3	
Dysosmia				NC
Before use				
No	28	0	28	
Yes	0	0	1	
Hearing impairment				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Back pain				NC
Before use				
No	28	0	28	
Yes	0	0	0	
Lower extremity numbness				NC
Before use				
No	27	0	27	
Yes	1	0	1	
Podalgia				1
Before use				
No	27	0	27	
Yes	0	1	1	
Stress				NC
Before use				
No	26	0	26	
Yes	2	0	2	
Hand tremor				NC
Before use				
No	27	0	27	
Yes	1	0	1	
Myalgia				1
Before use				
No	25	1	26	
Yes	2	0	2	
Migraine				NC
Before use				
No	27	0	27	
Yes	1	0	1	
Sleep disorder				1
Before use				
No	22	3	25	
Yes	2	1	3	
Paresthesia in the foot				1
Before use				
No	26	1	27	
Yes	1	0	1	
Cholicray® (n = 27)				
Cephalalgia				0.375
Before use				
No	22	4	26	
Yes	1	0	1	
Dysosmia				1
Before use				
No	25	1	26	
Yes	1	0	1	
Hearing impairment				NC
Before use				
No	25	0	25	
Yes	2	0	2	
Back pain				NC
Before use				
No	25	0	25	
Yes	2	0	2	
Lower extremity numbness				NC
Before use				
No	27	0	27	
Yes	0	0	0	
Podalgia				1
Before use				
No	25	0	25	
Yes	1	1	2	
Stress				NC
Before use				
No	26	0	26	
Yes	1	0	1	
Hand tremor				NC
Before use				
No	27	0	27	
Yes	0	0	0	

Variables	After Use		Total	P
	No	Yes		
Myalgia				0.687
Before use				
No	21	2	23	
Yes	4	0	4	
Migraine				NC
Before use				
No	26	0	26	
Yes	1	0	1	
Sleep disorder				1
Before use				
No	19	3	22	
Yes	3	2	5	
Paresthesia in the foot				1
Before use				
No	25	1	26	
Yes	1	0	1	

Abbreviation: NC, not calculated due to insufficient events.