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Ursodeoxycholic acid: a systematic review on the chemical and biochemical properties, biosynthesis, sources and pharmacological activities

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ABSTRACT

Ursodeoxycholic acid (UDCA), a secondary bile acid (BA), is an acidic steroid synthesized from cholesterol in hepatocytes. UDCA is widely used for the treatment of various diseases related to liver injury. The use of UDCA to treat non-liver diseases has also been developed recently, such as neurodegenerative diseases, cancer, and obesity. Due to the important role of UDCA on human health, numerous studies in understanding its chemical and pharmacological properties have been published. Literature sources were obtained from online databases such as Science Direct, Google Scholar, Scopus and PubMed using keywords relating to the purpose of study. Critical analysis and review were performed for all literature. UDCA is a steroid compound with pharmacological properties. Seventeen enzymes are involved in its biosynthesis, which has been proposed in four pathways: classic, alternative, the Yamazaki, and 25-hydroxylation pathways. UDCA can be isolated from bovine bile, bear bile or all Ursidae, human, rabbit, cow, rat, hamster, sheep, pig, and plant. UDCA has been used in the treatment of several diseases such as primary biliary cirrhosis, intrahepatic cholestasis of pregnancy, hepatolithiasis associated with Caroli syndrome gallstones, cystic fibrosis, hepatitis C virus, chronic heart failure, neurodegenerative diseases, and obesity, as well as in the prevention of cancer. UDCA has a wide range of pharmacological properties. Further investigations on its efficacy and safety on humans are required before it could be used for several indications. All genes which are responsible in UDCA biosynthesis have been elucidated. That said, further genetic engineering studies in order to find other prospective sources of UDCA could be a challenge for the future research.

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1. Introduction

Cholesterol is a steroid compound used as a precursor in the biosynthesis of several compounds such as steroid hormones and bile acids (BAs) which have pharmaceutical properties. The accumulation of these sterols in the human body tends to be a risk factor for a number of diseases (Norlin and Wikvall, 2007). BAs derived from cholesterol serves as a physiological agent which facilitates the absorption of cholesterol, dietary fat, and lipid-soluble vitamins in the small intestine and the secretion of cholesterol and other compounds via defecation, to induce a biliary lipid secretion and bile flow (Chiang, 1998). Secondary BAs, such as lithocholic acid (LCA), deoxycholic acid (DCA) and ursodeoxycholic acid (UDCA), are formed from primary BAs and are modified by intestinal bacteria (Goossens and Bailly, 2019; Hofmann and Hagey, 2014). Particularly for UDCA, human liver only synthesizes it in a very small quantity, which is about 3-4% of the BA pool (Goossens and Bailly, 2019). UDCA, 3α,7β-dihydroxy-5β-cholanic acid), is an acidic steroid that is synthesized from cholesterol in hepatocytes (Wang and Wu, 2017). Among all the BAs, only UDCA was approved by the US Food and Drug Administration (FDA) for the treatment of PBC (Šarenac and Mikov, 2017). UDCA is widely utilized in the treatment of various diseases related to liver injury. However, the use of UDCA as an ingredient to treat non-liver-related diseases, such as neurodegenerative diseases, cancer, and obesity, has also been developed recently. Due to the important role of UDCA on human health, a lot of studies designed to better understand all aspects of the compound have been published. This article aims to provide a comprehensive, critical review on UDCA, especially those related to the chemical and biochemical properties, biosynthetic pathway, sources, and pharmacological properties of the compound.

2. Methods

This research was conducted in August 2020 - August 2021. All information in this report was obtained from several scientific online databases. A total of 69 research reports and review articles were sourced, compiled, and reviewed. The information sources consisted of 15 articles from ScienceDirect (key words: UDCA, ursodeoxycholic acid, bile acid biosynthesis, cyp7a1, sources of UDCA, clinical uses of UDCA, and UDCA cholestatic), 36 articles from PubMed (keywords: UDCA, ursodeoxycholic acid, bile acid biosynthesis, cyp7a1, UDCA for cholestatic, enzymes of UDCA biosynthesis, UDCA for liver diseases, uses of UDCA, apoptosis regulation of UDCA, mechanism action of UDCA, and chemical characteristic of UDCA, UDCA and cancer), four articles from Springer (keywords: bile acid biosynthesis, sources of UDCA, pharmacology of UDCA and sterols from microorganisms), 13 articles from Google Scholar (keywords: bile acid biosynthesis, ursodeoxycholic acid, UDCA for cholestatic, and sources of UDCA), and one article from Scopus (keyword: Sources of UDCA). All the publications were taken without any year limitation.

3. Results and discussion

A literature search using several keywords related to all aspects about UDCA, especially its biochemical properties, biosynthesis pathway, natural sources, and pharmacological properties, has been carried out. Critical analysis and comprehensive review have been done to all the literatures, with no literatures being excluded due to lack of quality. From the most popular scientific online databases explored, 69 literature sources were collected. The small number of reports from online search indicated that studies on UDCA are still scarce. However, these studies were able to inspire further research to better understand the properties of UDCA considering its importance in drug development.

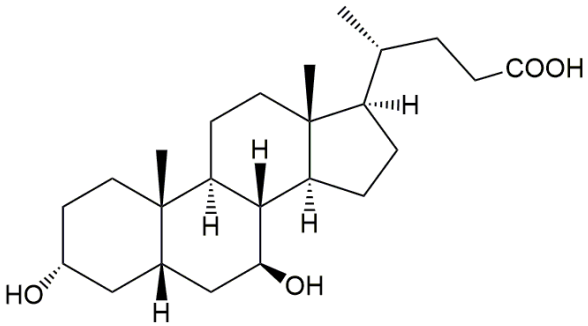

Fig.1. Chemical structure of UDCA

3.1. Chemical and biochemical properties of UDCA

BAs vary in orientation, position, and number in the steroid structures. The attached hydroxyl group could affect their adsorption, metabolism, distribution, solubility, as well as chemical and biochemical properties (Eggert et al., 2014; Poupon and Poupon, 1995; Tonin and Arends, 2018). Structurally, the BA steroid ring is exceptionally stable, rendering BAs difficult to metabolize (Lazaridis et al., 2001). Furthermore, the orientations (α or β) of the hydroxyl group in the structure determines the hydrophilicity of the BAs (Chiang and Ferrell, 2020; Lazaridis et al., 2001). The hydrophobic 7α-OH group in CDCA is converted into the 7β-OH group in UDCA, turning it hydrophilic (Fig. 1) (Ishizaki et al., 2005; Šarenac and Mikov, 2018). A higher level of hydrophilicity occurs when both hydroxyl groups of the steroid nucleus are located in α and β orientations, compared to when the hydroxyl groups are both in α position (Ishizaki et al., 2005; Šarenac and Mikov, 2018). In addition, BAs are amphipathic in nature as they comprise both hydrophilic and hydrophobic surfaces in the structures, allowing lipophilic xenobiotics to be digested, emulsified, and absorbed after having a meal (Ishizaki et al., 2005; Šarenac and Mikov, 2018). Moreover, in terms of cytotoxicity, unconjugated BAs are found to be more toxic than the conjugated ones in general. For instance, UDCA, one of the 7β-hydroxy epimer of the conjugated primary BA CDCA, is less toxic than the other unconjugated BAs (Ishizaki et al., 2005; Noshiro et al., 1989).

3.2. Biosynthesis of UDCA

BAs in human liver are biosynthesized from cholesterol and the process involves 17 enzymes (Table 1) via several pathways. The enzymes involved in the biosynthesis of BAs are located in several cell compartments, such as mitochondria, peroxisomes, endoplasmic reticulum, and cytosol (Norlin and Wikvall, 2007; Schwarz et al., 1996). Chenodeoxycholic acid (CDCA) and cholic acid (CA) and, two primary BAs which are also synthesized from cholesterol, are conjugated with either glycine or taurine and are excreted with bile into the intestine (Ishizaki et al., 2005; Noshiro et al., 1989). Intestinal bacteria modify the side chains by deconjugation and dehydroxylation of CA and CDCA portions to form secondary BAs; deoxycholic acid, lithocholic acid, and also ursodeoxycholic (UDCA), albeit in a very small amount (Eggert et al., 2014). UDCA, in particular, can be synthesized from CA, which is the most abundant and inexpensive BA (Eggert et al., 2014). The modification of cholesterol to secondary BAs involves three main steps, which are 1) the addition of hydroxyl groups to specific positions on the sterol nucleus; 2) the saturation of the steroid nucleus and epimerization of the 3p-hydroxyl group, and 3) the side-chain oxidation and shortening by three carbon atoms (Vlahcevic et al., 1999).

Primary and secondary BAs that have been formed, in a process called enterohepatic circulation, can be reabsorbed into the bloodstream, back to the liver, and then secreted (Eggert et al., 2014). There are two driving forces in the enterohepatic circulation pattern. Firstly, approximately 95% of BAs are absorbed through the intestine and are returned to the liver; this happens in the terminal ileum. Secondly, bile salts are extracted by hepatocytes and present in low concentrations in the systemic circulation; this occurs in the liver (Poupon and Poupon, 1995). Ultimately, the biosynthetic pathway and the type of BAs synthesized can be different for each species (Chiang, 1998). Currently, there are four known main pathways of BA biosynthesis, including the classic, alternative, Yamasaki, and 25–hydroxylation pathways (Fig. 2) (Šarenac and Mikov, 2018; Vaz and Ferdinandusse, 2017). Each pathway will be discussed in the next parts of this report.

3.2.1. The classic BA biosynthetic pathway

The classic pathway in BA biosynthesis is also called the neutral pathway because BA precursors are used as neutral steroids in most of the pathway (Norlin and Wikvall, 2007). Cholesterol 7α-hydroxylase (CYP7A1), a cytochrome P450 microsome enzyme, converts cholesterol to 7α-hydroxycholesterol (Ferdinandusse and Houten, 2006). In the classic pathway, the steps that are involved include the modification of the sterol nucleus, the epimerization of the 3β-hydroxyl group, and the hydroxylation at the 7α and 12α-positions which precedes the oxidative cleavage of the side chain (Chiang, 2004). Some other enzymes are also involved in this pathway, consisting of a cascade of 14 steps (Chiang, 2004). In physiological conditions, the classic pathway may be the main pathway, constituting about 90% and 75% in human and mice, respectively, in the total contribution (Šarenac and Mikov, 2017).

3.2.2. The alternative (acidic) BA biosynthetic pathway

The alternative pathway is called the acidic pathway because BA precursors for the pathway are carboxylic acids (Norlin and Wikvall, 2007). This pathway has the main function of removing cholesterol from the extrahepatic tissues (Norlin and Wikvall,

2007). The alternative pathway contributes predominantly to patients with liver disease (Chiang, 2004).

In the alternative BA biosynthetic pathway, side chain modifications occur before the modification of the sterol nucleus (Vlahcevic et al., 1999). The biosynthesis is initiated by the conversion of cholesterol to 27-hydroxycholesterol and 3β-hydroxy-5-cholestenoic acid by mitochondrial sterol 27-hydroxylase (CYP27) (Chiang, 1998). Sterol 27-hydroxylase forms 27-hydroxycholesterol and hydroxylates cholesterol at carbons 24 and 25 (Ferdinandusse and Houten, 2006). These two sterols further undergo 7α-hydroxylation to be converted into BAs (Ferdinandusse and Houten, 2006).

3.2.3. The Yamasakhi BA biosynthesic pathway

As in the alternative pathway, the Yamasaki pathway also results in C24 BAs and 3β-hydroxy-5-cholenoic acid and is followed by structural modifications of the steroid ring (Šarenac and Mikov, 2018). In human, the Yamasaki pathway has a major product, chenodeoxycholic acid (CDCA), and may contributes to fetal development. However, this pathway contribution to BA pool is not clear (Vaz and Ferdinandusse, 2017).

3.2.4. 25–hydroxylation BA biosynthesic pathway

BA biosynthesis via 25–hydroxylation pathway is initiated by CYP7B1 enzyme converting 25-hydroxycholesterol to 5β-cholesten-3α,7α,25-triol which is then transformed into BAs in the liver (Chiang, 2004). The 25-hydroxylation pathway undergoes ring structure modifications without the need for 27-hydroxylation and subsequent peroxisome β-oxidation to obtain C24-carboxylic acid (Vaz and Ferdinandusse, 2017). The contribution of this pathway is minuscule to BAs synthesis in human (Chiang, 2004).

3.3. Sources of UDCA

UDCA can be obtained naturally from animals and plants (Table 2). While UDCA can be synthesized directly due to it being the primary BA in some animals, UDCA can also be synthesized naturally and chemically from its raw materials.

3.3.1. Sources of UDCA from animals

Animals, especially vertebrates, can produce UDCA from its precursors like CA and CDCA in varying proportions depending on the species. CA is known as the main precursor in UDCA synthesis because it is found in large amount in bovine bile compared to CDCA (Tonin and Arends, 2018).

All Ursidae can produce UDCA because it is their primary BA (Hagey et al., 1993). One of the reasons is the non-exposure of all BAs in Ursidae to bacterial enzymes, and this factor is not found in human (Hagey et al., 1993). This is one of the causes that UDCA is produced in an extremely small quantity in human. On the contrary, pork is widely used in the production of UDCA owing to its high level of hyocholic and hyodeoxycholic acids (Hagey et al., 1993).

The use of animals in UDCA production has its advantages and disadvantages. The advantages are that many animals can produce UDCA precursors and that UDCA is found as primary BAs in some animals. Nevertheless, several drawbacks related to the synthesis of UDCA are also existent, including problems related to the initial process of slaughtering particularly with bovine and weaknesses related to sanitation and the complexity of the synthesis process which requires a lot of money (Tonin and Arends, 2018). Furthermore, Feng et al. (2009) also found that there are concerns growing over the existence of wild bears due to the sale of their gall bladders offers ludicrous profit, especially in China and Hong Kong.

Table 1. Enzymes of BA synthesis

Genes	Enzymes	References
Cytochrome P450 Family 7 Subfamily A Member 1 (CYP7A1)	Cholesterol 7αa-hydroxylase	Noshiro et al. (1989); Schwarz et al. (1996)
Cytochrome P450 Family 46 Subfamily A Member 1 (CYP46A1)	Cholesterol 24-hydroxylase	Lund et al. (1999)
Cholesterol 25-Hydroxylase (CH25H)	Sterol 25-hydroxylase	Shefer et al. (1976)
Cytochrome P450 Family 27 Subfamily A Member 1 (CYP27A1)	Sterol 27-hydroxylase	Björkhem et al. (1994); Reiss et al. (1994)
Cytochrome P450 Family 39 Subfamily A Member 1 (CYP39A1)	Oxysterol 7α-hydroxylase	Li-Hawkins et al. (2000a)
Cytochrome P450 Family 7 Subfamily B Member 1 (CYP7B1)	Oxysterol 7α-hydroxylase	Li-Hawkins et al. (2000a, 2000b); Schwarz et al. (1997)
Hydroxy-Delta-5-Steroid Dehydrogenase, 3 Beta- And Steroid Delta-Isomerase 7 (HSD3B7)	3β-hydroxy-A5-C27 steroid oxidoreductase	Buchmann et al. (1990); Schwarz et al. (2000)
Cytochrome P450 Family 8 Subfamily B Member 1 (CYP8B1)	Sterol 12α-hydroxylase	Andersson et al. (1989); Usui et al. (1990)
Aldo-Keto Reductase Family 1 Member D1 (AKR1D1)	A4-3-Oxosteroid 5β-reductase	Clayton et al. (1996); Pawlowski et al. (1991); Setchell et al. (1988)
Aldo-Keto Reductase Family 1 Member C4 (AKR1C4)	3α-Hydroxysteroid dehydrogenase	
Cytochrome P450 Family 27 Subfamily A Member 1 (CYP27A1)	Sterol 27-hydroxylase	Björkhem et al. (1994); Reiss et al. (1994)
Solute Carrier Family 27 Member 5 (BACS/SLC27A5)	Bile acid CoA ligase	Prydz et al. (1988)
Alpha-Methylacyl-CoA Racemase (AMACR)	2-Methylacyl-CoA racemase / α-Methylacyl-CoA racemase	Schmitz et al. (1994)
Acyl-CoA Oxidase 2 (ACOX2)	Branched-chain acyl-CoA oxidase / Acyl-CoA oxidase 2	van Veldhoven et al. (1991)
D-Box Binding PAR BZIP Transcription Factor (DBP) /Hydroxysteroid 17-Beta Dehydrogenase 4 (HSD17B4)	D-bifunctional protein hydratase	Suzuki et al. (1997)
Sterol Carrier Protein 2 (SCP2) /SCPx	Peroxisomal thiolase 2	Antonenkov et al. (1999)
Bile Acid-CoA:Amino Acid N-Acyltransferase (BAAT)	Bile acid CoA: amino acid N-acyltransferase	Kase and Björkhem, (1989)

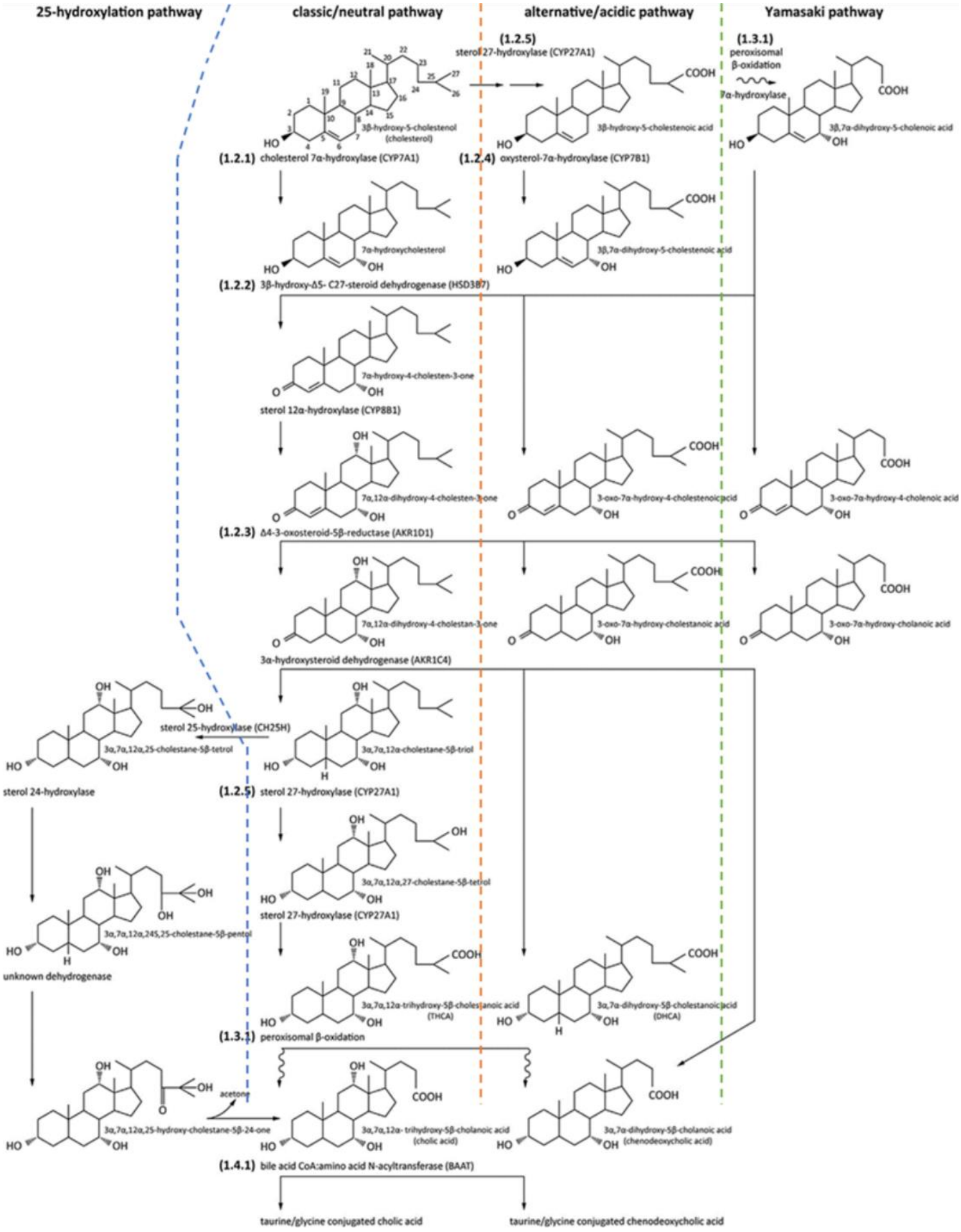

Fig. 2. Biosynthesis of UDCA precursors

3.3.2. Sources of UDCA from plants

So far, no synthesis route has been discovered in UDCA production using precursors from plants. However, in a recent study, Wang et al. (2020) succeeded in using plant bisnoralcohol (Fig. 3) obtained from side-chain degradation of the phytosterols with the help of bacteria to produce UDCA. They claim that the UDCA synthesis route from this plant-sourced bisnoralcohol is more efficient and economical because it can be produced on a large scale. Moreover, the use of eukaryotic microorganisms, like yeast and algae, in UDCA production is also being considered but is still in the early stages of investigation (Tonin and Arends, 2018). Ultimately, chemical and enzymatic manipulations can be developed from microalgae cultivation to provide new varieties in the sterol structures (Volkman, 2003).

3.4. Pharmacological activities of UDCA

UDCA has been used in ancient Chinese medicine 'Yutan', which is derived from the dry bile of adult bears for the treatment of hepatobiliary disorders (Ishizaki et al., 2005; Noshiro et al., 1989). Further development of UDCA from successful studies on its pharmacological activities has brought this compound to the FDA approval specifically for its treatment of primary biliary cirrhosis (PBC) and for its utilization for various liver diseases in general. The main use of UDCA in therapeutic purposes is for the patient with PBC. The studies also revealed that UDCA showed exhibited other biological activities on non-liver diseases such as cancer, chronic heart failure, degenerative diseases, microbial infection, and obesity. The pharmacological properties of UDCA are summarized in Table 3. In addition, UDCA has been clinically used in the pharmaceutical industry and is known for its anti-inflammatory and immunomodulating actions. Recently, several researchers recommended UDCA to be added to the current treatment protocols of COVID-19 (Abdulrab et al., 2020).

3.4.1. Liver disease

The application of UDCA has been shown to improve hepatic histology and reduce serum bilirubin level as important analytic markers in PBC (Šarenac and Mikov, 2018), including defective bile secretion, inflammation, cholangiocyte senescence and apoptosis, and innate and adaptive immune responses (Corpechot et al., 2020). In general, major mechanisms of action of UDCA in cholestatic diseases involve the stimulation of cholangiocellular, the stimulation of hepatocellular secretion, secretion, antiapoptotic effects, and the reduction in bile toxicity (Beuers et al., 2015). A double-blind clinical study has been conducted in 12 centers involving 55 patients receiving daily dose of UDCA of 15 mg/kg bodyweight for the duration of one a year. The results demonstrated that UDCA was able to improve the biochemical and clinical parameters of the patients (Colombo et al., 1996). Furthermore, a recent clinical study which involved a larger number of participants (780 patients from 16 centers from 9 countries) to investigate the preventive capability of UDCA against the recurring of PBC after liver transplantation has been reported. The study revealed the reduction in the risk of PBC recurrence, graft lost, and mortality of patients after liver transplantation, owing to the use of UDCA in the post-surgery treatment (Corpechot et al., 2020).

3.4.2. Cancer

Several studies investigating the biological activities of UDCA for cancer diseases have been reported. These studies, ranging from preclinical and clinical trials, were emphasizing on the utilization of UDCA in the cancer prevention and treatment. The preventive effect and the treatment of UDCA against cancer diseases may happen via several possible mechanisms. *In vitro* studies using several cell lines such us melanoma, colon cancer, and gastric cancer showed that UDCA could inhibit apoptosis in some situations, while also being able to induce apoptosis in other conditions. A study by Chen et al. (2019) showed the proliferation of human M14 melanoma cells can be suppressed by UDCA via a mitochondria-associated pathway triggered by ROS. In a pancreatic cancer study, UDCA depressed the stem cell formation of HPAC and Capan-1 cells (Kim et al., 2017). Contrariwise, UDCA can also inhibit apoptosis induced by deoxycholic acid (DCA) in HCT116 human colon cancer cell line, through modulation of EGFR/Raf-1/ERK signaling (Shah et al., 2005). In addition, *in vivo* investigations using animal models as well as clinical studies on human subjects showed that UDCA, with and without combination with other drugs, exhibited cytotoxicity against those cancer cell lines and could reduce cancer risk in human (Kim et al., 2018; Kohno et al., 2007; Lee et al., 2020; Park et al., 2008).

Table 2. Sources of UDCA

Sources	Precursors	References
Bovine bile	CA and CDCA	Tonin and Arends (2018)
All Ursidae	The average content of UDCA is 1-39% of biliary BAs depending on the species	Feng et al. (2009); Hagey et al. (1993)
Human, rabbit, cow, rat, hamster, sheep, pig, goose, birds, fishes, ox	UCDA, CA, CDCA, hyodeoxycholic acid (HDCA)	Kuhajda et al. (2006); Russell (2003); Elfahmi and Chahyadi (2020)

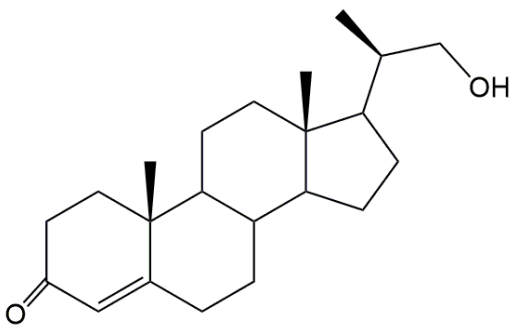

Fig.3. Chemical structure of bisnoralcohol

3.4.3. Chronic heart failure

The potential prospect of the use of UDCA as a drug for chronic heart diseases have been revealed from several studies. Numerous reports signify *in vitro*, *in vivo*, and clinical studies of the pharmacological activities of UDCA against heart diseases. *In vitro* studies in rat model organs showed that UDCA has the potential to be developed as a drug for chronic diseases. The mechanisms of UDCA were revealed through the induction of cyclic adenosine monophosphate (cAMP), reduction of lactate dehydrogenase (LDH) release and the enhancement of the cardiac contractile function (Ibrahim et al., 2018; Lee et al., 1999); the improvement in calcium level intracellularly and the activation of ATP-sensitive calcium (KATP) channels (Miragoli et al., 2011); and downregulation of caspase-9 and reactive oxygen species (ROS) regarding Hypoxia (Hanafi et al., 2017). Other *in vivo* studies on mouse models of diabetic atherosclerosis revealed that UDCA could reduce endoplasmic reticulum stress as one of indicators for antiatherogenic activity (Chung et al., 2016). Additionally, the clinical studies on patients with coronary heart diseases found that UDCA was able to improve endothelium and NO-independent vasodilatation which maintain the arterial flow of the patients (Sinisalo et al., 1999).

3.4.4. Neuro-degenerative diseases

Lots of research of pharmacological properties of UDCA and its conjugate with taurine on neurogenerative diseases have been also reported. A study on Huntington's disease (HD) conducted by Keene et al., (2001) exhibited that depletion of 3-nitropropionic acid (3-NP)-mediated striatal nerve cell death in cell culture was affected by TUDCA treatment. HD is a disease that is associated with disruption of mitochondrial energy metabolism, such as Parkinson's disease, Alzheimer's disease, Freidreich's ataxia or some related neurodegenerative diseases, so it is very likely that treatment with TUDCA is predicted to be applied to these diseases (Keene et al., 2001). In the *in vitro* study using cell line SH-SY5Y, UDCA demonstrated the capability of protecting the human dopaminergic neuronal against the cytotoxicity induced by sodium nitroprusside in the cells. That said, along with its conjugates and other derivatives, UDCA has shown to be a promising candidate to be developed as a drug for the therapy of neurodegenerative diseases in the future.

Table 3. Pharmacological uses of UDCA

Pharmacological uses	Clinical/laboratory features	References
Primary Biliary Cholangitis (PBC)	UDCA decreased risk of graft loss, disease recurrence, and death.	Corpechot et al. (2020)
Intrahepatic cholestasis of pregnancy (ICP)	UDCA improved the biochemical and clinical parameters of cholestasis and safe for the fetus.	Mazzella et al. (2001)
Hepatolithiasis associated with Caroli syndrome	UDCA caused sustained clinical remission, return to normal liver function, and dissolution of intrahepatic stones on ultrasound in all patients.	Ros et al. (1993)
Cystic fibrosis	UDCA increased biochemical indications of cholestasis, nutritional status, and general condition.	Colombo et al. (1996)
Prevention of cancer	UDCA not only protected cells from damages and supressed apoptosis but also can induce apoptosis.	Chen et al. (2019); Kim et al. (2017); Shah et al. (2005)
Autoimmune hepatitis	UDCA may have depressed T-cell activity and instigated a decline of HLA class I antigens against hepatocytes together with prednisolone in a synergistic manner.	Mima et al. (1994)
Hydroxy-Delta-5-Steroid Dehydrogenase, 3 Beta- And Steroid Delta-Isomerase 7 (HSD3B7)	The use of UDCA indicated a degradation in serum alanine transferase (ALT) and serum BA hydrophobicity index.	Takano et al. (1994)
Chronic heart failure	*In vitro* studies mechanisms of UDCA were referred through the induction cAMP, reduction of LDH release and the enhancement of the cardiac contractile function; the improvement in calcium level intracellularly and the activation of KATP channels; and the inhibition of the expression of hypoxia factor 1 alpha and downregulation of caspase-9 and ROS. UDCA could reduce endoplasmic reticulum stress and improve endothelium and NO-independent vasodilatation regarding *in vivo* studies.	Chung et al. (2016); Hanafi et al. (2017); Ibrahim et al. (2018); Lee et al. (1999); Miragoli et al. (2011); Sinisalo et al. (1999)
Neurodegenerative diseases	T/UDCA serves as a neuroprotectant against acute injuries and could inhibit apoptosis by interfering early on with the mitochondrial pathway of cell death and associated processes.	Chun and Low (2012); Keene et al. (2001)
Obesity	UDCA remarkably diminished lipid droplets, enhanced mitochondrial function, decreased free fatty acids (FFA) and triglycerides (TG), and increased white adipose tissue browning in ob/ob mice.	Chen et al. (2019)
Antibacterial activity	UDCA affected the composition of the intestinal microflora and preserved the sterility of the biliary tract.	Šarenac and Mikov (2018)
Hepatoprotective effect	TUDCA dose-dependently protected TCDCA-induced GPT release in hepatocytes	Ishizaki et al. (2005)
Nonalcoholic fatty liver disease	Inhibiting apoptosis and improving autophagy by activating AMPK	Wu et al. (2020)

3.4.5. Diabetes and obesity

In vivo study on obese mice models, UDCA exhibited a potential anti-obesity property. This effect was indicated by several parameters related to obesity-related diseases such as decreasing the level of lipid, fatty acids, and triglycerides; improving the function of mitochondria; and enhancing adipose tissue browning of animal models. UDCA also showed the modulation in glucose and lipid biosynthesis, anti-inflammatory property, macrophage differentiation, and angiogenesis. All parameters related for obesity suggested the potential of UDCA to be developed as a drug to treat obesity. Furthermore, as obesity could lead to other metabolic diseases such as diabetes (Chen et al., 2019), it is also promising that the conjugate of UDCA, tauroursodeoxycholic acid, protects podocytes by inhibiting autophagy damage in diabetes (Fang et al., 2013).

4. Conclusion

In this review, the chemical and biochemical properties, biosynthesis, sources and pharmacological activities have been described. UDCA is a hydrophilic and non-toxic secondary BA. The elucidation of all enzymes in every step of UDCA biosynthesis has provided adequate insights for further research. Ultimately, the availability of their gene sequences which code the enzymes could

be capitalized in for the genetic engineering of these genes to produce UDCA and its derivatives with synthetic biology. Up until now, the sources of UDCA and its derivatives are mostly from animals with low concentration. The efforts in finding other sources of UDCA such as plants or engineered microorganisms are of essence. Ursodeoxycholic acid (UDCA) has been proven as a drug for liver-related diseases, especially for primary biliary cholangitis (PBC). Numerous studies have been reported to support this therapeutic use. In addition to PBC, UDCA also showed the pharmacological properties in the prevention and treatment of other liver diseases, such as hepatolithiasis, cystic fibrosis autoimmune hepatitis, and hepatitis virus infection. Recent clinical study proved that UDCA could reduce the risk of the recurrence of PBC in patients post liver transplantation. It strengthened the evidence of therapeutic use of UDCA for PBC. Furthermore, UDCA could be developed as a potential drug for other illnesses such as cancer, obesity, heart failure, neurodegenerative diseases and others. Nevertheless, further studies on the clinical trial are still lacking.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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