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URSODEOXYCHOLIC ACID: REMARKABLE DERIVATIVE AS LIVER PROTECTANT

Tushar Nehere, Purva Kolhe, Revati Khawale, Snehal Chakorkar*
Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra, India.

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ABSTRACT

Ursodeoxycholic acid is a choleretic. Ursodeoxycholic acid responsible for raising bile production in body and ultimately bile is necessary for the breakdown of lipids. Additionally, bile is responsible for removal body's toxin. In addition to its choleretic effect, ursodeoxycholic acid also has anti-inflammatory and antioxidant properties. This characteristic may help in preventing liver injury and promoting repair. Additionally, ursodeoxycholic acid has been demonstrated to have cytoprotective properties, which implies that it may aid in preventing the death of liver cells. People who have liver problems that cause bile to build up may benefit from ursodeoxycholic acid's ability to increase bile flow. It helps the liver by various complementary mechanisms. It helps the liver by its cytoprotective, Immunomodulatory, and Anti apoptotic. A non-toxic, hydrophilic bile acid called ursodeoxycholic acid (ursodiol) is used mostly to treat cholestatic liver diseases. It improves the biochemical parameters in various diseases and widely used in treatment of Primary biliary cirrhosis, Primary sclerosing cholangitis, Intrahepatic cholestasis of pregnancy, Cystic fibrosis, but furthermore studies are need to be done in clinical uses. The only medication authorized for use as the first-line treatment for PBC is ursodeoxycholic acid (UCDA). Overall, ursodeoxycholic acid is a potent molecule with a wide range of beneficial effects on the liver. The ability of ursodeoxycholic acid to treat various liver conditions, including alcoholic liver disease and hepatitis C, is currently being researched. This review summarizes the current understanding of the ursodeoxycholic acid mechanisms of action and offers data from clinical studies on its application to chronic liver disorders.

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Corresponding author
Snehal Chakorkar
Assistant Professor
Department of Pharmacology
Dr. D. Y. Patil Institute of
Pharmaceutical Sciences and Research, Pimpri,
Pune, Maharashtra, India.
snehalchakorkar@gmail.com
86009373143

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INTRODUCTON

DISCOVERY & FURTHER HISTORY:

Ursodeoxycholic acid (UDCA) is widely used to treat various chronic cholestatic liver diseases. It has been used in traditional Chinese medicine for centuries as a treatment for liver disease. In fact, the Chinese medicine 'Yutang', a powdered preparation made from dried adult bear bile, has been used to relieve liver and biliary tract disorders[1]. In 1902, **Hammarsten** first reported the presence of an unknown bile acid in polar bear bile, which he called 'ursocholic acid'.In 1927, **Shoda** first defined the chemical form of his ursodeoxycholic acid from the bile of Chinese black bears. **Masada** named this bile acid "ursodeoxycholic acid". This is because it was originally found in bear bile (called 'ursus' in Latin) and thought to be a chemical isomer of deoxycholic acid [(1)] . The hydrophilic dihydroxylated bile acid ursodeoxycholic acid, also known as ursodiol or ursodeoxycholic acid, was first discovered in the bile of Chinese black bears and was given the genus name ursus (Latin for bear). A long-term follow-up study of individuals with PBC included a Chinese population. Zhang et al. examined 187 patients' prospectively collected data and reported long-term outcomes as measured by at least one of the following events: liver-related death, LT, or cirrhosis-related sequelae. When reviewed at 3, 6, and 12 months after ursodeoxycholic acid therapy, the use of the Paris, Barcelona, Toronto, and Ehime definitions of treatment response—but not the Rotterdam definition—significantly distinguished the patients in terms of long-term results. In that study, the long-term outcome of primary biliary cirrhosis was predicted by a biochemical response by the predetermined criteria as early as 6 months following ursodeoxycholic acid medication. When compared to the 1-year assessment, biochemical reactions at 6 months had a high or equivalent diagnostic value for negative outcomes[(2).] In humans, ursodeoxycholic acid is also present in very small amounts as a secondary bile acid (1-3% of the total bile acid pool), where it is produced by intestinal bacteria by the 7-epimerization of the primary bile acid chenodeoxycholic acid. In contrast to humans, bears and nutria directly synthesize ursodeoxycholic acid from cholesterol, making it a main bile acid in those species. Based on a long-held idea that bear bile can treat liver disease, dried bear bile has been utilised for generations in China as an empirical treatment.After **Iwasaki** revealed the structure of ursodeoxycholic acid in 1936, it was later synthesized and sold in Japan as a hepatoprotective drug in combination with vitamins. According to early reports from Europe and Japan, ursodeoxycholic acid can dissolve gallstones similarly to chenodeoxycholate but is not hepatotoxic. In 1975, **Makino** reported the first prospective study of patients with gallbladder stones treated with ursodeoxycholic acid demonstrating gallstone dissolution. In 1985, **Leuschner** first observed improved liver tests of patients with chronic active hepatitis treated with ursodeoxycholic acid for gallstone dissolution. In 1987, **Poupon** suggested that long-term use of ursodeoxycholic acid is safe and effective in patients suffering from primary biliary cirrhosis (PBC). Since then, a variety of studies have shown the beneficial effect of ursodeoxycholic acid in liver disorders. In clinical practice, ursodeoxycholic acid possesses a defined role in treating patients with cholestatic liver diseases [(3-4).] Ursodeoxycholic acid demonstrated a favorable effect on liver biochemistry levels and histological advancement in contrast to placebo in a systematic evaluation of sixteen randomized clinical trials (RCTs) involving 1447 primary biliary cirrhosis patients. Oral administration of 13–15 mg/kg per day for PBC is advised. Higher doses have not demonstrated greater benefits and are linked to an increased frequency of negative effects. It is very well tolerated at appropriate levels and rarely causes negative effects. Diarrhea, a modest weight increase during the first few months of treatment, and hair thinning are a few of the side effects that have been reported. For the treatment of patients with primary biliary cholangitis (PBC), hepatic societies advise the use of ursodeoxycholic acid (UDCA). Actigall was initially approved by the food and drug administration in1987 for the purpose of dissolving gallstones, then in 1997 it was authorized for the purpose of avoiding gallstones in obese patients while on aggressive weight-loss programmes. In December 1997, ursodiol (Urso) received approval to treat primary biliary cirrhosis (PBC) and was given the orphan drug designation. A biliary lithotripsy device was food and drug administration -approved in 2000 for use with Actigall in certain patients who had a single radiolucent gallstone with a diameter of 4 to 20 mm.[(5)] nThe Allergan-submitted application for ursodeoxycholic acid was approved for use in the United States December 1987 and was given the orphan drug designation [(6)].

PHYSICOCHEMICAL PROPERTIES:

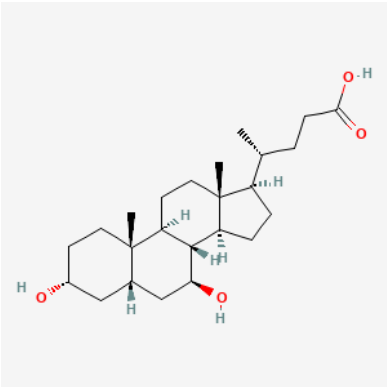

Figure 1.1: Chemical structure of ursodeoxycholic acid [(7)]

IUPAC Name:
(4R)-4-[(3R,5S,7S,8R,9S,10S,13R,14S,17R)-3,7-dihydroxy-10,13-dimethyl-2,3,4,5,6,7,8,9,11,12,14,15,16,17-tetradecahydro-1H-cyclopenta[a]phenanthren-17-yl]pentanoic acid [7]

Molecular Formula: C24H40O4

Table 1: All chemical properties of ursodeoxycholic acid [7-8]

Sr.No.	Property name	Property Value
1	Molecular Weight	392.6 g/mol
2	Solubility	20mg/L (at 20°C)
3	Melting point	203 °C
4	Log P	3
5	pKa	5.1
6	XLogP3-A4	4.9
7	Hydrogen Bond Acceptor Count	4
8	Rotatable Bond Count	4
9	Exact mass	392.29265975 g/mol
10	Monoisotopic Mass	392.29265975 g/mol
11	Topological Polar Surface Area	77.8 Å²
12	Heavy Atom Count	28
13	Formal Charge	0
14	Complexity	605
15	Isotope Atom Count	0
16	Defined Atom Stereocenter Count	10
17	Undefined Atom Stereocenter Count	0
18	Covalently-Bonded Unit Count	1
19	Compound is Canonicalized	Yes

PHARMACOKINETIC PROPERTIES:

Table 2: All Physicochemical properties of ursodeoxycholic acid. [7-8,11-12]

Sr. No.	Properties	Values
1	BCS Classification	class II drug
2	Cmax	24-413 nmol/mL
3	Tmax	1.8-3.39 hours,
4	T half	6-10 hours.
5	Absorption	Proximal small intestine
6	Distribution	throughout the body
7	Metabolism	Liver and intestine
8	Excretion	Bile acid excretion into urine
9	Aqueous solubility	9 µmol/L
10	Protein binding	76.4% + 7.7
11	VLDL binding	10.8
12	LDL binding	16.1
13	HDL Binding	27.6

DOSE GIVEN FOR DISEASES:

Table 4: Dose Given For Diseased Condition.

Sr. No.	Disease Name	Dose
1	Cholelithiasis via the dissolution of radiolucent cholesterol gallstones	8 to 10 mg/kg/day
2	Primary biliary cirrhosis Ursodiol is designated an orphan drug by the food and drug administration for this indication.	13 to 15 mg/kg/day
3.	Primary sclerosing cholangitis	13 -15 mg/kg/day
4	Intrahepatic cholestasis of pregnancy	5 to 20 mg/kg /day 500 mg PO BD (controlled trials)
5	Cholestasis	Adolescent, children and infants:-15 to 30 mg/kg/day Premature neonates and neonates:- 10 to 30 mg/kg/day
6.	Gallstone prophylaxis during rapid weight loss	300 mg BD

MECHANISM OF WORKING:

Ursodeoxycholic acid function via several potentially intercollerated pathway , such as alteration of bile acid pool,effective immune modulation, cytoprotective action, choleresis. The overview is shown in fig. Below

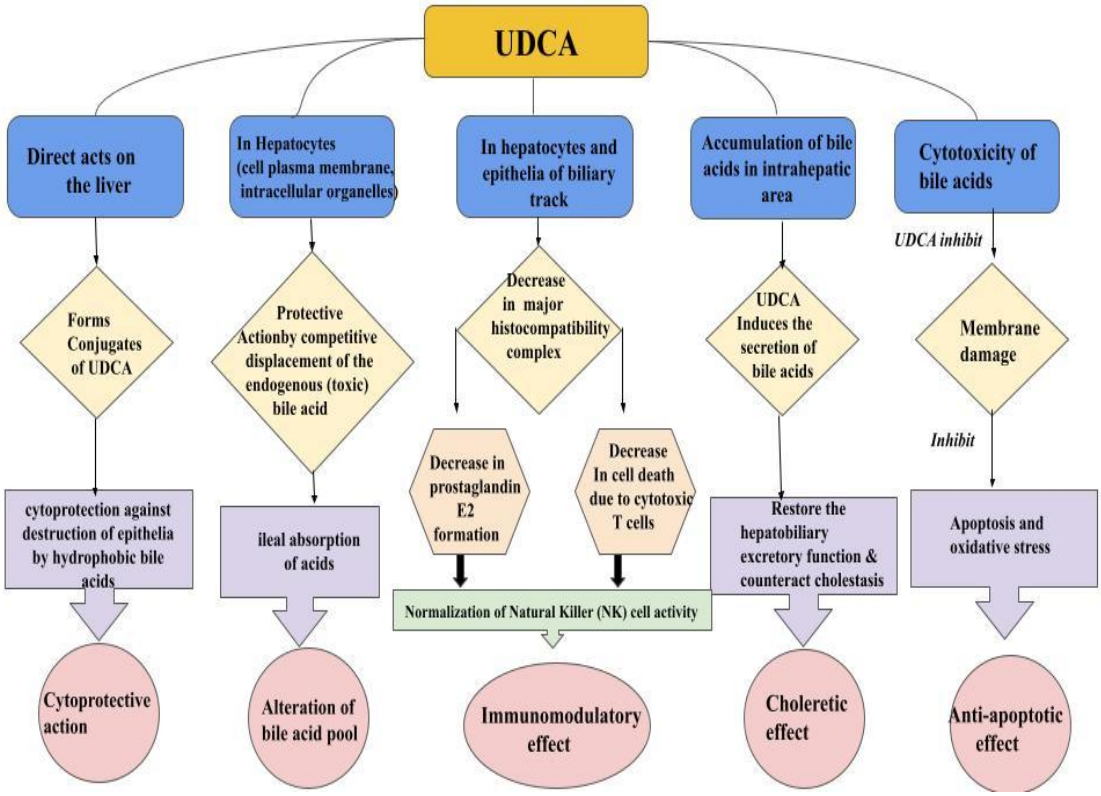

Fig. 1.2: Mechanism of action of ursodeoxycholic acid.

Various Modes of actions are as below;

1. Alteration of bile acid pool [13-14]
2. Immunomodulation [15-19]
3. Cytoprotective action [20-22]
4. Choleretic effect (Stimulation of bile secretion) [3]
5. Anti-apoptotic effect [23]

METHODS OF SYNTHESIS:
MEDICAL/CLINICAL USES:

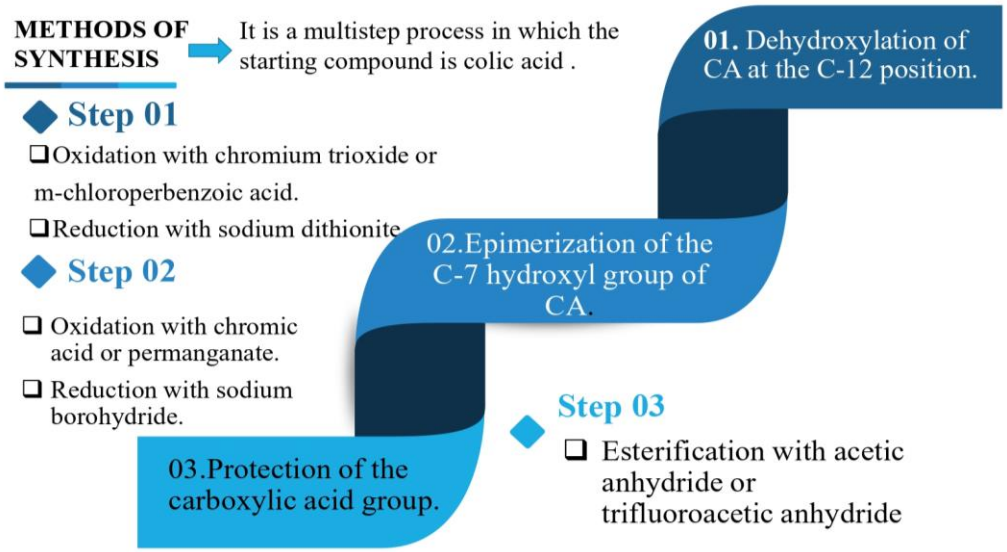

Fig. 1.3: Synthesis of ursodeoxycholic acid (24)

Ursodeoxycholic acid is used for treatment of various hepatic diseases, the drug is affecitve in liver disease. The clinical uses of ursodeoxycholic acid is given below

Primary biliary cirrhosis (PBC)

It is an autoimmune disorder which mainly affects the women's over the age of 20 years .Patients with primary biliary cirrhosis, the ursodeoxycholic acid treatment is safe and effective.[25]. In a clinical study it was concluded that the usage of ursodeoxycholic acid for long time delays the progression of the primary biliary cirrhosis and the chances of the liver transplantation has been decreased. [26]

The ursodeoxycholic acid is life extending treatment the patients with ursodeoxycholic acid treated are relatively better in health as compared to the placebo group([27] In combined clinical trial of Primary biliary cirrhosis patients it was observed that the patients of Primary biliary cirrhosis when treated with ursodeoxycholic acid have improved the survival free time of liver transplantation [28] .as per the american association for the study of liver disease they recommend ursodeoxycholic acid 13-15 mg /kg per day in treatment of Primary biliary cirrhosis which gives a effective and highly potential therapy . [29]

Primary sclerosing cholangitis (PSC)

In a clinical trail on 15 patients with primary sclerosing cholangitis, the ursodeoxycholic acid (750-1250 mg/day) was a effective treatment. The biochemical improvement was observed in patients, discontinuation of therapy associated increase of liver problems. Ursodeoxycholic acid at high dose can be a effective treatment [30]. long term use of ursodeoxycholic acid (28-30 mg/kg/day) gives a positive results associated with serum liver tests in patients with Primary sclerosing cholangitis.[31]

Intrahepatic cholestasis of pregnancy (ICP)

It is an cholestatic disorder of undifferentiated cause in which the liver acid levels are elevated and pruritis occur at third trimester of pregnancy . In a study conducted pregnant patient , the ursodeoxycholic acid (16 mg/kg body weight) treated patient having significant development in pruritus and other liver acids levels were normalizing , it was an effective treatment with no adverse effect were seen in mother and babies .[32]. In a clinical trial on the patient receiving the ursodeoxycholicacid (1gm/day) on interval of 14 days , the pruritus and laboratory parameters relapsed after discontinuation , the improvement is observed again after starting ursodeoxycholic acid [33] ursodeoxycholic acid in high dose is more effectively treat and control Intrahepatic cholestasis of pregnancy[34]

Pediatric cholestatic hepatic diseases

Cystic fibrosis (CF)

Thick biliary secretions are caused due to the cystic fibrosis which ultimately resulting into obstruction and plugs formation in bile duct. Liver diseases were observed as prominent cause of cystic fibrosis . in a double blind clinical trail on cystic fibrosis patients with liver disease where treated with Ursodeoxycholic acid(15mg/kg) and taurine (30 mg/ kg) with placebo , it was observed that the Ursodeoxycholic acid patients have a significant progress in their health and improvement in their live function tests [35] . a long therm Ursodeoxycholic acid therapy spontaneously increases the live health in cystic fibrosis associated liver disease patients [36] . treatment of severe cholestasis(associated with cystic fibrosis) by Ursodeoxycholic acid(15-20 mg/kg) prolongs the liver functioning capacity and nutritional status [37] . high dose therapy of Ursodeoxycholic acid(20 mg/kg) have more benefits and improvement in LFT as compared to low doses. [38] overall the conclusion is that the Ursodeoxycholic acid is affective in cystic fibrosis in high dose around 20 mg/kg of body weight .

Progressive familial intrahepatic cholestasis (PFIC)

Byler's disease or a progressive familial intrahepatic cholestasis is an inherited disorder in which cirrhosis progress to the liver failure. In a clinical trial on progressive familial intrahepatic cholestasis patients with Ursodeoxycholic acid 20-30 mg /kg per day, it was observed that there is a improvement in liver working and normalizing liver tests [39]

Gallstone dissolution

Ursodeoxycholic acid is used in dissolution of cholesterol gallstones. it stops the synthesis and secretion of hepatic cholesterol .[40] . in clinical trail the Ursodeoxycholic acid given in variable doses , it was concluded that the dose range 500-600 mg and 900-100mg/day was effective , it suggested to that it is effective and safe in patients [41]. recurrent gallstone is a severe problem in treatment of gallstones , the maintenance dose of 300 mg/day is given in gallstone recurrence .[42]

Biliary sludge

Biliary sludge is formed in biliary system due to large scale use of ultrasound , these could be due to rapid wight loss ,pregnancy, total parenteral nutrition and octreotide therapy . [43] in a clinical trial on idiopathic pancreatitis and gallbladder sludge patients , Ursodeoxycholic acid therapy of 10 mg/kg have eradicate gallbladder microlithiasis . in maintenance treatment,Ursodeoxycholic acid 300 mg/kg is given for next follow up period.[44]

ADVERSE EFFECTS: [45-46]

The patient had ursodeoxycholic acid treatment again the following year, and she continued to do so without experiencing any side effects until she passed away after an additional 12 years (P. M. Battezzati, personal communication, 2003). The clinical investigator states that it appears there was no connection between this significant adverse event and the study drug.

The **most frequent adverse events** during Ursodeoxycholic acid treatment are as follows:

Gastrointestinal disorders: In patients with gallstone disease receiving ursodeoxycholic acid **diarrhoea** was the one adverse event that occurred the most frequently (incidence: 2-9%).Diarrhoea was infrequently noted in patients with primary biliary cirrhosis and was only incidentally documented in three of five large-scale trials. Ursodeoxycholic acid treatment of individuals with primary sclerosing cholangitis and inflammatory bowel disease may result in an increased incidence of diarrhoea. Following the administration of ursodeoxycholic acid, two patients with primary biliary cirrhosis complained of right upper quadrant **abdominal pain. Nausea and vomiting** were recorded in three of 111 ursodeoxycholic acid-treated patients and in one of 111 placebo controls in the Canadian primary biliary cirrhosis trial.

Hepatobiliary disorders: An **increase in serum bilirubin** after the initiation of ursodeoxycholic acid treatment may require the discontinuation of ursodeoxycholic acid therapy.

Pregnancy: In intrahepatic cholestasis of pregnancy, ursodeoxycholic acid is administered during the (second and) third trimester of pregnancy only when typical symptoms, such as **pruritus**, develop. In pregnant rats, no significant fatal adverse effects were observed when ursodeoxycholic acid was fed daily at up to 2000 mg/kg, except for tail malformation in the highest dose group.

Skin Disorders: Allergic exanthema and related skin reactions may be due to drug adjuvants rather than ursodeoxycholic acid. A skin eruption initially attributed to ursodeoxycholic acid was caused by allergy to a co-ingredient, as shown by lymphocyte stimulating tests.

Respiratory effects: They include bronchitis, cough, pharyngitis, rhinitis, sinusitis and upper respiratory tract infection.

TOXICOLOGICAL INFORMATION:

Toxicity:

There have been no reports of unintentional or purposeful ursodeoxycholic acid overdoses. Seven patients have tolerated doses of ursodeoxycholic acid in the range of 16–20 mg/kg/day for 6-37 months without experiencing any side effects.Ursodeoxycholic acid has a lethal dose (LD50) of about 5000 mg/kg in rats when administered over 7–10 days and over 7500 mg/kg in mice. The most typical symptom of a severe ursodeoxycholic acid overdose would likely be diarrhea, which should be managed symptomatically.[7]

Hepatotoxicity:

Ursodiol is not known to aggravate underlying liver illness, enhance blood enzyme elevations, or result in clinically significant liver damage in multiple studies under a variety of circumstances.However, there have been a few instances of clinical decompensation in individuals using ursodiol who had advanced liver disease and cirrhosis, however the cause of these reactions remains unknown.Jaundice returned after restarting ursodiol in at least one case. As a result, ursodiol is effective against a variety of liver diseases and hasn't been conclusively related to cases of clinically evident acute liver injury in individuals without cirrhosis.There is some concerns that ursodiol could be unfavorable to those with advanced liver disease (Children classes B-moderately impaired hepatic function, and C-advanced hepatic dysfunction), so such people should probably not use ursodiol [47]

Drug induced liver injury:

Ursodeoxycholic acid may lower serum alkaline phosphatase in individuals with drug-induced liver injury, however it has no clinical advantage in terms of lowering mortality or severe drug-induced liver injury.Only two out of six instances involving anabolic androgenic steroid with or without dietary supplements showed clinical improvement following Ursodeoxycholic acid treatment, compared to nearly all cases involving amoxicillin-clavulanate (4 out of 5). With the exception of one report linked to brentuximab vedotin, the other nine drug induced liver injury studies' therapeutic response to Ursodeoxycholic acid was found to be beneficial.
Ursodeoxycholic acid has been suggested to be helpful in the treatment of drug induced liver injury, although according to international recommendations,Ursodeoxycholic acid is not an approved treatment for drug induced liver injury [48-49]

Effects during Pregnancy and Lactation:

In women patients with intrahepatic cholestasis of pregnancy with early onset, ursodeoxycholic acid is efficient and safe, reducing pruritus and reversing several biochemical abnormalities in the mothers.Human milk naturally contains ursodiol. The amount of ursodiol (ursodeoxycholic acid) consumed by the newborn is minimal, and it is not anticipated to have any negative effects on breastfed infants due to the low levels of ursodiol (ursodeoxycholic acid) in breastmilk following exogenous administration. No particular safety measures are necessary.[7]

Effects in Breastfed Infants

During the first six months of life, one breastfed (to what extent is not stated) infant underwent daily maternal ursodiol medication of 750–1000 mg developed normally.

Seven pregnant and postpartum women who were taking ursodiol 14 mg/kg daily. During the initial postpartum period, they reported no adverse responses in their breastfed infants.Although the extent and duration of breastfeeding were not specified, it was reported that a mother using oral ursodiol 250 mg three times day for primary biliary cirrhosis nursed her child normally.

Three weeks after giving birth, a lady with primary biliary cirrhosis experienced significant pruritus and increased serum bile acids. Over the course of the following 8 weeks, the dose of ursodiol was increased from 500 mg (7.5 mg/kg) to 1500 mg (25 mg/kg) daily. Her breastfed infant's psychomotor development was normal, and there were no obvious negative effects seen in the child.There were 8 patients who took ursodiol postpartum at doses of 13–15 mg/kg daily, according to a retrospective assessment of the medical records of pregnant patients at a hospital in Ankara, Turkey, who were diagnosed with primary biliary cirrhosis. The degree of most of the patients' breastfeeding is unmentioned. There were no adverse effects in infants.A lady breastfeeding her 8-day-old premature baby 10 times a day for approximately 15 minutes each. At 34 weeks gestation, the baby was delivered via c-section and weighed 3600 grams. Cholestasis, type 1 diabetes, and hypothyroidism were all identified in her. Levothyroxine, levemir, and 500 mg of ursodiol were used in her treatment. Additionally, she was taking coffee, acetaminophen, propyphenazone, flurbiprofen, and cefuroxime. The mother took flurbiprofen for 15 days, cefuroxime and the analgesic mixture for 10 days, and ursodiol for a total of 12 days. No side effects were observed while receiving ursodiol medication.

Ursodiol was being used daily by 20 nursing moms for cholestasis at doses ranging from 500 to 1500 mg or 13 to 15 mg/kg, depending on the situation. Three days after delivery, ursodiol was stopped. Early postnatal clinical examinations of newborn infants did not reveal any obvious adverse effects, and normal pediatric examinations conducted one year later did not reveal any regression in postnatal development.

TREATMENT OF OVERDOSE: [50-52]

Over the consequences and treatment of overdose administered by different routes.

1.Diarrhea is the only main symptom of overdose of Ursodeoxycholic acid. According to the symptoms the symptomatic treatment should be given.

•Ursodiol overdoses, whether unintentional or purposeful,have not been reported
•Ursodiol 10 g/kg for mice and dogs and 5 g/kg for rats was not deadly when administered orally in a single dosage.
•Ursodiol 1.5 g/kg given orally once was fatal to hamsters.
•Dogs exhibited salivation and vomiting as signs ofacute poisoning,while hamsters had ataxia,dyspnea,ptosis, agonal convulsions, and coma.

CONTRAINDICATIONS:

Ursodioxycholic acid is contraindicated if having allergy, stomach ulcer, intestinal ulcers or bleeding, liver disease, dysfunction of gallbladder and having bowel surgery of any part of it.

NOTE:-Do not take Ursodeoxycholic acid if you are **pregnant** or **breastfeeding** unless prescribed.

Ursodeoxycholic acid is contraindicated in following diseases:

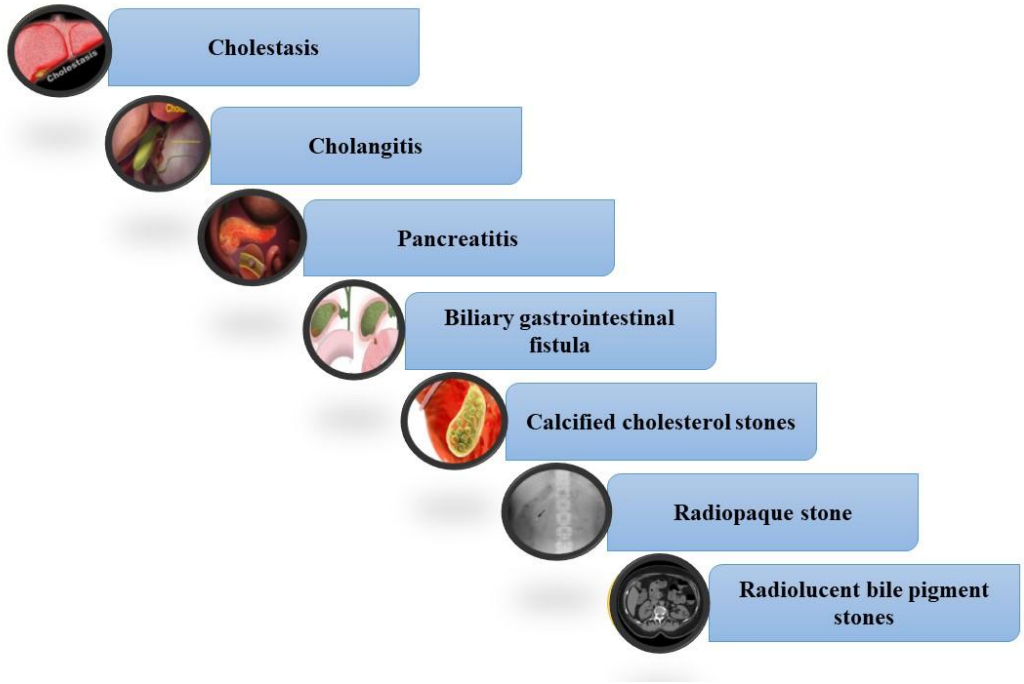

Fig. 1.4: Disease contraindicated with treatment of Ursodeoxycholic acid.

Cholestasis in infants:Ursodeoxycholic acid is not licensed for use in children. Its effectiveness and safety in the pediatric age group was never established. Ursodeoxycholic acid use in neonatal and infancy cholestasis was associated with more than double fold the risk of failure of resolution of cholestasis, and life threatening complications, liver cell failure and death.

Obstruction cholestasis:-Ursodeoxycholic acid is usually contraindicated in obstructive cholestasis, due to the alleged risk of biliary integrity disruption due to its choleretic effect.

- Cholangitis
- Pancreatitis
- Biliary gastrointestinal fistula
- Calcified cholesterol stones
- Radiopaque stone
- Radiolucent bile pigment stones

INTERACTION:

Drug-Drug interaction-

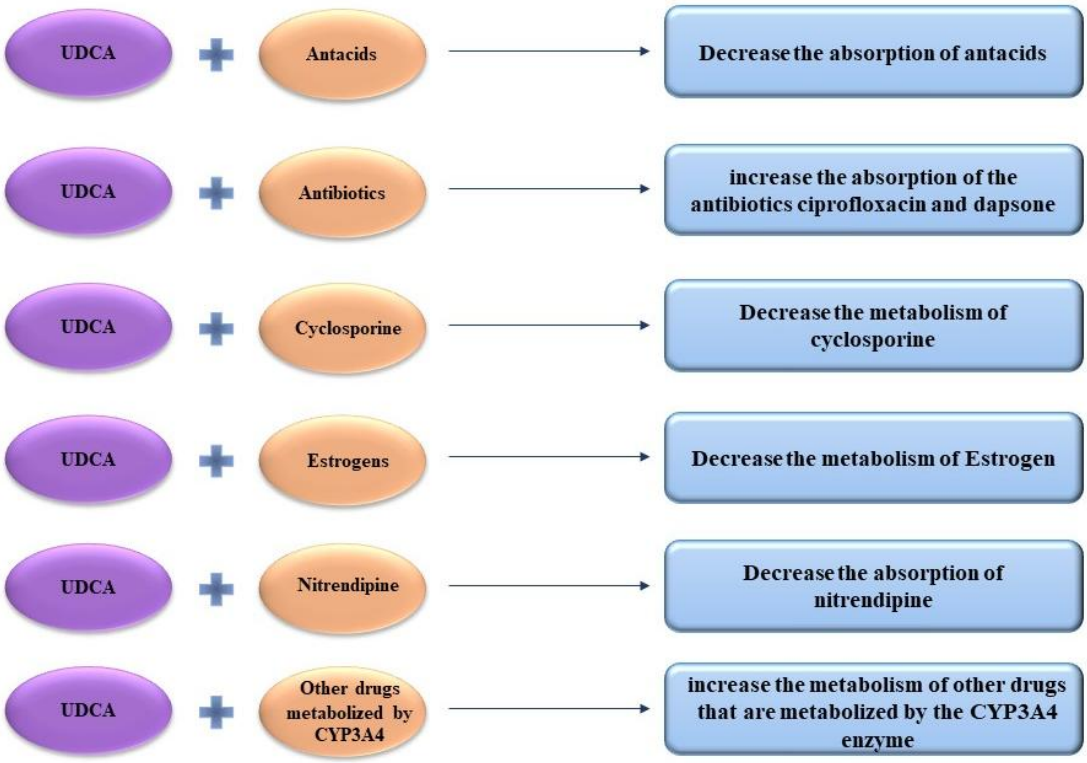

Fig. 1.5: interaction of Ursodeoxycholic acid with various drugs.

Antacids: Ursodeoxycholic acid can decrease the absorption of antacids, such as aluminum hydroxide, aluminum carbonate, and magaldrate. This can lead to decreased efficacy of the antacid.

Antibiotics: Ursodeoxycholic acid can increase the absorption of the antibiotics ciprofloxacin and dapsone. This can lead to increased levels of these antibiotics in the blood, which could increase the risk of side effects.

Cyclosporine: Ursodeoxycholic acid can decrease the metabolism of cyclosporine, an immunosuppressant drug. This can lead to increased levels of cyclosporine in the blood, which could increase the risk of side effects.

Estrogens: Ursodeoxycholic acid can decrease the metabolism of estrogens, such as ethinyl estradiol and norethindrone. This can lead to increased levels of estrogens in the blood, which could increase the risk of side effects such as breast cancer.

Nitrendipine: Ursodeoxycholic acid can decrease the absorption of nitrendipine, a calcium channel blocker. This can lead to decreased efficacy of nitrendipin.

Other drugs **metabolized by CYP3A4:** Ursodeoxycholic acid can increase the metabolism of other drugs that are metabolized by the CYP3A4 enzyme. This can lead to decreased levels of these drugs in the blood, which could decrease their efficacy.

Drug-food interactions-

No interaction found. Drug should be **taken with food**

Ursodeoxycholic acid can cause diarrhoea in some people. If you experience diarrhoea, you may need to reduce the dose or stop taking ursodeoxycholic acid together. Consult your physician.

Ursodeoxycholic acid may affect the results of some laboratory tests. Before having any blood or urine tests, be sure to let your doctor know if you are taking ursodeoxycholic acid

PATENTS: [53-55]

Sr.no.	Inventor	Invention	Year of grant	Year of Expiry
1	Chandanmal pukhraj BOTHRAN sv RAJUK and arapu RaghupathiR Srinivasan Maram SAMBASIVA RAO	Pharmaceutical compositions of ursodeoxycholic acid	2012	2032
2	Pradeep SHIVAKUMAR Purushothama NARASIYAPPA Kiran Kumar CHERUKURI	Injectable compositions of ursodeoxycholic acid	2020	2040
3	Massimo Ferrari Matteo Bonaldi Fabrizio Zinetti	Process for preparing ursodeoxycholic acid di-sodium 3,7-disulfate	2003	2023
4	Peter Ian Dosa (Vadnais Heights, MN), Clifford John Steer (Eagan, MN), Ingrid Gunda Georg (St. Paul, MN)	Water-soluble ursodeoxycholic acid prodrugs	2017	2037
5	Sawada, Haruji, Tokyo (JP) Taguchi, Hisaharu, Osaka (JP)	A method for producing ursodeoxycholic acid	1983	2003
6	Massimo Ferrari, Fabrizio Zinetti	Process for preparing high purity ursodeoxycholic acid	2012	2032
7.	-Antonio Bonaldi (Schilpario), Egidio Molinari (Erba)	Process for the purification of ursodeoxycholic acid	1982	2002
8.	Maria ENQUIST-NEWMAN (Radford, VA), Erin TOM (Radford, VA), Cleo HO (Radford, VA), Christopher SAVILE (Radford, VA) et al.	Cells and Methods for the Production of Ursodeoxycholic Acid and Precursors Thereof	2019	2039
9.	Tadakatsu MandaiHiroshi OkumotoKatsuyoshi NakanishiKoji HaraKatsuhiko MikuniKozo HaraTeruhiko	Ursodeoxycholic acid derivatives and methods for producing them	1998	2018
10.	Krishnamurthy TOPPALADODDI Pradeep SHIVAKUMAR Chaturvedi AKSHAY KANT	Dispersible tablet comprising ursodeoxycholic acid or its salts	2015	2035

CONCLUSION

In conclusion, it can be said that ursodeoxycholic acid is a promising new medication that has the potential to significantly enhance the lives of many liver disease patients. Currently, chemical synthesis is still the primary way for producing large quantities of ursodeoxycholic acid but this process is insufficient to satisfy market demand because of things like low yield, onerous procedures, and environmental unfriendliness. Ursodeoxycholic acid is considered to be safe for use in infants and pregnant women. There have been no long-term studies on the safety of Ursodioxycholic acid infants, but short-term studies have not shown any harmful effects. In pregnant women, ursodeoxycholic acid as been shown to be effective in treating intrahepatic cholestasis of pregnancy (ICP), a condition that can cause severe itching and other liver problems. Ursodeoxycholic acid s also thought to be safe for the fetus. Ursodeoxycholic acid is a potentially effective novel treatment for liver disease, but further research is required to evaluate its efficacy and safety.

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