Research Article **ISSN 2639-9334**

Gastroenterology, Hepatology & Digestive Disorders

Ursodeoxycholic Acid Treatment in Primary Biliary Cirrhosis Patients (Stage I-II): Thirteen Years Follow-up: Evaluation of Standard Versus High Dosage, a Randomized Open Controlled Trial

Giulia Roda[1]*, Francesco Azzaroli[1], Marco Montagnani[1], Giuseppe Mazzella[1], Aldo Roda[2], Emanuele Porru[2] and Enrico Roda[3]

[1]*Department of Medical and Surgical Sciences, Gastroenterology Unit, University of Bologna, Italy.*

[2]*Departmento of Chemistry G. Ciamician University of Bologna, Italy.*

[3]*Fondazione Istituto di Scienze della Salute, Bologna, Italy.*

***Correspondence:**

Giulia Roda, Department of Medical and Surgical Sciences, Gastroenterology Unit, University of Bologna, Italy.

Received: 11 Dec 2025; **Accepted:** 14 Jan 2026; **Published:** 25 Jan 2026

Citation: Giulia Roda, Francesco Azzaroli, Marco Montagnani, et al. Ursodeoxycholic Acid Treatment in Primary Biliary Cirrhosis Patients (Stage I-II): Thirteen Years Follow-up: Evaluation of Standard Versus High Dosage, a Randomized Open Controlled Trial. Gastroint Hepatol Dig Dis. 2026; 9(1): 1-5.

ABSTRACT

Background: *Ursodeoxycholic Acid (UDCA), at a dose of 13-15 mg/kg daily is the only recommended drug for patients with primary biliary cirrhosis (PBC). Recent meta-analysis point-out the need of a re-evaluation of the role of UDCA in PBC. One of the criticisms risen to UDCA therapy is the range of the dose (8-15 mg/Kg/day) since at this dosage UDCA doesn't exceed 35-45 % of total biliary bile acids (BA). On the other hand, higher dosage (30 mg/Kg/day) of UDCA can produce up to 65-75% of biliary UDCA accumulation with a potentially higher activity for the higher enrichment of this poor detergent BA. The aim of our study is to evaluate the long-term effect (up to 12 years) of high dose UDCA on liver and bile biochemistry, and histology in a randomized open controlled study.*

Methods: *40 non icteric PBC patients (I-II stage) have been randomized to receive high (H-UDCA;30 mg\Kg\day: 17 female and 3 male) or conventional UDCA dose (m-UDCA,15 mg\Kg\day: 18 female, and 2 males). Clinical and biochemical evaluations were performed twice per years. Liver biopsy was performed at baseline and after 6 years of treatment.*

Results: *Serum liver enzymes (ALT, AST, y-GT, ALP) and bilirubin significantly decreased in patients treated with H-UDCA compared to m-UDCA. Patients who normalized all the serum liver enzymes tests were defined "responders", while patients who normalized only three parameters were defined "partial responders". The other cases were considered "non-responder". Among patients receiving H-UDCA, 85,7% were "responders" and 14,3% were "partial responders". Instead, in the m-UDCA group, "responder", "partial responder" and "non-responder" were respectively 23%, 35% and 42% ($p<0.001$). Biliary BA composition was significantly modified by the administration of both doses after 6 years of treatment. Total UDCA (glycol-UDCA + tauro-UDCA) become the predominant bile acids reaching value up to 70% in the H-UDCA group twice than the value reached in the m-UDCA group. UDCA and endogenous BA become almost conjugated with the glycine (G\T ratio 9-10) at both doses similarly to endogenous BA. Histological stage improved in 13 pts treated on H-UDCA dosage.*

Conclusion: *In PBC patients (stage I-II) high UDCA dosage seems to be more effective than conventional one on serum biochemistry and liver histology with a significant increased accumulation of UDCA in the enterohepatic circulation and bile suggesting that in early detection of the disease (stage I-II) high doses of UDCA might represent the ideal treatment without any major side effect. The extraordinary long-term result is represented by a steady state UDCA accumulation producing a less toxic and mild detergent bile facilitating the membrane cytotoxicity, recovery and patients improvement.*

Keywords

Ursodeoxycholic Acid, PBC, Antimitochondrial antibodies.

Introduction

Primary biliary cholangitis (PBC) is a rare autoimmune cholestatic liver disease that may progress to fibrosis or cirrhosis and which

pathogenesis remains still unknown. The diagnosis relies on antimitochondrial antibodies (AMA) or specific antinuclear antibodies, and on a serum cholestatic biochemical profile by current guidelines. Treatment is based on UDCA as first line at a dose of 15 mg/Kg/day. UDCA normalizes serum liver function tests, pauses histologic progression [1]. However, 30% of patients with PBC exhibit the suboptimal response to UDCA increasing the UDCA response score (URS) [2]. Moreover, budesonide add on treatment didn't improve histology in several studies [3] and Obeticholic acid (OCA) add on therapy in non-responders or intolerant patients to UDCA is, despite a potential activity, frequently associated with pruritus limiting its use in clinical practice [4]. Biopsy is recommended in selected cases, and recent evidence suggests that it may provide relevant information for risk stratification and prediction of UDCA response [5].

The mechanisms by which UDCA exerts its anticholestatic, antifibrotic and antiproliferative function are poorly understood but well demonstrated in experimental animal studies. UDCA has anti-fibrotic activity by protecting hepatic stellate cells against production of collagen [6]. Recently, it has been shown that UDCA regulated TREM-1 and 2 expression in primary cultured mouse Kupffer cells and dampened inflammatory gene transcription via a TREM-2-dependent mechanism [7,8]. Moreover, UDCA produces many beneficial effects on metabolism and immune responses via its interaction with the membrane G protein-coupled bile acid receptor (GPBAR) [8].

Recently, a prospective multicenter study has shown that in non-advanced PBC the biochemical response to UDCA is maintained up to 15 years. Additionally, data have proved that patients with a PBC showing lack of serum biochemical tests response to UDCA by 6 months after treatment initiation, should be considered for further treatments [9].

A recent metanalysis of all long-term randomized controlled trials (RCTs) suggested that long-term treatment with mid-dose UDCA can improve liver biochemistry and survival free of liver transplantation in patients with PBC and delay the histological progression of the liver involvement [10]. Of interest, in a study including 262 patients with PBC who had received 13-15 mg/kg UDCA daily for a mean of 8 years, UDCA alone normalizes the survival rate of patients with PBC when given at early stages [11].

UDCA in PBC leads to a significant increase in its own concentration in serum and bile, while reducing levels of other BA more detergent and potentially toxic like chenodeoxycholic acid (CDCA) and Deoxycholic acid [12]. This shift is associated with the stabilization of intestinal detoxification through the upregulation of efflux pumps. In healthy individuals, UDCA administration also enriches bile, but the effects on intestinal detoxification are less studied [13]. Few studies have evaluated high dose of UDCA in PBC. It has been shown that biliary enrichment with UDCA increased from 37% to 46% in a 20 mg/kg group (P = 0.02) in respect to the 10 mg/kg group. Serum Liver biochemistry improved in PBC patients receiving UDCA 20 mg/kg/day compared to a dose of 10 mg/kg/day [14]. These results indicate that UDCA 10 mg/kg/ day is a suboptimal dose for the treatment of PBC.

In our study, we investigated whether, in patients with early PBC, high doses of UDCA are superior to standard doses in obtaining an enduring efficacy on biochemical, histology and clinical findings without the risk of accumulation or modified bioavailability of UDCA.

Materials and Methods

Study Population

Forty consecutive histologically proven AMA+ PBC patients at I and II stage were randomized to receive: high dose of UDCA (30 mg/Kg/day) (H-UDCA group: 20 patients, (mean age 49±2.11) and conventional doses (15 mg/Kg/day) (m-UDCA group:20 patients (mean age 50.1±1.86). The ratio M:F was 1:20 in the m-UDCA and 1:20 in the H-UDCA group. Follow-up time was 13,4±1.2 years in the m-UDCA and 13,3±1,5 in the H-UDCA group. UDCA 500 mg gelatine capsules were given in two or three divided doses after meals according to the weight and randomized treatment algorithm. None of the patients was taking cholestyramine or other drugs at the time of the enrollment.

Inclusion criteria were chronic cholestatic liver disease of at least six months of duration, serum alkaline phosphatase (ALP) upper limit of normal in the same period (ALP>300 IU-normal value 270 UI), AMA >100 units (normal value <50), a liver biopsy in the previous 3 months diagnostic of PBC I-II stage, absence of biliary tract obstruction by ultrasound, CT scan or RMN cholangiography.

Exclusion criteria were cirrhosis, pregnancy, age<18 or >70 years, previous therapy for PBC, systemic use of steroids or immunosuppressant.

Serum biochemical liver function tests and bile acid evaluation

Conventional clinical and biochemical evaluations were performed twice per year. Liver biopsy was performed at baseline and after 6 years of treatment (Ludwing criteria and Metavir point score were used) in a limited number of cases. (n 16 H-UDCA, n 14 m-UDCA).

Conventional String test (Enterotest) was used to collect duodenal bile after induction of gallbladder contraction with 5 mg i.v cerulein administration. BA collected by Enterotest were extracted from fiber and biliary BA composition was evaluated by HPLC_ ES-MS/MS as previously described [15].

Statistical analysis

Comparisons between groups were performed by Mann-Whitney U test for continuous variables. Odds ratios (ORs) and confidence intervals (CIs) were calculated. P value < 0.05 was considered significant.

Results

Patients' characteristics

Patients' characteristics are shown in Table 1. Most of the patients

were female and AMA+. Half of the patients included in the 2 groups were ANA+. Patients were followed for 15 years. During the 12 years follow up patients did not modify significantly their body weight and style of life.

Table 1: Patients Characteristics.

	m-UDCA	h-UDCA
N° Patients	20	20
Age	49.0±2.11	50.1±1.86
M:F	2:18	3:17
Follow up years	13.4±1.2	13.11.5
AMA (+/-)	16:4	18:2
ANA (+/-)	8:16	7:13
ALT (U/L)	64.4±10.8	51.6±5.2
AST (U/L)	53.65±8.14	48.47±7.03
ALP (U/L)	602±56	484.4±44.8
yGT (U/L)	209±23.5	206.5±33.5
Bilirubin (mg/dL)	0.87±0.04	0.76±0.07

Biliary bile acid composition

Biliary BA composition evaluated by HPLC -mass spectrometry in both groups after 6 years of treatment is reported in Figure 1. Glycine and taurine conjugates which represent the only form recovered in bile while the free BA are not present for all BA. Percentage of total UDCA was significant increased after 6 years in the H-UDCA group in respect to m-UDCA group ($p<0.001$) Figure 2. The UDCA accumulates in bile as glycine and taurine. A significant reduction of primary BA cholic and chenodeoxycholic acid and a reduction of Deoxycholic acid was observed. The Endogenous BA are significantly reduced and became like UDCA mainly conjugated with glycine with a ratio 8-9/1 with taurine in respect to untreated patients where this ratio in 2-3/1. The enrichment of UCDA increased with the dose and in the H-UDCA group became the major BA present in bile representing up to 60-80% of total BA. The LCA was present in minor amount and do not increase with the dose suggesting the poor 7-dehydroxylase metabolism of UDCA with formation of potential toxic LCA particularly in the H-UDCA group.

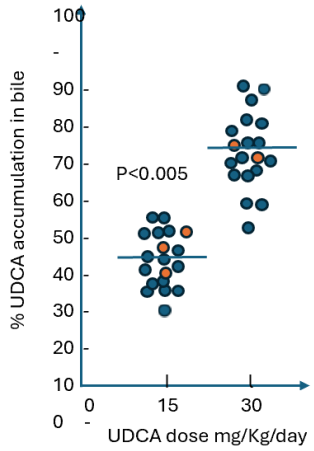

Figure 2: Mean % biliary UDCA in the two group after UDCA treatment (6 years). The percent UDCA in bile was calculated as the sum of free UDCA, GlycoUDCA and TauroUDCA in respect to total BA.

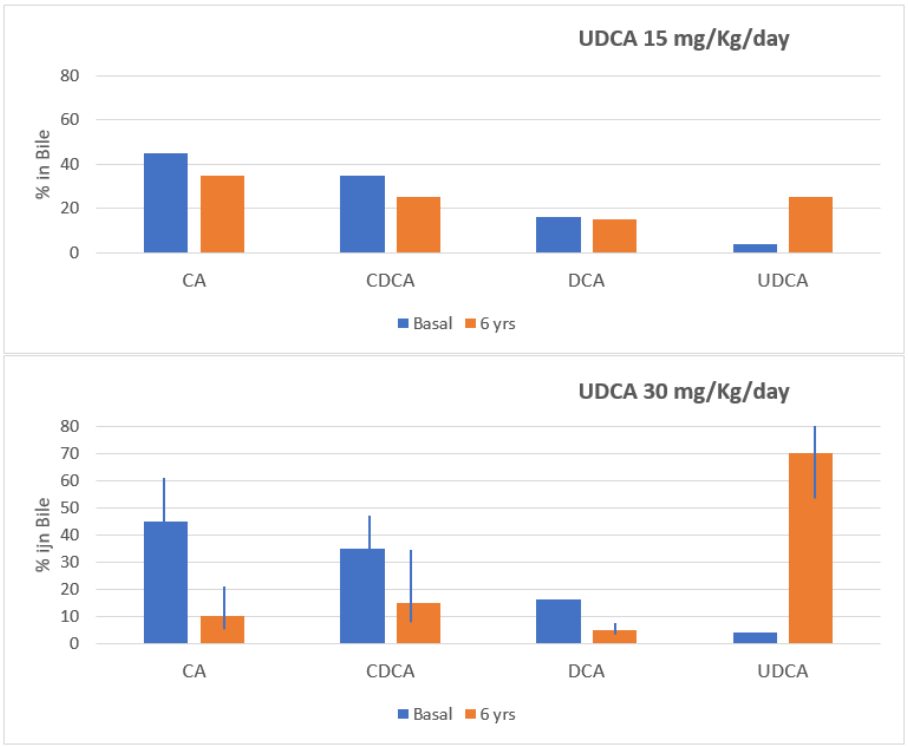

Figure 1: Biliary BA composition in the two group of patients. Data were expressed as % of total UDCA, CDCA, CA, DCA and LCA reporting the sum of the respective Gycine and taurine conjugates.

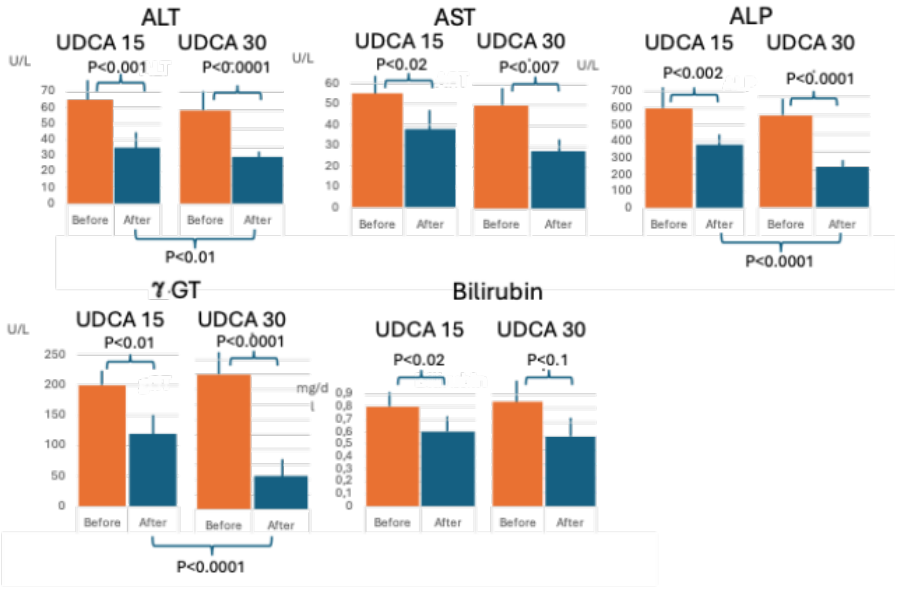

Figure 3: Serum Liver function test before and after chronic feeding o UDCA at the two doses of 15 and 30 mg/Kg. Mean values – standard deviation.

Serum liver function test

Alkaline phoshatase was decreased after treatment in both groups after 12 years Figure 3. A significant reduction was found in the H-UDCA group when compared with the m-UDCA (p<0,0001).

γGT and ALT were also significant lower in the H-UDCA group when compared with the m-UDCA group (p<0,0006). Instead, bilirubin and AST were reduced in both groups without any significant difference. Among patients receiving H-UDCA, 85,7% were "responder" and 14,3% were "partial responder". Instead, in the m-UDCA group, "responder", "partial responder" and "non-responder" were respectively 23%, 35% and 42%(p<0.001).

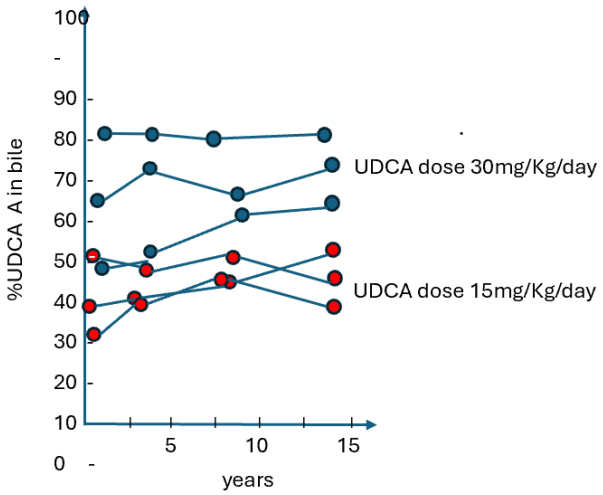

Figure 4: Biliary UDCA % at different time point.

Histological stage

In the m-UDCA group, 14 patients had paired biopsies after 6 years. 8 vs 6 pts (57.1% vs 42.9%) showed improvement in the liver histology (p value <0.01) whereas in the H-UDCA group 15 patients had paired biopsies and 13 vs 2 pts (86.6% vs 13.4%) showed improvement of the liver histology (p value < 0.01).

Discussion

Our study is the first study evaluating in patients with early PBC, efficacy of high doses of UDCA compared to standard doses in obtaining an enduring efficacy (over 12 years) on biochemical, histology and clinical findings. UDCA is the established first-line therapy for primary biliary cholangitis (PBC), yet up to 30% of patients show an incomplete biochemical response to the standard 13–15 mg/kg/day dose, a condition consistently associated with poorer long-term outcomes. Evidence from previous randomized trials indicates that UDCA efficacy is dose-dependent, with higher doses producing greater reductions in cholestatic markers and increased biliary enrichment of hydrophilic BA. In our long-term randomized study, high-dose UDCA at 30 mg/kg/day demonstrated clear superiority over the standard regimen in patients with early-stage PBC, resulting in markedly higher rates of biochemical normalization, lower proportions of partial or non-responders, and substantially greater histologic improvement after 12 years of follow-up. These findings align with mechanistic data showing that UDCA at higher concentrations more effectively displaces hydrophobic and cytotoxic BA such as chenodeoxycholic and deoxycholic acid, thereby reducing bile detergent activity, membrane injury, cholangiocyte apoptosis, and inflammatory signaling. The pronounced biliary enrichment observed in the high-dose group (>60% of the BA pool) supports the biological plausibility of dose escalation and is consistent with prior work demonstrating that UDCA promotes hepatocellular protection, stabilizes canalicular transport, reduces oxidative stress, and modulates innate immunity, including TREM-2-mediated anti-inflammatory pathways and GPBAR1 signaling. Compared with second-line agents such as Obeticholic acid, which may exacerbate pruritus and contribute to a

less favorable bile acid milieu due to its increased hydrophobicity, dose optimization of UDCA appears safer, better tolerated, and more physiologically coherent as a first therapeutic adjustment in patients with suboptimal response. High doses of UDCA is best treatment option for PBC patients unless a more bioavailable formulation of UDCA will be developed. Potentially by increasing the rate of UDCA intestinal solubilization will increase the intestinal absorption of the soluble form (ionized) reaching an accumulation in bile potentially like the high dose with the m-dose. It has been previously reported that the bioavailability of UDCA is less than 50 % of the administered dose [16]. The low recovery is related to the poor solubility kinetic to the administered protonated UDCA acid to form the ionized soluble salt; it will take hours when the pH is higher than 7. The formation of soluble and absorbable form therefore requires long time and the physiological intestinal transit time do not allow the efficient formation of the sodium salt soluble and efficiently absorbed by passive diffusion [16]. The high dose compensates the stool excretion of the UDCA and the 60-70% biliary accumulation represent the ideal percentage to render the bile less detergent and cytotoxic. PBC patients with limited biliary secretion and impaired BA uptake for cholestatic involvement could accumulate in the liver in higher amount of BA which are hepatotoxic. In presence of the high amount of UDCA the cytotoxicity is strongly reduced with a therapeutic benefit for the patient.

In conclusion our study has demonstrated that a biliary accumulation up to 70% highly reduced the BA pool detergency and therefore membrane toxicity. UDCA and its Conjugates exhibit a high Critical micellar concentration (CMC) and the bile became less enriched of micelles moving to a phosphlipids vescicle phases. This is one of the main benefit of UDCA treatment at high dose creating a bile much less toxic than the endogenous in these patients which prevent the liver damage by the intrahepatic accumulation. On the other hand, the UDCA accumulation reaches a steady state value similar for at least 12 years' treatment (Figure 4).

The extended duration of our study, the availability of repeat biopsies, and the assessment of bile acid profiles strengthen the robustness of our conclusions, although the relatively small sample size and single-center design remain limitations. Overall, our data indicate that early-stage PBC patients may benefit substantially from high-dose UDCA, achieving durable biochemical and histologic improvement without safety concerns, suggesting that dose escalation could play a central role in optimizing first-line therapy before considering more aggressive or less tolerable second-line interventions.

References

1. Namisaki T, Fujinaga Y, Moriya K, et al. The association of histological progression with biochemical response to ursodeoxycholic acid in primary biliary cholangitis. Hepatol Res. 2021; 51: 31-38.
2. Kawata K, Joshita S, Shimoda S, et al. The Ursodeoxycholic Acid Response Score predicts pathological features in primary biliary cholangitis. Hepatol Res. 2021; 51: 80-89.
3. Hirschfield GM, Beuers U, Kupcinskas L, et al. A placebo-controlled randomised trial of budesonide for primary biliary cholangitis following an insufficient response to UDCA. J Hepatol. 2021; 74: 321-329.
4. Alvaro D, Carpino G, Craxì A, et al. Primary biliary cholangitis management: controversies, perspectives and daily practice implications from an expert panel. Liver Int. 2020; 40: 2590-2601.
5. Aguilar MT, Chascsa DM. Update on emerging treatment options for primary biliary cholangitis. Hepat Med. 2020; 12: 69-77.
6. Ye HL, Zhang JW, Chen XZ, et al. Ursodeoxycholic acid alleviates experimental liver fibrosis involving inhibition of autophagy. Life Sci. 2020; 242: 117175.
7. Labiano I, Agirre-Lizaso A, Olaizola P, et al. TREM-2 plays a protective role in cholestasis by acting as a negative regulator of inflammation. J Hepatol. 2022; 77: 991-1004.
8. Lu R, Yan X, Fang G, et al. A molecular mechanism of UDCA engagement with GPBAR and subsequent G protein interaction revealed by scattered alanine scanning. Bio chem Bio phys Res Commun. 2022; 600: 14-21.
9. Kuiper EM, Hansen BE, Lesterhuis W, et al. Dutch PBC Study Group. The long-term effect of ursodeoxycholic acid on laboratory liver parameters in biochemically non-advanced primary biliary cirrhosis. Clin Res Hepatol Gastroenterol. 2011; 35: 29-33.
10. Gong Y, Huang Z, Christensen E, et al. Ursodeoxycholic acid for patients with primary biliary cirrhosis: an updated systematic review and meta-analysis of randomized clinical trials. Am J Gastroenterol. 2007; 102: 1799-1807.
11. Corpechot C, Carrat F, Bahr A, et al. The effect of ursodeoxycholic acid therapy on the natural course of primary biliary cirrhosis. Gastroenterology. 2005; 128: 297-303.
12. Del Barrio M, Díaz-González Á, Alonso-Peña M. Primary biliary cholangitis: immunopathogenesis and the role of bile acid metabolism in disease progression. Int J Mol Sci. 2025; 26: 7905.
13. Dilger K, Hohenester S, Winkler-Budenhofer U, et al. Effect of ursodeoxycholic acid on bile acid profiles and intestinal detoxification machinery in primary biliary cirrhosis and health. J Hepatol. 2012; 57: 133-140.
14. Van Hoogstraten HJ, De Smet MB, Renooij W, et al. A randomized trial in primary biliary cirrhosis comparing ursodeoxycholic acid 10 mg/kg versus 20 mg/kg. Aliment Pharmacol Ther. 1998; 12: 965-971.
15. Franco P, Porru, E, Fiori J, et al. Identification and quantification of oxo-bile acids in human faeces with liquid chromatography–mass spectrometry: A potent tool for human gut acidic sterolbiome studies. J. Chromatogr. 2018; 1585: 70-81.
16. Simoni P Cerrè, Cipolla A, Polimeni C, et al. Bioavailability study of a new, sinking, enteric-coated ursodeoxycholic acid formulation Pharmacological Research. 1995; 31: 115-119.