UDCA, NorUDCA, and TUDCA in Liver Diseases: A Review of Their Mechanisms of Action and Clinical Applications

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Contents

Abstract

Bile acids (BAs) are key molecules in generating bile flow, which is an essential function of the liver. In the last decades, there have been great advances in the understanding of BA physiology, and new insights have emerged regarding the

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role of BAs in determining cell damage and death in several liver diseases. This new knowledge has helped to better delineate the pathophysiology of cholestasis and the adaptive responses of hepatocytes to cholestatic liver injury as well as of the mechanisms of injury of biliary epithelia. In this context, therapeutic approaches for liver diseases using hydrophilic BA (i.e., ursodeoxycholic acid, tauroursodeoxycholic, and, more recently, norursodeoxycholic acid), have been revamped. In the present review, we summarize current experimental and clinical data regarding these BAs and its role in the treatment of certain liver diseases.

Keywords
Bile acids · Bile flow · Cell injury · Cholestasis · Inflammation · Liver diseases · Signaling

1 Introduction

Bile acids (BAs) are amphipathic species composed of four steroid rings forming a hydrocarbon lattice having hydrophobic and hydrophilic regions, containing hydroxyl groups, within their structure (Hofmann and Hagey 2008; Hofmann 2009; Russell 2009). The balance between hydrophobic and hydrophilic characters varies markedly among different BAs, which account for differences in their biological properties including their choleretic potency, solubilization properties (Carey 1984), and activation of bile acid receptors (Monte et al. 2009; Hofmann and Hagey 2014). The number of hydroxyl groups (the hydrophilicity of a given bile acid is greater if the number of hydroxyl groups is higher) and its orientation (i.e., α or β orientation at position 3, 6, 7, and 12 on the steroid backbone) are critical in determining hydrophobicity (Carey 1984). Thus, while hydrophobic BAs (i.e., lithocholic acid (LCA), deoxycholic acid (DCA), chenodeoxycholic acid [CDCA], and cholic acid [CA]) are potent detergents, hydrophilic BAs (i.e., ursodeoxycholic acid [UDCA], tauroursodeoxycholic acid [TUDCA]) are not (Hofmann and Small 1967). More importantly, they lack membrane-disrupting properties being nontoxic to the liver cell even in high concentrations (Paumgartner and Beuers 2004; Ashby et al. 2018). This is relevant for the therapeutic use of hydrophilic BA in the treatment of liver diseases although a myriad of additional mechanisms may be at play (Arab et al. 2017a; Beuers et al. 1998; Lazaridis et al. 2001; Beuers 2006) particularly in the case of new semisynthetic bile acid derivatives such as 24-norursodeoxycholic acid (NorUDCA), which seem to exercise hepatoprotective actions by novel mechanisms (Halilbasic et al. 2017). In this chapter, we summarize current data on the mechanisms of actions underlying the beneficial effects of selected hydrophilic BA (Fig. 1) in liver diseases as well as the information on the present and future clinical applications of these compounds.

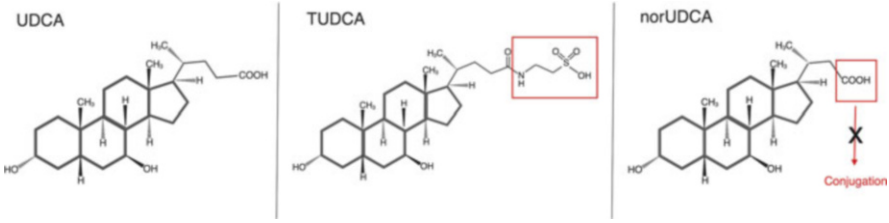

Fig. 1 Molecular structure of UDCA, TUDCA, and NorUDCA. Ursodeoxycholic (UDCA) is a hydrophilic dihydroxy (i.e., 3α,7β-dihydroxy-5β-cholan-24-oic acid) bile acid that represents 4% of bile acids in human bile. It likely originates in the colon by bacterial 7β epimerization of the primary bile acid chenodeoxycholic. The 17 carbon of UDCA may be amidated with glycine, which is the predominant pathway in humans, or with taurine, which is the predominant pathway in rodents. The taurine conjugate (TUDCA) has potent hepatoprotective actions. Norursodeoxycholic acid (NorUDCA) is a side chain-shortened (C23 instead of C25) synthetic bile acid with derivate from UDCA. NorUDCA is relatively resistant to amidation, which allow this compound to undergo cholehepatic shunting

2 Historical Remarks

The use of hydrophilic BA in the treatment of liver disease can be tracked back more than 1,000 years ago when ancient Chinese practitioners (Tang dynasty, 618–907 A.D.) discovered the therapeutic effects of bear bile in several conditions including chronic liver diseases (Hofmann and Hagey 2014; Marin et al. 2015; Li et al. 2016; Beuers et al. 2015a). Bear bile continues to be used until nowadays in some Asian countries where bile is obtained from farmed animals (Li et al. 2016), which poses some ethical issues considering the availability of alternative compounds (British Veterinary Association 2018).

In 1927, Shoda published his findings on a unique bile acid he found in bile of the Chinese black bear (Shoda 1927). This author named this bile acid as UDCA in reference to the Latin name of bear (ursus). Several years after, the structure of UDCA was better defined and the substance synthetized for its use in research (Lazaridis et al. 2001). Then in the 1950s, it was proposed that the beneficial effects of the bear bile were likely related to the high concentrations of the taurine-conjugated form of UDCA and TUDCA observed in that fluid (Li et al. 2016). Further research showed that UDCA and TUDCA were found to be potent choleretic agents when infused to rats (Hofmann and Hagey 2008; Makino and Tanaka 1998), and Japanese researches first investigated its use in chronic liver disease (Mijayi et al. 1976; Yamanaka et al. 1976). Later, in gallstone dissolution trials, the authors observed that, in contrast with chenodeoxycholic acid (CDCA), UDCA administration was not associated to liver toxicity (Ashby et al. 2018; Leuschner et al. 1985). For this reason, UDCA soon replaced CDCA for gallstone dissolution due to its similar efficacy and lack of hepatotoxicity (Paumgartner et al. 1994). With the advent of laparoscopic cholecystectomy, the use of BA for gallstone disease

decreased markedly, and interest in their biological properties and chemistry declined. It was in 1987 when the German hepatologist Ulrich Leuschner and coworkers (Leuschner and Kurtz 1987) reported beneficial effects of UDCA in patients with primary biliary cholangitis [PBC, a disease previously known as primary biliary cirrhosis (Beuers et al. 2015b)]. This, along with important advances made at the time in the understanding of the mechanisms at play in the generation and regulation of BA flux in the enterohepatic circulation (Blitzer and Boyer 1982; Coleman 1987), revamped the interest in the use of BA in the clinic. Subsequent studies by Poupon et al. (1987, 1991) and Lindor et al. (1994) paved the road to generate the evidence that support the routine use of UDCA as standard of care in PBC patients (Lindor et al. 2019; European Association for the Study of the Liver 2017). The use of UDCA in other cholestatic diseases although less evidence-based became common practice in the field of hepatology given the lack of toxicity of the drug.

After the journey that led UDCA to become an established drug in hepatology, studies with its taurine conjugate TUDCA have been conducted with similar results. However, in some basic and human studies, some differences were found (Setchell et al. 1996; Beuers et al. 1996), which led to new studies that derived in the potential use of TUDCA in neurodegenerative diseases (reviewed in Vang et al. 2014). More recently, considerable attention has been given to a parent compound of UDCA, norursodeoxycholic acid (NorUDCA), which is a side chain-shortened homologue of UDCA that is partially resistant to amidation, which theoretically enables its cholehepatic shunting (Halilbasic et al. 2017; Li and Lu 2018). This compound was developed after seminal work from Alan F. Hofmann in California (Schteingart and Hofmann 1988) whom confirmed the potent choleretic properties of NorUDCA (Hofmann et al. 2005) and predicted its clinical potential in cholestatic diseases. As described below, NorUDCA is a unique bile acid that has potential for treatment of several cholestatic and metabolic liver diseases. Studies with this bile acid as well as with other bile acid analogues have indeed represented an uptick in bile acid research, which opened new avenues for treatment of liver and biliary diseases.

3 Current Knowledge on the Mechanisms of Action of Hydrophilic Bile Acids in Liver and Biliary Diseases

An important body of information regarding the hepatoprotective and beneficial effects of hydrophilic BA on liver injury has been generated in the last three decades using different models of liver injury (Mariotti et al. 2018; Sharma et al. 2011). Also, research advances on the pathophysiology of cholestasis (Wagner and Trauner 2016; Jansen et al. 2017) and in the particular role of BA in determining cell injury (Perez and Briz 2009; Trauner et al. 2017) and death in both hepatocytes and cholangiocytes as well as in triggering an inflammatory response in the setting of cholestasis had led to a focused research on BA-mediated liver injury. This new knowledge had revamped bile acid-based therapeutic strategies for liver diseases (Arab et al. 2017a; Hegade et al. 2016). Although most of the available information

regarding the mechanisms underlying the hepatoprotective effects of hydrophilic BA has been tested in experimental models of cholestasis using either in vitro systems or whole animals (Mariotti et al. 2018, 2019), some of these hepatoprotective properties seem to operate also in other models of injury and eventually apply to metabolic diseases. In the following paragraphs, a brief summary of the importance of the hepatotoxicity of retained endogenous BA in cholestasis is provided as well as information on the particular features that explain the hepatoprotective properties of hydrophilic BA.

3.1 Core Concepts on Bile Acid Transport, Bile Acid-Induced Toxicity, and Hepatocellular Adaptive Responses in Cholestasis

The vectorial transport of BA by the hepatocytes involves several transport proteins and enzymes including the sinusoidal transporter sodium taurocholate cotransporting polypeptide (NTCP/SLC10A1), members of the anion transporting polypeptide (OATPs/SLCO) family, conjugation enzymes, and the ATP-dependent efflux pump BSEP (bile salt export pump [also known as ABCB11]) (Trauner and Boyer 2003; Halilbasic et al. 2013). These proteins allow a rapid transition of BA from blood to bile and maintain a low intracellular BA concentration (estimated in the micromolar range). This is crucial to maintain hepatocyte integrity as BAs are signaling and detergent molecules that at higher concentration ($\geq$50 μM or mM concentrations) may cause apoptosis, activate pro-inflammatory genes, and eventually induce cellular necrosis (Jansen et al. 2017; Li et al. 2017a; Woolbright and Jaeschke 2016). This inherent cytotoxicity of BA plays a role in liver damage in cholestatic conditions where bile secretion is impaired and BA accumulate inside hepatocytes and, in the case of cholangiopathies, leak into the surrounding tissue due to injury of bile ducts (Jansen et al. 2017). Of note, in the cholestatic setting, changes in the expression of hepatobiliary transporters occur that may represent a compensatory response aiming to limit the accumulation of potentially toxic biliary constituents (Arrese and Trauner 2003). These changes include downregulation of BA uptake, downregulation of BA synthesis, and upregulation of BA excretion through increased BSEP or transporters able to provide alternative excretory routes (Wagner et al. 2010; Arrese and Karpen 2010). These adaptive responses are mediated by the activation of several nuclear receptors such as farnesoid X receptor (FXR), pregnane X receptor (PXR), Constitutive Androstane Receptor (CAR), and the small heterodimer partner (SHP) as well as by entero-hormones such as Fibroblast growth factor 19 (FGF19), which is produced in the ileum and also in hepatocytes (in humans) (Halilbasic et al. 2013; Arrese and Karpen 2010). FXR is a major player and is a dedicated BA receptor that influences a myriad of pathways both in hepatocytes and in other resident cells such as Kupffer, endothelial, and hepatic stellate cells (Matsubara et al. 2013). In hepatocytes in particular, upon upregulation of SHP, FXR mediates a downregulation of NTCP and of cholesterol 7α-hydroxylase (CYP7A1), a key enzyme in BA synthesis. FXR also directly

upregulates BSEP, thus promoting BA excretion (Halilbasic et al. 2013). In humans, but not in mice, hepatic production of FGF-19 may also play a role in down-regulating CYP7A1 (Jansen et al. 2012). Finally, alternative excretory transport proteins located at the basolateral membrane of hepatocytes (i.e. the heteromeric transporter Organic solute transporter α-β [OST-α-β] and the ABC transporters MRP3, and MRP4) that are expressed at low levels in physiological conditions become upregulated during cholestasis (Halilbasic et al. 2013). Thus, if BA secretion is impaired, adaptive responses may limit BA accumulation inside hepatocytes, thus preventing hepatocellular damage. If these responses are insufficient, cell damage and death may occur either by apoptosis or necrosis (Woolbright and Jaeschke 2016). Of note, it has been shown that cholestatic hepatocytes can trigger hepatocyte-specific inflammatory response that involves increased expression of cytokines such as C-C Motif Chemokine Ligand 2 (CCL2), Chemokine (C-X-C motif) ligand 2 (CXCL2), and Interleukin 8 (IL-8) that in turn can contribute to neutrophil recruitment and augment local inflammation (Li et al. 2017a; Cai et al. 2017). This response is partially dependent on activation of toll-like receptor-9 presumably by BA-induced mitochondrial damage and the release of mitochondrial DNA (Cai et al. 2017). In addition to the local inflammation promoted by BA in other scenarios such as in cholangiopathies or bile duct diseases, mechanical obstruction leads to increased biliary pressure and the occurrence of biliary infarcts and the leak of BA and other biliary constituents into surrounding tissue that may activate proliferative reactions and hepatic fibrogenesis leading to disease progression and ultimately to cirrhosis (Jansen et al. 2017).

3.2 Bile Acids and Cholangiocytes in Cholestasis

Advances in the pathobiology of biliary epithelia have also been significant in the last two decades (Cheung et al. 2017; Han et al. 2013; Banales et al. 2019). Cholangiocytes, the epithelial cells lining the intra- and extrahepatic biliary tree, are heterogeneous polarized cells that contain a significant amount of transport proteins that allow the secretion of large amounts of bicarbonate (via the Cl^-/HCO_3^- exchanger (anion exchanger 2 [AE2])), water (through aquaporin-1 [AQP-1]), and chloride (through the low conductance cystic fibrosis transmembrane conductance regulator [CFTR]) that enrich canalicular bile and contribute to regulate biliary pH, which is important for activation of pancreatic enzymes and the absorption of lipophilic organic compounds. Cholangiocytes also express BA transporters (the apical sodium-dependent bile acid transporter [ASBT] is present in the apical membrane, and a truncated form of the same transporter [referred to as t-Asbt] is located at basolateral membrane of cholangiocytes) that allow for reabsorption of conjugated BA. It is important to note that cholangiocytes exhibit morphological, biochemical, and functional heterogeneity throughout the biliary system (i.e., from small to large bile ducts) with different cellular processes taking place at different locations of the biliary tree (Banales et al. 2019). Also, passive absorption of protonated unconjugated BA can occur. The reuptake of BA in cholangiocytes

followed by re-secretion into the blood of peribiliary plexuses is referred as the "cholehepatic shunt pathway," which leads to BA return to hepatocytes for re-secretion into bile augmenting its choleretic action. Finally, some in vitro and in vivo evidence suggest that biliary BA concentration and composition may eventually regulate some cholangiocyte functions by activating differing signaling pathways and (i.e., calcium protein kinase C [PKC], phosphoinositide 3-kinase [PI3K], mitogen-activated protein [MAP] kinase, and extracellular signal-regulated protein kinase [ERK], among others), thus inducing changes in cholangiocyte secretion, proliferation, and survival. It has been also shown that cholangiocyte proliferation is critically dependent of the BA receptor TGR5, which is located in the cholangiocyte cilia.

Cholangiocyte injury is a key phenomenon in certain cholestatic diseases, and therefore aspects related to cholangiocyte responses to injury are also of importance to the understanding of cholestasis pathophysiology and treatment (Banales et al. 2019; Sato et al. 2018). When injured, cholangiocytes respond acquiring a neuroendocrine phenotype and, in response to a myriad of stimuli, proliferate leading to bile duct hyperplasia, which is a common histological hallmark of cholestatic diseases (Cheung et al. 2017). Injury of biliary cells can be immune-mediated, toxically induced, or related to mechanical factors (i.e., biliary obstruction). In all these settings, direct cytotoxicity of BA could play a role as increased luminal BA can damage cholangiocyte membrane, induce autophagy, and promote cellular senescence, which is associated to secretion of pro-inflammatory and pro-fibrotic signals (Cheung et al. 2017; Xia et al. 2006). Bicarbonate secretion and the existence of an intact cholangiocyte glycocalyx have been hypothesized to form a "bicarbonate umbrella" that prevents protonation of biliary BA and cellular damage by bile acid monomers (Beuers et al. 2015a; Hohenester et al. 2012).

3.3 Mechanisms Underlying the Hepatoprotective Properties of Hydrophilic Bile Acids

Based on the information summarized above, strategies that have been exploited (Beuers et al. 2015a; Wagner and Trauner 2016; Trauner et al. 2017) therapeutically for cholestatic diseases include the following: (a) to limit BA injury through modulation of BA pool hydrophobicity or reducing bile acid pool size by interfering with intestinal bile acid absorption, (b) to induce choleresis to deload hepatocytes from BA and to limit cholangiocyte damage, and (c) to modulate inflammation. Hydrophilic BA can exercise some of these functions, which explain their usefulness in liver diseases (Figs. 2 and 3). Their effects on the hepatobiliary system are summarized below.

3.3.1 UDCA and TUDCA

UDCA (3α,7β-dihydroxy-5β-cholanoic acid) is normally present in human bile, amounting to 1–3% of biliary BA (Marin et al. 2015). In physiological conditions most of the UDCA is conjugated with glycine, which is the preferred amidation

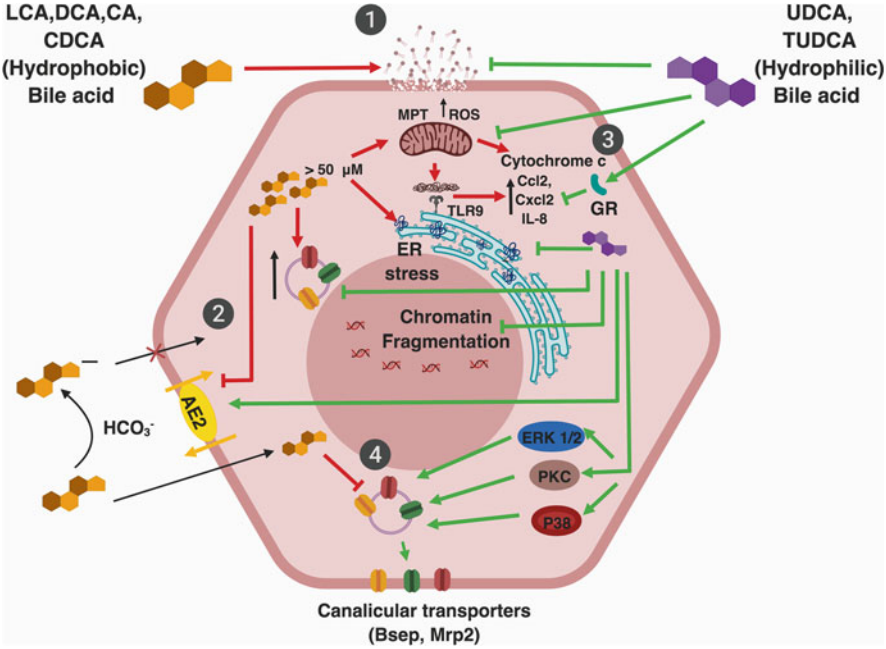

Fig. 2 Overview of the main hepatoprotective mechanisms of action of UDCA and TUDCA. In cholestasis, hydrophobic bile acids induce many cellular changes that can be counteracted by hydrophilic bile acids such as UDCA and TUDCA. (1) Hydrophobic bile acids are strong detergents that can cause membrane disruption by lipid solubilization, while hydrophilic bile acids like UDCA can bind to the apolar domain of cell membranes, stabilizing its molecular structure. (2) Bicarbonate secretion by hepatocytes and cholangiocytes has protective action against the detergent effects of hydrophobic bile acids. Treatment with hydrophilic bile acids induces bicarbonate secretion by several mechanisms including increasing of the anion exchanger 2 [AE2] expression. AE2 exchanges chloride by bicarbonate in both hepatocytes and cholangiocytes. (3) Hydrophilic bile acids can also inhibit apoptotic signaling pathways at the level of mitochondria or indirectly through anti-inflammatory effects by binding the glucocorticoid receptor (GR) and counteracting the pro-inflammatory effects of bile acids, which are mediated by toll-like receptor 9 (TLR9). (4) Cholestasis induces endocytic internalization of canalicular transporters, like the bile salt export pump (BSEP) and the multidrug resistance-associated protein 2 (MRP2). Treatment with hydrophilic bile acids increases the translocation of transporters such as BSEP and MRP2 into the canalicular membrane

pathway in humans (Hofmann 2009). Oral administration of UDCA is able to enrich the biliary bile acid pool with this hydrophilic bile acid up to 40% of biliary BAs (Rost et al. 2004; Dilger et al. 2012), which is thought to decrease BA pool hydrophobicity and therefore reduce its hepatotoxic effects if hepatocyte BA retention occurs. This was thought to be central to the effects of UDCA in cholestatic diseases given the role of hepatic retention of hydrophobic bile acids as a major cause of liver damage, by inducing membrane damage, necrosis, and apoptosis, in this setting (Wagner and Trauner 2016; Arrese and Trauner 2003). However, one

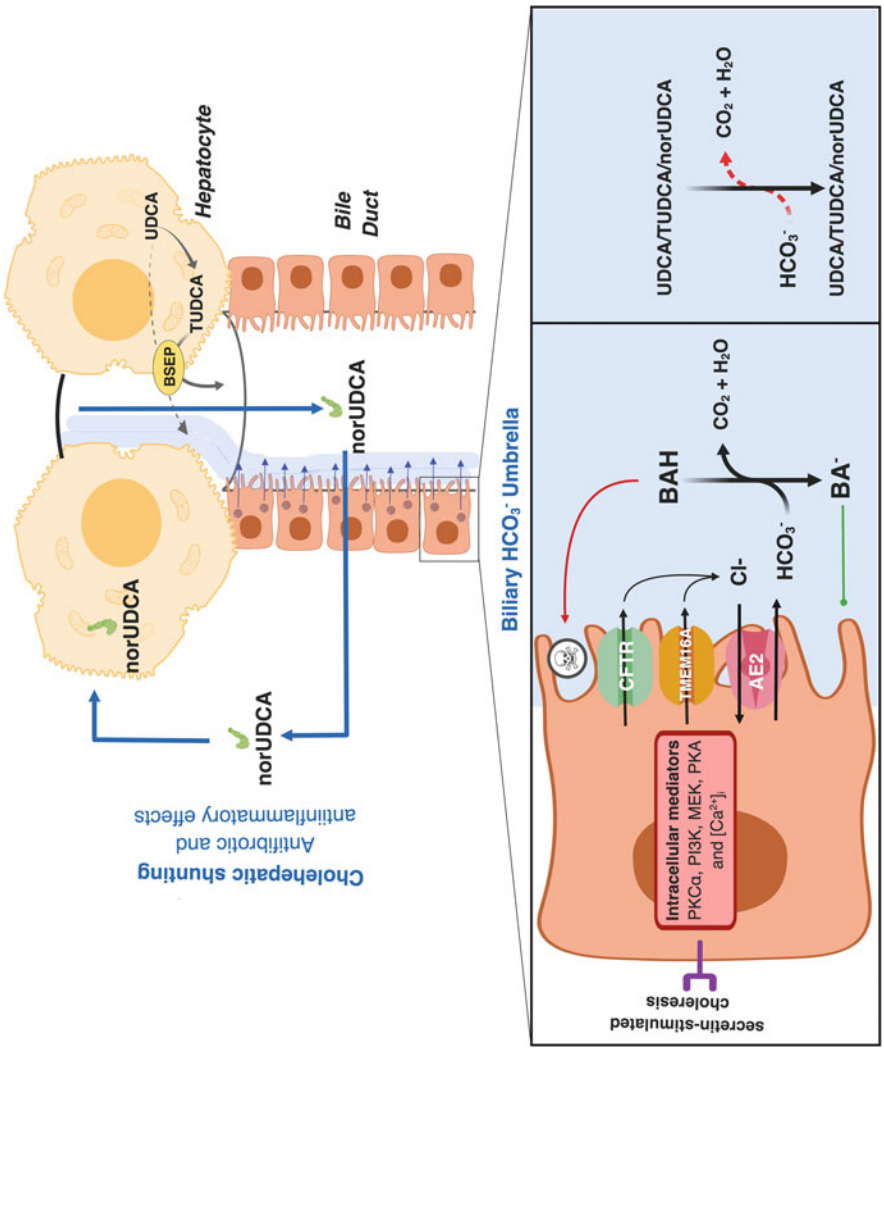

Fig. 3 The biliary HCO_3^- umbrella hypothesis and the hepatoprotective actions of TUDCA, UDCA, and NorUDCA. Hydrophobic bile acids are toxic to cholangiocytes, inducing senescence, endoplasmic reticulum stress, autophagy, and cell death. These effects are counteracted by bicarbonate secretion via the

Fig. 3 (continued) Cl^-/HCO_3^- anion exchanger 2 [AE2] in hepatocytes and cholangiocytes and likely also by transmembrane member 16A (TMEM16A) in cholangiocytes. UDCA, TUDCA, and NorUDCA have been observed to have protective effects in the liver by preventing bicarbonate depletion on the apical side of cholangiocytes, thus exercising cytoprotective effects. Particularly, NorUDCA, due to its resistance to amidation, can undergo cholehepatic shunting and potently promote bicarbonate secretion into the bile duct. Although most of the UDCA is secreted as a glycine conjugate in humans, taurine conjugation predominates in rodents. Secretion of TUDCA is mediated by the canalicular bile salt export pump (BSEP)

report (Beuers et al. 1992) showing that hydrophobic BA pool sizes remained stable during short treatment with UDCA suggests that this would not be the major mechanism of action of the drug. Rather, UDCA-induced signaling changes in hepatocytes that modulate relevant pathways for hepatobiliary secretion, cellular stress, and apoptosis would underlie the hepatoprotective effects of UDCA (Beuers et al. 2015a). Of note, UDCA seems to exert its beneficial effects mainly at the level of hepatocytes and cholangiocytes. Additional effects may be related to some actions at the intestinal level since amidated forms of UDCA inhibit gut absorption of endogenous bile acids (Lanzini et al. 2003). The multiple mechanisms of action described for UDCA (reviewed in depth in refs. Beuers 2006; Beuers et al. 2015a) are delineated below.

Actions of UDCA/TUDCA in Hepatocytes

Most of the data regarding the effects of UDCA in the liver has been generated using the nonconjugated form as well as its taurine conjugate TUDCA with few differences between them. At the level of hepatocytes, UDCA has been shown to stimulate bile flow as well as the secretion of organic anions (Beuers 2006). Early studies with continuous intravenous infusion of TUDCA in whole animals (Kitani and Kanai 1981, 1982) and perfused rat livers (Beuers et al. 1993a) showed that the UDCA induced higher flow rate and higher total bile salt secretion than taurocholate. Further studies suggested that UDCA-induced choleresis is attained through post-transcriptional actions that lead to increased insertion of transporters such as BSEP and MRP2 into the canalicular membrane (Kurz et al. 2001; Beuers et al. 2001) and stimulation of hepatic bicarbonate secretion, which stimulates the secretion of an alkaline bile (Takikawa et al. 1992). Some of these effects may be related to a potent stimulation of intracellular Ca2+ signaling (Beuers et al. 1993a, b) and other pathways such as that of protein kinase C (cPKCa) (Beuers et al. 1996; Stravitz et al. 1996), mitogen-activated protein kinases (MAPK, Erk1/2, p38MAPK), and alpha-5-beta-1 integrins in hepatocytes (Haussinger and Kordes 2017). Importantly, the effect of UDCA on hepatic transport protein expression in vivo is rather modest stressing the relevance of posttranscriptional effects of UDCA as responsible of some of its beneficial effects in the liver (Fickert et al. 2001). Of note, it has been also shown that UDCA also prevents the endocytic internalization of canalicular transporters, a common feature in cholestasis (Roma et al. 2011). Finally, it must be kept in mind that all the abovementioned effects have been shown only in experimental models and is uncertain to which extent they operate in humans (Beuers et al. 2015a).

Other important mechanism by which UDCA is hepatoprotective is related to its antiapoptotic activity. Cellular toxicity of BA is in part related to apoptosis induction, and UDCA and TUDCA have been shown to inhibit classic pathways of apoptosis (Amaral et al. 2009; Azzaroli et al. 2002; Benz et al. 1998; Rodrigues and Steer 2001). Using primary rat hepatocytes and HUH-7 hepatoma cell lines, Rodrigues et al. showed that, in contrast to DCA, UDCA is innocuous in terms of apoptosis induction (Rodrigues et al. 1998a). When the two bile acids were combined in the diet, UDCA completely inhibited cell death by apoptosis associated with

the hydrophobic bile acid alone. UDCA can abolish typical morphological changes of apoptotic nuclei like nuclear fragmentation of condensed chromatin. Also, UDCA has been shown to inhibit apoptosis induction driven by ethanol, TGF-β1, FAS ligands, and okadaic acid (a robust apoptotic stimulus) suggesting a ubiquitous antiapoptotic effect of UDCA (Amaral et al. 2009). Additional reports have shown that UDCA markedly reduces mitochondrial release of cytochrome c into the cytoplasm, in liver cells treated with hydrophobic BA by inhibition of both channel-forming activity and depolarization of the mitochondrial membrane (Rodrigues et al. 1998a, 1999). These findings support the concept that UDCA can modulate the apoptotic threshold by its protective role over mitochondrial membrane perturbation (Rodrigues et al. 1998a, b). In addition, activation of survival pathways such as p38, ERK, MAPK, and PI3K pathways has been also demonstrated in vitro (Schoemaker et al. 2004). Finally, it has been described that UDCA and TUDCA also attenuate endoplasmic reticulum stress by acting as cellular chaperones (Ozcan et al. 2006), which may also account for the antiapoptotic effects of these BA. Of note, the antiapoptotic properties of UDCA and its taurine conjugate TUDCA have been demonstrated also in other cell types particularly in neurons (Abdelkader et al. 2016). These effects are currently being explored with therapeutic purposes in some neurodegenerative diseases such as Parkinson's diseases and lateral amyotrophic sclerosis (Vang et al. 2014; Abdelkader et al. 2016; Castro-Caldas et al. 2012; Elia et al. 2016).

In addition to its effects on hepatobiliary transport capacity and to its antiapoptotic properties, existing data also support some action on oxidative injury as well as membrane stabilization and anti-inflammatory effects. Mitsuyoshi et al. assessed the effects of UDCA on oxidative injury and antioxidative systems in cultured rat hepatocytes. They found that UDCA significantly prevented cellular damage after hydrogen peroxide or cadmium challenge (Mitsuyoshi et al. 1999). UDCA also increased the amounts of glutathione (GSH) and thiol-containing proteins as well as the mRNA levels of γ-glutamylcysteine synthetase suggesting hepatoprotective effects against oxidative injury. With regard to membrane stabilization, experimental in vitro data from Guldutuna et al. proposed that UDCA can bind to the apolar domain of cell membranes stabilizing its structure and avoiding the lipid solubilization induced by hydrophobic BA such as CDCA (Guldutuna et al. 1993). More recent evidence suggest that UDCA prevents damaging effects of hydrophobic BA only in the presence of membrane cholesterol (Zhou et al. 2009). Finally, UDCA has been described as a ligand of glucocorticoid receptor, which could be related to an anti-inflammatory effect (Tanaka and Makino 1992; Miura et al. 2001), and has been postulated to have some immunomodulatory effects (Yoshikawa et al. 1992). The relevance of the UDCA actions described above remains unclear in the human setting.

Actions of UDCA/TUDCA in Cholangiocytes

As mentioned earlier, cholangiocyte injury is a key phenomenon in certain cholestatic diseases contributing to local inflammation and fibrosis development (Sato et al. 2019; Fabris et al. 2017). Among the phenomena involved in cholangiocyte damage in

cholangiopathies are direct effects of hydrophobic bile acids on cell membrane, activation of autophagy, and induction of senescence as well as induction of endoplasmic reticulum stress and immune-mediated injury (Banales et al. 2019; Sasaki and Nakanuma 2017). Clinical and experimental data indicates that UDCA may act modulating these phenomena. Current concepts are summarized below.

Several authors have pointed to the importance of bicarbonate secretion for the protection of cholangiocytes against the damaging effect of protonated BA present in bile. Conceptually, bicarbonate secretion increases biliary pH and determines a shift of BA toward ionized forms, thus decreasing their ability to diffuse and reducing their cytotoxic effects (Banales et al. 2019). This concept has been stated as the "biliary bicarbonate umbrella hypothesis" (Hohenester et al. 2012; van Niekerk et al. 2018), which is thought to be defective in cholangiopathies such as PBC (Rodrigues et al. 2018). Biliary bicarbonate secretion is carried out by AE2 (SLC4A2), which is expressed in the apical membrane of cholangiocytes and depends on active chloride secretion by these cells. Of note, both messenger RNA and protein levels of AE2 as well as biliary bicarbonate secretion are reduced in PBC, a prototypic cholestatic disease (Prieto et al. 1993, 1999). UDCA treatment determines increased fluid secretion from cholangiocytes as well as increases biliary bicarbonate secretion via activation of [AE2] and also transmembrane member 16A (TMEM16A) (Fiorotto et al. 2007; Li et al. 2018). Also, UDCA restores cholestasis-associated reduced AE2 mRNA and protein expression, which is thought to be an important mechanism of action of UDCA in cholangiopathies. Importantly, recent evidence suggests that dysregulated autophagy and cholangiocyte senescence in PBC may also be related to a defective biliary bicarbonate umbrella since AE2 knockdown evokes these phenomena in biliary cells (Sasaki et al. 2018). Additional effects of UDCA in cholangiocytes include restoration of secretin-stimulated choleresis via multiple mediators (i.e., AE2, PKCα, PI3K, MEK, PKA, and intracellular Ca2+) (Uriz et al. 2011; Jones et al. 2015). More recently, two new players have been added to the list of potential mediators of the beneficial effects of UDCA in cholangiocytes. On one hand, a recent study showed that the bile acid sensitive ion channel (BASIC), which is highly expressed in cholangiocytes, is strongly activated by UDCA (Wiemuth et al. 2013). On the other hand, Li et al. recently show that both UDCA and TUDCA stimulate Cl_2 secretion through activation of TMEM16A, which is thought to be, instead of CFTR, the dominant Cl_2 channel regulating anion efflux in biliary epithelia (Li et al. 2018). While further studies are needed to better determine the role and cellular activities of these channels, the abovementioned studies suggest that the therapeutic effects provided by UDCA might be related to modulation of their channel activities.

Effects of UDCA on Gut Microbiome

Information on the role of microbiome in chronic liver disease has surged in recent years (Wahlstrom 2019), but the existence of many confounders in available studies makes clear conclusions difficult to reach. Indeed, there is a close and bidirectional interplay between BA metabolism and the gut microbiota, and cholestasis may alter intestinal bacterial populations. Recent studies have explored the effects of UDCA

on gut microbiome composition in healthy subjects and also in individuals with liver dysfunction (Kim et al. 2018; Pearson et al. 2019). Interestingly, UDCA influenced bacterial populations inducing marked decrease in abundance of *Bifidobacterium*, *Lactobacillus*, and *Lactobacillaceae* (Kim et al. 2018). It remains to be determined if these effects have any relevance for the therapeutic action of UDCA. One interesting recent study showed that the absence of the intestinal microbiota results in exacerbation of liver injury in a murine model of primary sclerosing cholangitis (PSC), the *mdr2−/−* mice (Tabibian et al. 2016). This genetically engineered mouse is deficient of the canalicular transporter of phospholipid and has very low levels of biliary phosphatidylcholine, which results in biliary injury. The biliary alterations of this experimental model are similar to that observed in PSC (Mariotti et al. 2019). In the study by Tabibian et al. (2016), germ-free *mdr2−/−* mice exhibited significantly worse liver chemistry and histological lesions than conventionally housed mice underscoring the importance of commensal microbiota in protecting against biliary damage.

Few studies have analyzed the gut microbiome in cholestatic diseases (Quigley 2016; Li et al. 2017b). Of note, a significant reduction of within-individual microbial diversity has been found in PBC (Tang et al. 2018a), which is partially relieved by UDCA administration. Similarly, reduced diversity and significant shifts in the microbiome composition have been found in stool samples from PSC patients (Kummen et al. 2017), but it is unclear if they are primary or secondary to the bile secretory failure present in cholestatic disorders.

3.3.2 NorUDCA

As mentioned earlier, 24-norursodeoxycholic (NorUDCA) is a non-amidated, side chain-shortened C23 derivative of UDCA that in virtue of its relative resistance to amidation undergoes biliohepatic shunting being a potent choleretic compound due to the amplification of its effect on bicarbonate secretion by cholangiocytes (Halilbasic et al. 2017; Trauner et al. 2015; Yoon et al. 1986). NorUDCA has been shown to have profound beneficial effects in experimental models of biliary injury particularly in the *mdr2−/−* mice. In this mouse model, NorUDCA exercise marked beneficial effects by reducing injury and biliary fibrosis (Halilbasic et al. 2009; Fickert et al. 2006). It is thought that the lack of biliary phospholipid facilitates cholangiocyte injury by hydrophobic BA and that this phenomenon is counteracted by a bicarbonate-rich bile induced by NorUDCA administration (Halilbasic et al. 2017). Of note, biliary bicarbonate enrichment induced by NorUDCA is much stronger than its parent compound UDCA (Trauner et al. 2017). In addition to the induction of bicarbonate-rich bile, NorUDCA seems to have some relevant immunological actions since it has been shown that it is able to affect antigen presentation and inhibit T-lymphocyte proliferation in a mouse model of schistosomiasis (Sombetzki et al. 2015). Also, antifibrotic effects have been described in the thioacetamide-induced liver fibrosis rat model (Buko et al. 2014) although the underlying mechanisms are unclear.

Table 1 Current therapeutic uses of hydrophilic bile acids in liver diseases

Efficacy established	Efficacy likely	Efficacy uncertain
UDCA/TUDCA for primary biliary cholangitis UDCA for cholesterol gallstone dissolution UDCA for cholestasis of pregnancy	UDCA for prevention of gallstones after bariatric surgery UDCA for low phospholipid-associated cholelithiasis UDCA for progressive familial intrahepatic cholestasis type 3 UDCA to prevent liver disease in cystic fibrosis UDCA to prevent hepatic injury after stem cell transplantation NorUDCA for primary sclerosing cholangitis	UDCA for drug-induced cholestatic liver injury UDCA to prevent total parenteral nutrition-induced cholestasis UDCA for primary sclerosing cholangitis UDCA and NorUDCA for NAFLD/NASH

UDCA ursodeoxycholic acid, *TUDCA* tauroursodeoxycholic acid, *NorUDCA* norursodeoxycholic acid, *NAFLD/NASH* nonalcoholic fatty liver disease/nonalcoholic steatohepatitis

4 Clinical Applications of Hydrophilic Bile Acids in Liver and Biliary Diseases: Current Status and Perspectives

Hydrophilic BA has been studied in different liver diseases. While ample evidence is available for UDCA, the amount of studies carried out with TUDCA and NorUDCA are less abundant. As shown in Table 1, there are settings in which these drugs can be considered clinically useful and other that await further confirmation. A summary of current data is provided below.

4.1 Efficacy Established

Several clinical uses of UDCA or its taurine conjugate have been proven in prospective clinical trials. This prerequisite is met for PBC, cholesterol gallstone disease, and intrahepatic cholestasis of pregnancy.

UDCA/TUDCA for PBC After the seminal reports of the effects of UDCA on liver test in patients with PBC (Leuschner and Kurtz 1987), most of the reports published confirmed the positive effects on liver markers of cholestasis particularly on serum alkaline phosphatase levels, which is currently considered a surrogate marker of outcomes in patients with PBC (Lammers et al. 2014). However, the utility of UDCA in PBC remained a matter of debate due to the lack of evidence of efficacy on hard end points (i.e., survival or liver transplantation (LT)-free survival). To prove benefit on these outcomes remained difficult due to the long natural history of the disease and the lack of power of studies that include small number of patients as well as patients with different disease stages. The latter is relevant as patients with

earlier histologic stage may respond better to UDCA than patients with more advanced disease stage (Ali et al. 2017).

Although analysis of pooled cohorts of treated patients comparing outcomes with the predicted survival by mathematical models suggested that UDCA prolonged LT-free survival (Lindor et al. 1994; Poupon et al. 1997), several meta-analysis, including a recent report of the Cochrane hepatobiliary group, concluded that there is no demonstrated benefit of UDCA on LT-free survival and/or mortality (Saffioti et al. 2017; Goulis et al. 1999). In spite of that, UDCA at a dose of 13–15 mg/kg/day is the recommended first-line treatment of PBC in current guidelines (Lindor et al. 2019; European Association for the Study of the Liver 2017) based on indirect evidence that the drug slows disease progression and reduces the need of LT (Lindor et al. 2019). Response is monitored using serum alkaline phosphatase levels, and those patients that reduce this parameter significantly (greater than 25% of the basal level) are considered responders with a complete response defined as normalization of serum alkaline phosphatase levels (Pares et al. 2000). Several other criteria for response have been published and validated (Ali et al. 2017). A more recent study from the Global PBC Study Group database including data from 3,902 patients confirmed that UDCA confers a survival benefit for PBC patients even for patients with incomplete response (Harms et al. 2019). These findings provide further support to the use of UDCA as standard medical therapy for PBC.

Most of the clinical studies carried out with UDCA have used the unconjugated form of the drug, which undergoes extensive conjugation primarily with glycine, before being excreted into bile (Crosignani et al. 1996). The use of the taurine-conjugated form of UDCA has been less common although, theoretically, it could have some potential advantages related to a greater hydrophilicity and reduced biotransformation to more hydrophobic metabolites (Setchell et al. 1996; Invernizzi et al. 1999). A recent study from China shows that TUDCA is equally safe and efficacious as UDCA with regard to its effects on serum levels of alkaline phosphatase in patients with PBC (Ma et al. 2016).

UDCA and TUDCA for Cholesterol Gallstone Disease Before the introduction of laparoscopic cholecystectomy, several nonsurgical treatments of gallstone disease were attempted. In the 1970s, it was demonstrated that BA could promote the dissolution of gallstones, and oral dissolution therapy using both CDCA and UDCA was studied in prospective clinical trials (Bell et al. 1972; Portincasa et al. 2012; Danzinger et al. 1972). UDCA became the drug of choice for this purpose since several studies demonstrated higher efficacy than CDCA in decreasing biliary cholesterol saturation as well as fewer side effects such as diarrhea or elevations of serum aminotransferases (Stiehl et al. 1978; Mok et al. 1974). At present time less than 10% of total patients are considered for gallstone dissolution therapy with UDCA (Portincasa et al. 2012) that can be suggested for symptomatic gallstone patients who are not eligible for surgery and have small (<5 mm in size), radiolucent stones in a functioning gallbladder with a patent cystic duct (Paumgartner et al. 1994). TUDCA is thought to be equally effective than UDCA for gallstone dissolution (Portincasa et al. 2012).

UDCA for Cholestasis of Pregnancy (ICP) Being a pregnancy-specific disorders, ICP occurs mainly in the third trimester of pregnancy and is characterized by pruritus and elevated bile acid levels with few cases developing jaundice (Arrese and Reyes 2006; Wood et al. 2018). The disease usually improves spontaneously after delivery (Wood et al. 2018). ICP is regarded as a benign disease with no meaningful consequences to the mother but associated to an increased perinatal risk with increased rates of fetal morbidity and mortality. The pathogenesis of the disease is unknown but likely involves a genetic hypersensitivity to estrogen or estrogen metabolites. Mutations or polymorphisms of some hepatobiliary transport proteins may contribute to disease pathogenesis or severity (Arrese et al. 2008). In addition to an adequate obstetric management to prevent fetal distress, UDCA is recommended to treat ICP. This is based on several prospective studies (Bacq et al. 2012; Palma et al. 1997) that showed beneficial effects on liver function test and resolution or improvement of pruritus in a significant proportion of patients (Bacq et al. 2012, 2017). Although the benefit of UDCA for reducing stillbirth in ICP remains unproven, its use as first-line therapy in ICP is recommended in current guidelines (Bicocca et al. 2018).

4.2 Efficacy Likely

Available studies suggest that the use of hydrophilic BA is likely effective in several other than the abovementioned diseases (Table 1). This is based on large clinical series and early clinical phase trials or inference from the observed effects of UDCA in other diseases. Evidence supporting these clinical uses are summarized below.

UDCA for Prevention of Gallstones After Rapid Weight Loss or Bariatric Surgery Based on the proven efficacy of UDCA in gallstone dissolution, its use in the prevention of gallstone formation in several clinical settings where bile become transiently lithogenic has been advocated. Among these conditions the effect of UDCA in prevention of gallstone disease after rapid weight loss and after bariatric surgery has been studied in formal clinical trials. Rapid weight loss (>1.5 kg/week) induces a supersaturated bile and determines gallstone formation in up to one third of bariatric surgery patients (Guzman et al. 2019). Updated meta-analysis suggests that UDCA administration significantly reduces gallstone formation in the setting of rapid weight loss induced either by very-low-calorie diets (Stokes et al. 2014) or bariatric surgery (Magouliotis et al. 2017) being a well-tolerated and safe medication. Thus, although the quality of evidence is moderate, administration of 500–600 mg of UDCA may be recommended during periods of rapid weight loss until body weight has stabilized. In the case of bariatric surgery, a period of 6 months after the surgical procedure is suggested (Magouliotis et al. 2017; European Association for the Study of the Liver 2016).

UDCA for Low Phospholipid-Associated Cholelithiasis (LPAC) LPAC is a rare condition characterized by low biliary phospholipid concentration, which

determines the occurrence of symptomatic and recurring cholelithiasis. This occurs usually before the age of 40 years with frequent concomitancy of intrahepatic bile duct and gallbladder cholesterol stones. The underlying causes are mutations in the ABCB4 gene that encodes the hepatocanalicular phospholipid transporter. LPAC patients may benefit from prophylactic UDCA therapy (15 mg/kg body weight per day) that seems to prevent the occurrence and recurrence of stones (European Association for the Study of the Liver 2016; Poupon 2012).

UDCA for Progressive Familial Intrahepatic Cholestasis Type 3 (PFIC3) PFIC3 is a genetic cholestatic disease seen in early life, which is also related to a defective expression or function of the hepatocanalicular phospholipid transporter due to mutations of the ABCB4 gene. As in LPAC, PFIC3 patients develop severe liver and cholangiocyte injury due to BA-mediated damage. Up to one third of patients may exhibit biochemical response to UDCA (Baker et al. 2019), but its use has not been proven in large clinical trials.

UDCA to Prevent Liver Disease in Cystic Fibrosis Patients with cystic fibrosis have a defective function of the cholangiocytes' low conductance chloride channel, CFTR. This leads to a reduced biliary bicarbonate and a "thick" bile, which in turn determine the formation of biliary plugs and the occurrence of biliary injury due to a defective biliary bicarbonate "umbrella." These phenomena trigger biliary obstruction and inflammation potentially resulting in biliary cirrhosis and portal hypertension (Sakiani et al. 2019; Assis and Debray 2017). However, only few patients develop symptomatic hepatobiliary disease although many CF patients have abnormal liver tests. If liver disease is present, the use of UDCA is recommended although its efficacy remains unproven due to the lack of high-quality studies. A recent Cochrane review performed concluded that currently available data to support the use of UDCA is limited (Cheng et al. 2017). Some studies suggest that if used early (i.e., before cirrhosis is established), UDCA could prevent or even alleviate liver damage in cystic fibrosis patients as estimated by a decrease in liver stiffness as measured by transient elastography (van der Feen et al. 2016). Given the lack of alternative therapies and safety of UDCA, most experts recommend its use in cystic fibrosis although more studies are needed to confirm its efficacy in preventing liver disease in patients with this disease (Sakiani et al. 2019).

UDCA to Prevent Hepatic Injury after Stem Cell Transplantation (HSCT) Hematopoietic stem cell transplantation is routinely used for management of many hematological disorders. A frequent complication of this therapy is acute graft-versus-host disease (GVHD), an immune-mediated disorder resulting in recipient tissue damage by immune cells from the donor. One prospective randomized study evaluated the use of UDCA administration for prevention of hepatic complications after HSCT. This study found that UDCA significantly reduced the proportion of patients developing hyperbilirubinemia and that UDCA-treated patients exhibited a reduced incidence of severe acute GVHD (Ruutu et al. 2014). However, no other

studies have been published regarding the use of UDCA in hepatic GVHD, and its efficacy in this setting remains to be proved.

NorUDCA for Primary Sclerosing Cholangitis Due to its novel mechanisms of action and the wealth of experimental evidence in preclinical models, the use of NorUDCA as a useful therapeutic agent in several liver disease holds promise (Halilbasic et al. 2017; Trauner et al. 2015). To date only the phase II clinical trial assessing the effects of NorUDCA in PSC patients has been published (Fickert et al. 2017). In this study, 161 PSC patients were randomized for a 12-week treatment followed by a 4-week follow-up. NorUDCA reduced serum levels of alkaline phosphatase in a dose-dependent manner in up to 26% with few serious adverse events. Moreover, NorUDCA significantly reduced serum levels of amino-transferases and gamma-glutamyl transferase. Although promising the real efficacy of NorUDCA in PSC remains to be proved in larger trials and with a more accurate patient stratification (Chazouilleres 2017). Currently, the use of NorUDCA in PSC patients is being evaluated in a phase III clinical study (ClinicalTrials.gov number NCT01755507).

4.3 Efficacy Uncertain

Due to its lack of favorable safety profile, UDCA and other hydrophilic BA have been used in a myriad of other liver diseases (Table 1) without proof of efficacy. Thus, although UDCA may be used, the usefulness of UDCA in the setting of drug-induced cholestatic liver injury (Sundaram and Bjornsson 2017) or parenteral nutrition-induced cholestasis (San Luis and Btaiche 2007), its use is debatable due to the lack of evidence. In the case of UDCA use in PSC patients, controlled trials have shown no efficacy (Lindor et al. 2015) although the drug might be useful in some subsets of patients at dose of 17–22 mg/kg/day (Tabibian and Lindor 2014). Higher doses (25–30 mg/kg/day) may be harmful (Sedki and Levy 2018).

UDCA and NorUDCA have been also proposed as potential treatment of nonalcoholic fatty liver disease (NAFLD) currently the more common liver disease worldwide (Younossi et al. 2018; Arab et al. 2017b). NAFLD and its progressive form nonalcoholic steatohepatitis (NASH) can led to advanced liver fibrosis in up to a quarter of patients (Arab et al. 2017b). Although robust evidence of beneficial effects of these hydrophilic BA in preclinical models of NAFLD/NASH has been published (Steinacher et al. 2017), UDCA was found to be ineffective in a large clinical trial and therefore is not recommended as treatment of NAFLD in current guidelines (Chalasani et al. 2018). In the case of NorUDCA, a yet unpublished recent phase II study showed beneficial effects in patients with NAFLD and elevated liver enzymes (Traussnigg et al. 2017). A larger trial is being conducted, and its results will eventually support the use of NorUDCA in NAFLD/NASH.

Finally, some studies in preclinical models have suggested that hydrophilic BA might influence cyst formation in the liver (Munoz-Garrido et al. 2015) as well as promote degradation of α1-antitrypsin mutant Z protein (Tang et al. 2018b) opening

the possibility of using UDCA in polycystic liver disease and alpha-1 antitrypsin deficiency, two rare liver diseases. Unfortunately, a phase II clinical trial showed no effects of UDCA in reducing liver volume in patients with this disease (D'Agnolo et al. 2016). Clinical data on NorUDCA in alpha-1 antitrypsin deficiency is still unavailable.

5 Summary and Outlook

Significant advances have been made in the understanding of the beneficial effects of hydrophilic BA in the liver. Both basic science and clinical studies have either disclosed the mechanisms of action or proved the efficacy of compounds that were found to be medically useful hundreds of years ago. The science of BA will continue developing, and new evidence will likely provide foundations for new, evidence-based, and effective treatments for certain common and uncommon liver diseases.

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