ejpmr, 2018,5(2), 47-59

SJIF Impact Factor 4.161

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

BIOSYNTHESIS AND CHEMICAL SYNTHESIS OF BILE ACIDS AND THEIR BIOMEDICAL APPLICATIONS

Tanja Šarenac* and Momir Mikov

University of Novi Sad, Faculty of Medicine, Department of Pharmacology, Toxicology and Clinical Pharmacology, 21000 Novi Sad, Hajduk Veljkova 3, Republic of Serbia.

***Corresponding Author: Tanja Šarenac**
University of Novi Sad, Faculty of Medicine, Department of Pharmacology, Toxicology and Clinical Pharmacology, 21000 Novi Sad, Hajduk Veljkova 3, Republic of Serbia.

Article Received on 24/11/2017 **Article Revised on 14/12/2017** **Article Accepted on 04/01/2018**

ABSTRACT

Bile acids are amphiphilic molecules consisting of a hydrophobic and a rigid steroid nucleus, which they are attached a hydrophilic hydroxyl groups and a flexible acidic aliphatic side chain. The steroidal core of bile acids constitutes a saturated cyclopentanoperhydrophenanthrene skeleton, consisting of three six-membered (A, B and C) and one five-membered ring (D). The primary bile acids include cholic and chenodeoxycholic acid. They arise as result of chemical transformation of cholesterol by the effect of various enzymatic reactions in hepatocytes of the liver. Secondary bile acids, which include deoxycholic and lithocholic acid, are formed by the reactions of 7α−dehydroxylation and deconjugation of cholic and chenodeoxycholic acid. The aim of this paper is the discussion of biosynthesis and various chemical synthesis of bile acids, as well as the explanation of their biomedical applications. Bile acids, as signaling molecules are involved in the regulation of glucose and lipid metabolism, thermogenesis, inflammatory and immunomodulatory processes, antibacterial protection of the intestinal tract. The most of their effects, bile acids are mediated through nuclear receptor, such as FXR receptors and membrane TGR5 receptors. There are a various possibility for the development of semi−synthetic derivatives of bile acids and synthetic compounds of the nonsteroidal structure, which will have a greater affinity for these receptors, better selectivity and improved pharmacokinetic properties. These therapeutic agents would offer new pharmacotherapeutic possibilities in various metabolic disorders, but also in malignant diseases.

KEYWORDS: Biosynthesis of Bile Acids, Chemical Synthesis, Biomedical Applications of Bile Acids.

INTRODUCTION

Bile acids are steroidal compounds, which contain 24 C atoms. They can be divided into two most important groups: primary and secondary bile acids. The primary bile acids are cholic acid and chenodeoxycholic acid. The most important secondary bile acids are deoxycholic acid and lithocholic acid. All of the bile acids contain a cyclopentanoperhydrophenanthrene ring. The primary bile acids are synthesized in the liver. Further they can be conjugated with glycine and taurine, before secretion into the bile ducts and the digestive tract.[1,2] The conjugation reduces the hydrophobicity of bile acids. Also, in this manner increases the amphiphilic of the bile acids and makes them the less toxic. Secondary bile acids, which include deoxycholic acid and lithocholic acid, are formed by the reactions of 7α−dehydroxylation and deconjugation of cholic acid and chenodeoxycholic acid by the effect of anaerobic bacteria in the colon.[1,2] The planar amphiphilic structure of bile acids, that is, the existence of a hydrophilic and hydrophobic surface of the molecules, affects their physical and chemical characteristics and determines the ability of self−aggregation. In the aquatic environment, when placed in a concentration above the so-called, the critical micellar concentration (CMC), which is the characteristic of each surfactant, bile acids form micelles due to hydrophobic interactions of non-polar β-side of steroid skeletons. Bile acids in concentrations above the critical micellar concentration can perform solubilization of phospholipids from cell membranes and thus manifest their membranolytic and cytotoxic effects. The stabilization of micelles is achieved by intermediate hydrogen bonds between hydroxyl and / or carboxyl groups, where the position and stereochemistry of hydroxyl groups determine the degree of rigidity of these supramolecular aggregates.[2] The value of the critical micellar concentration is inversely proportional to their hydrophobicity, which can be easily determined by measuring the retention factors in reverse phase chromatography. At lower concentrations, hydrophobic bile acids may form micelles and solubilize different compounds. Hydrophobicity is the main determinant of toxicity of bile acids and depends on the number, position and orientation (stereochemistry) of the hydroxyl groups and from the amidation at position C_{24}. Hydrophilicity of bile acids decreases according to the following order: ursodeoxycholic acid (UDCA)> cholic

acid (CA)> chenodeoxychoic acid (CDCA)> deoxycholic acid (DCA)> lithocholic acid (LCA). It is important to note that conjugated bile acids are more hydrophilic in relation to unconjugated.[1,2] The ability to induce apoptosis depends directly from the hydrophobicity of bile acids and their concentration. Bile acids, such as a deoxycholic acid and chenodeoxycholic acid are well known inductors of apoptosis and damage of cells. Hydrophilic ursodeoxycholic acid has a cytoprotective effect, which also indicates the importance of stereospecificity in the mechanism of cytotoxicity of bile acids.[3,4]

Bile acids interact with phospholipid bilayer of biological membranes with hydrophobic bonds and comes to the partition of bile acids between the aqueous medium and membrane lipids, which leads to an increase in fluidity and permeability of the cell membrane. By the action of expression of membrane transport proteins, bile acids can increase the absorption of various xenobiotics. Bile acids regulate a various metabolic signaling pathways and they now being examined as new therapeutic agents, but also as auxiliary agents in combination with medicinal substances in order to increase their bioavailability. New therapeutic systems on basis of bile acids include mixed micelles, liposomes stabilized by bile acids and bile acid conjugates with medicinal substances. The significance of bile acid molecules in the mechanism of their action is best seen in the effects of chenodeoxycholic acid and ursodeoxycholic acid.[5,6] These two bile acids are epimers. Only structural difference is spacious orientation of hydroxyl group in position C_7. Chenodeoxycholic acid (3α, 7α−dihydroxy−5β−cholanic acid) represents hydrophobic and cytotoxic bile acid, which is also considered a carcinogen promoter. This bile acid is used as a therapeutic agent for the dissolution of cholesterol gallstones and in the treatment of gastritis.[6]

Ursodeoxycholic acid (3α,7β−dihydroxy−5β−cholanic acid) is cytoprotective agent with an established antiapoptotic, antioxidant and antiinflammatory effect. The semi−synthetic derivatives of bile acids are intensive developed and selective act on the appropriate receptors, which open new therapeutic options for the prevention and treatment of liver disease, atherosclerosis, obesity and diabetes of type 2. The possibility of antitumor activity by activation or inhibition of the receptor for bile acids is investigated. Four of bile acids have already been approved for clinical use and several of them are in the final stages of clinical studies. Ursodeoxycholic acid (3α, 7β−dihydroxy−5β−cholanic acid) has been used for the dissolution of radiolucent cholesterol gallstones and in the treatment of primary biliary cirrhosis. During 2015 and 2016, three bile acids are approved for human use.[3,4]

Cholic acid (3α, 7α, 12α−trihydroxy−5β−cholanic acid) is indicated in the therapy of a rare hereditary disorder of bile acid synthesis due to an enzymatic defect and in the supplemental therapy of peroxisomal disorders, including Zellweger's syndrome. Deoxycholic acid (3α,12α−dihydroxy−5β−cholanic acid) is the first approved injection drug for contouring of the fat tissue of the submental region. Despite hepatotoxicity and harmful effects on stomach mucosa, deoxycholic acid is used to synthesize corticosteroids, as well as inactivating viral particles in the production of flu vaccines.[5,6] The only semi−synthetic bile acid approved so far for clinical use is obetecholic acid, or 6α−ethyl−chenodeoxycholic acid. This bile acid is a potent and selective agonist of farnesoid X−receptor (FXR) and it is registered for primary biliary cirrhosis therapy in combination with ursodeoxycholic acid, but in clinical studies the potential use of this drug is been examined in the treatment of other liver diseases.[6] Lithocholic acid is selectively kills neuroblastoma cells, while sparing normal neuronal cells.[6]

Natural bile acids are derivatives of 5β−cholanic acid, wherein the rings A and B are bound in the cis configuration. This results to the curvature of the steroid core in the structure of bile acids, that is, the existence of two functionally different molecular surfaces.[1]

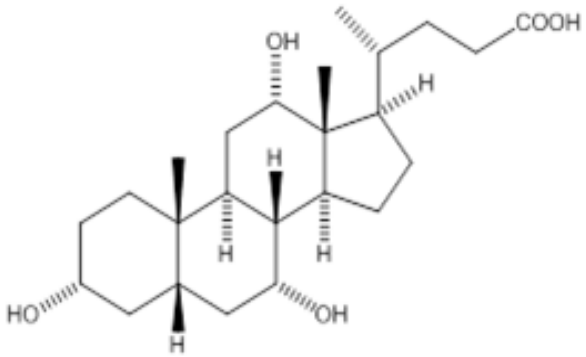


Figure 1: Cholic acid (3α,7α,12α-Trihydroxy-5β-cholanic acid).[1]

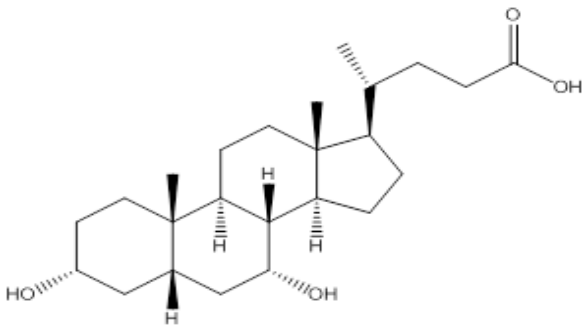


Figure 2: Chenodeoxycholic acid (3α,7α−dihydroxy−5β−cholanic acid).[1]

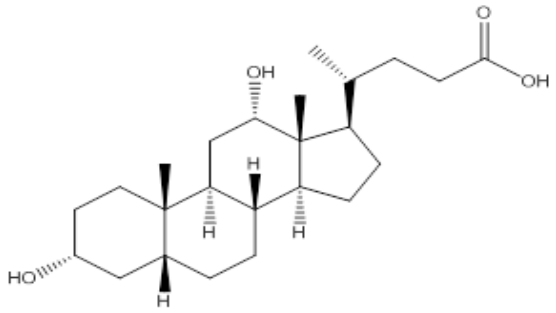


Figure 3: Deoxycholic acid (3α, 12α−dihydroxy−5β−cholanic acid).[1]

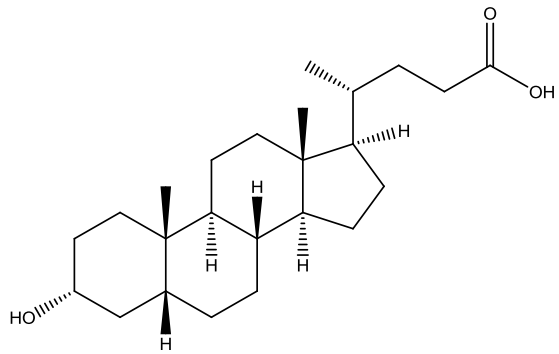


Figure 4: Lithocholic acid (3α−hydroxy−5β−cholanic acid).[1]

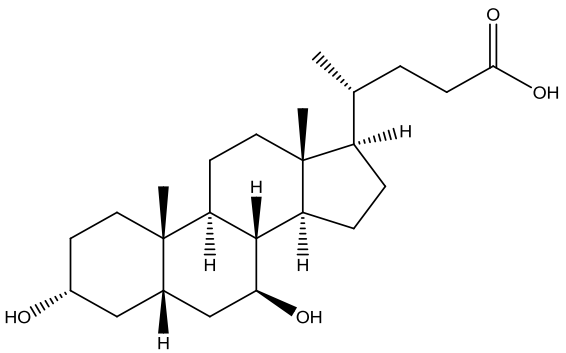


Figure 5: Ursodeoxycholic acid (3α, 7β−dihydroxy−5β−cholanic acid).[1]

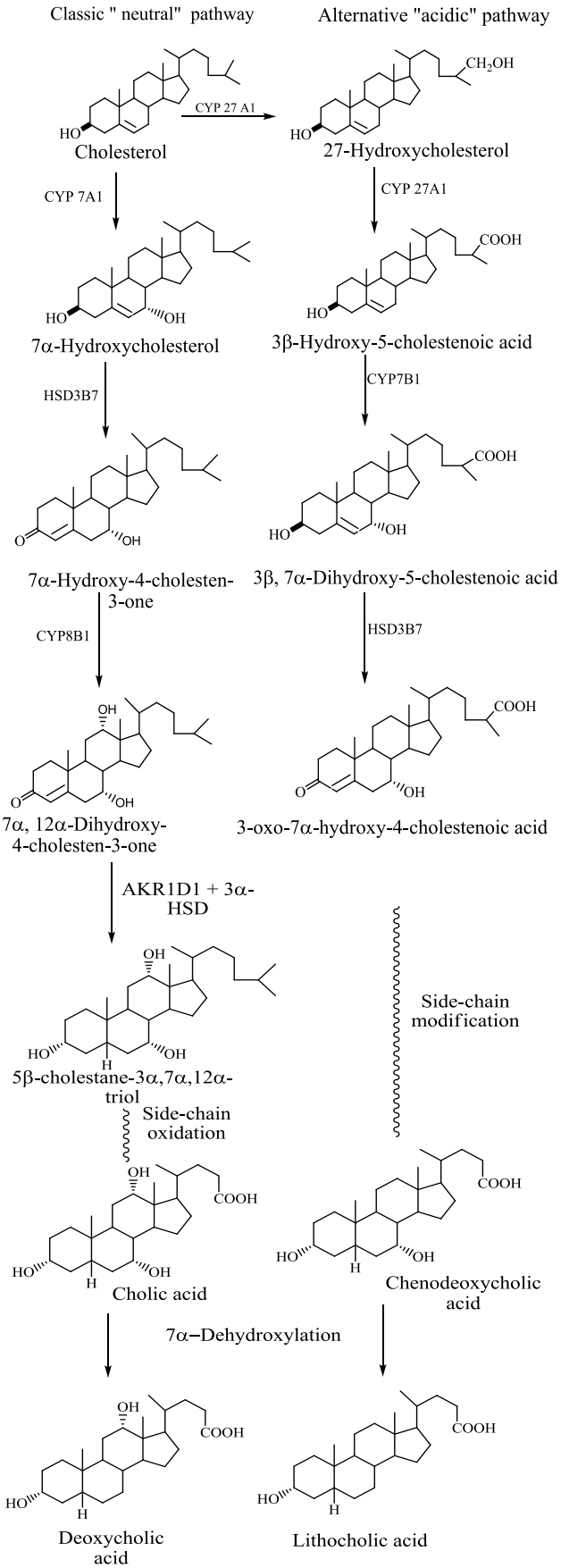
Biosynthesis of bile acids

The first step in biosynthesis of bile acids begins with the transformation of the steroidal cholesterol by the reaction of 7α−hydroxylation in the classic pathway of biosynthesis of bile acids. The conversion of cholesterol to 7α−hydroxycholesterol was catalyzed by microsomal cytochrome P450 7A1 (CYP 7A1) or under the influence of cholesterol 7α−hydroxylase. CYP 7A1 enzim is the main regulator of catabolism of cholesterol, or biosynthesis of bile acids. It has been proven that 85% CYP 7A1−deficient mice do not survive the first free postnatal weeks due to liver disfunction and malabsorption of lipids and vitamins, which is partially alleviated by supplementation of bile acids.[2]

Further, the 7α−hydroxycholesterol under the influence of enzyme 3β−hydroxy−Δ^5 C_{27} steroid oxidoreductase (HSD3B7) converts to 7α−hydroxy−4−cholesten−3−one.

This enzyme catalyses the reaction of epimerization of the hydroxyl group at position C_3.[2,3] The HSD3B7 enzyme catalyzes the inversion of the 3β-hydroxyl group of cholesterol to the 3α-hydroxyl group of bile acids. At the knockout mice, the elimination of HSD3B7 prevents epimerization of the hydroxyl groups at carbon C_3 of the sterol nucleus, resulting in the synthesis of 3β-hydroxylated bile acids.[2] This stereochemical alteration eliminates cholesterol absorption in the gut and feedback regulation in the enterohepatic. Alfa stereochemistry of the 3−hydroxyl group conferred by HSD3B7 is required to maintain the functional and regulatory properties of bile acids in mice and presumably other species in which this modification is conserved. Mutations that inactivate this gene in humans cause a recessive form of neonatal liver failure. Further, the obtained 7α-hydroxy-4-cholesten-3-one is converted to 7α,12α−dihydroxy−4-cholesten−3−one under the action of the CYP 8B1 enzyme.[2] The activity of CYP 8B1 (12α−hydroxylase) enzyme in hepatocytes regulates the ratio of cholic acid and chenodeoxycholic acid in body. Using the enzyme AKR1D1 (Δ^4−3−oxosteroid−5β−reductase) and enzym 3α−hydroxysteroid dehydrogenase (AKR1C4), 7α,12α−dihydroxy−4−cholesten−3−one is converted into 5β−cholestane−3α,7α,12α−triol, which in the process of the oxidation of side chain leads to the formation of cholic acid.[2]

Alternative acidic pathway in biosynthesis of bile acids is initiated by chemical transformation of cholesterol by the reaction of hydroxylation at position $C_{27,}$ under the action of 27−hydroxylase mitochondrial sterol (CYP 27A1), whereby the 27−hydroxycholesterol is formed. 27−Hydroxycholesterol under the action of the enzyme CYP27 A1 is converted to 3β−hydroxy−5−cholestenoic acid. The resulting 3β−hydroxy−5−cholestenoic acid is under the action of the oxysterol 7α−hydroxylase enzyme converted into a 3β,7α−dihydroxy−5−cholestenoic acid. Under the influence of enzyme 3β−hydroxy−Δ^5 C_{27} steroid oxidoreductase (HSD3B7), the 3β,7α−dihydroxy−5−cholestenoic acid is converted into a 3−oxo−7α−hydroxy−4−cholestenoic acid. The resulting 3−oxo−7α−hydroxy−4−cholestenoic acid is subjected to the reaction of the side chain modification, thereby forming chenodeoxycholic acid. Secondary bile acids, which include deoxycholic and lithocholic acid, are formed by the reactions of 7α−dehydroxylation and deconjugation of cholic and chenodeoxycholic acid.[2,3]



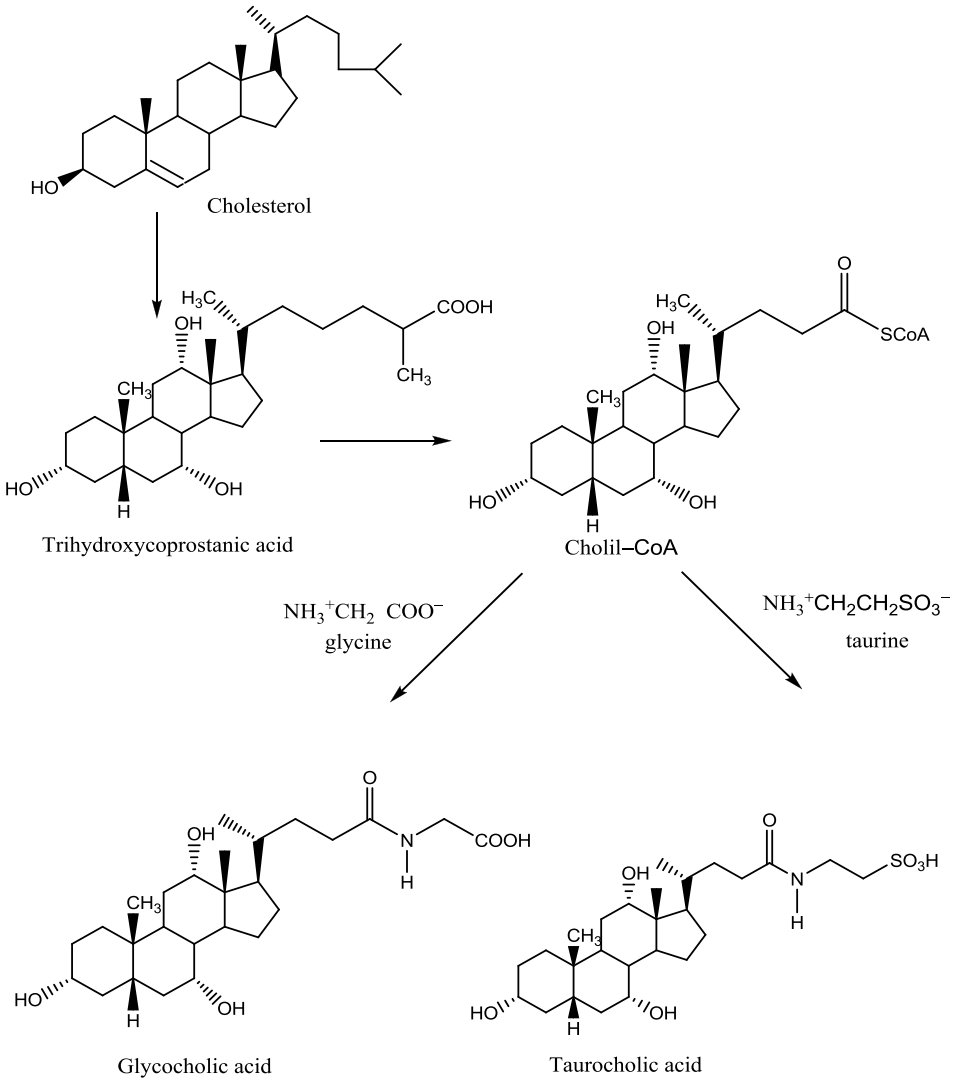
Scheme 1: Biosynthesis of bile acid synthesis via the classic "neutral" and alternative "acidic" pathways.[2]

Before the primary bile acids are secreted into the canalicular lumen, they are conjugated via an amide bond at the terminal carboxyl group with either of the amino acids glycine or taurine. This conjugation process increases the amphipathic nature of the bile acids making them more easily secretable as well as less cytotoxic.[4] The conjugated bile acids are the major solutes in human bile. As polar derivatives of bile acids, bile salts are highly effective detergents, because they contain both polar and non−polar regions. Bile acids are synthesized in the liver, stored and concentrated in the gallbladder and then released into the small intestine. Bile acids, the major constituent of bile, solubilize dietary lipids. Glycocholate and taurocholate are ionised at physiological pH and they are labeled as bile salts.[5] The conjugation of bile acids with glycine and taurine contributes to increased solubility in water and the cytostatic effect decreases. Conjugated bile acids are molecules with the hydrophilic groups than unconjugated bile acids, therefore with a increased emulsifying capacity. Cholesterol is converted into trihydroxycoprostanoate and then into cholyl CoA, the activated intermediate in the synthesis of most bile salts. The activated carboxyl carbon of cholyl CoA then reacts with the amino group with the amino group of glycine to form glycocholate or it reacts with the amino group of taurine ($H_3^+N\ CH_2CH_2SO_3^-$), derived from cysteine, to form taurocholate. Glycocholate is the major bile salt.[5]

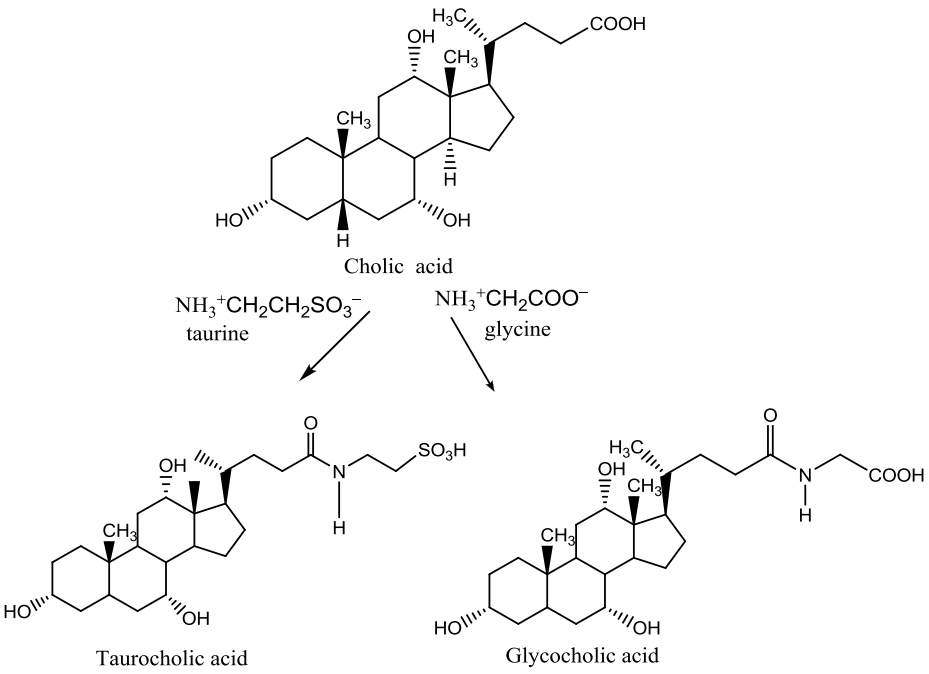
In fact conjugation decreases the pKa of bile acids, from about 6, a value typical of non-conjugated molecules, to about 4 for glycocholic acid and about 2 for taurocholic acid. This makes that conjugated bile acids are ionized in a broader range of pH to form the corresponding salts.

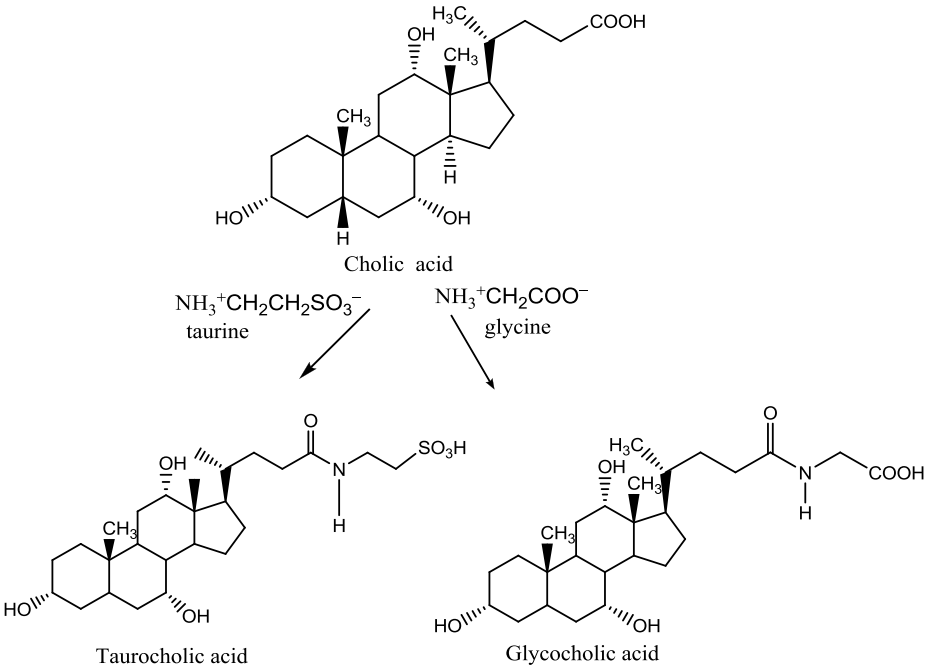
Approximately 75% of cholic acid and chenodeoxycholic acid are conjugated with glycine, to form glycocholic acid and glycochenodeoxycholic acid, the remaining 25% with taurine, to form taurocholic acid and taurochenodeoxycholic acid. Up to 95% of the secreted bile salts is reabsorbed from the gut, not together with the products of lipid digestion, but through a process called enterohepatic circulation.[5,6]

The hydrophilicity of the common acid and bile salts decreases in the following order: glycine-conjugated < taurine-conjugated < lithocholic acid < deoxycholic acid < chenodeoxycholic acid < cholic acid <ursodeoxycholic acid. Finally, conjugation also decreases the cytotoxicity of primary bile acids.[5]



Scheme 2: Synthesis of glycocholate and taurocholate from the cholesterol.[2]





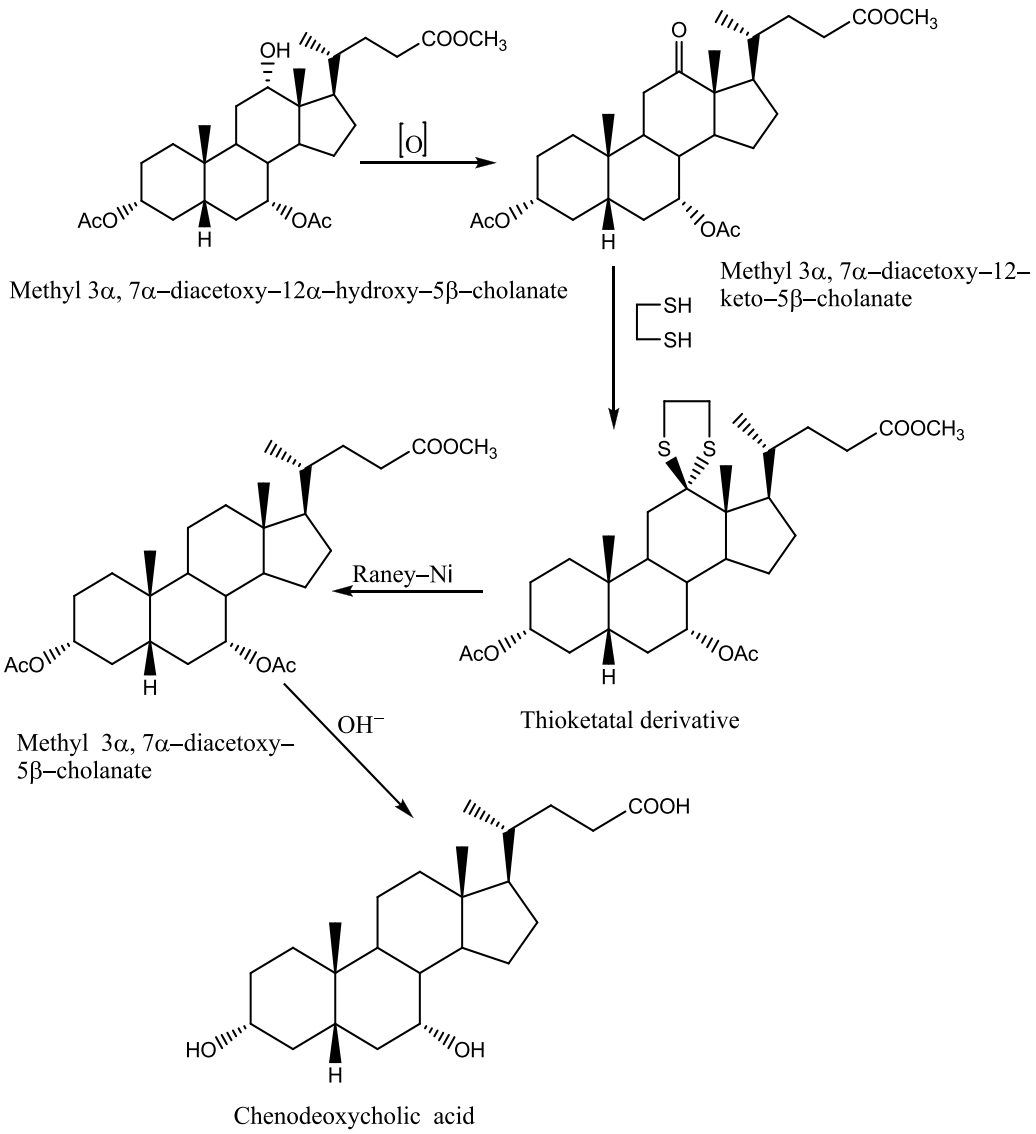
Scheme 3: Synthesis of glycocholic, taurocholic, glycochenodeoxycholic and taurochenodeoxycholic from cholic acid and chenodeoxycholic acid.[2]

Most of the bile salts are reabsorbed into the distal ileum, the lower part of the small intestine, by a sodium-dependent transporter within the brush border of the enterocytes, called sodium-dependent bile acid transporter or ASBT, which carries out the cotransport of a molecule of bile acid and two sodium ions.[2,5]

Chemical synthesis of bile acids

Sato and Ikekava carried out a reaction of the oxidation of methyl 3α,7α−diacetoxy−12α−hydroxy−5β−cholanate, resulting in the formation of methyl 3α, 7α−diacetoxy−12−keto−5β−cholanate. The resulting compound methyl 3α, 7α−diacetoxy−12−keto−5β−cholanate under the influence of 1,2−ethanedithiol (1,2−dimercaptoethane) is converted to the corresponding thioketal derivative. The resulting thioketal derivative is further desulfurized by Raney nickel, whereby is formed a methyl 3α, 7α−diacetoxy−5β−cholanate. The resulting methyl 3α,7α−diacethoxy−5β−cholanate is eventually hydrolyzed to form chenodeoxycholic acid in over 90% yield (Scheme 4).[8]

However, a drawback of this method is that the thioketal derivative is contaminated with 3α,7α−diacetoxy−12−keto−5β−cholanic acid which is difficult to separate from chenodeoxycholic acid.[8]

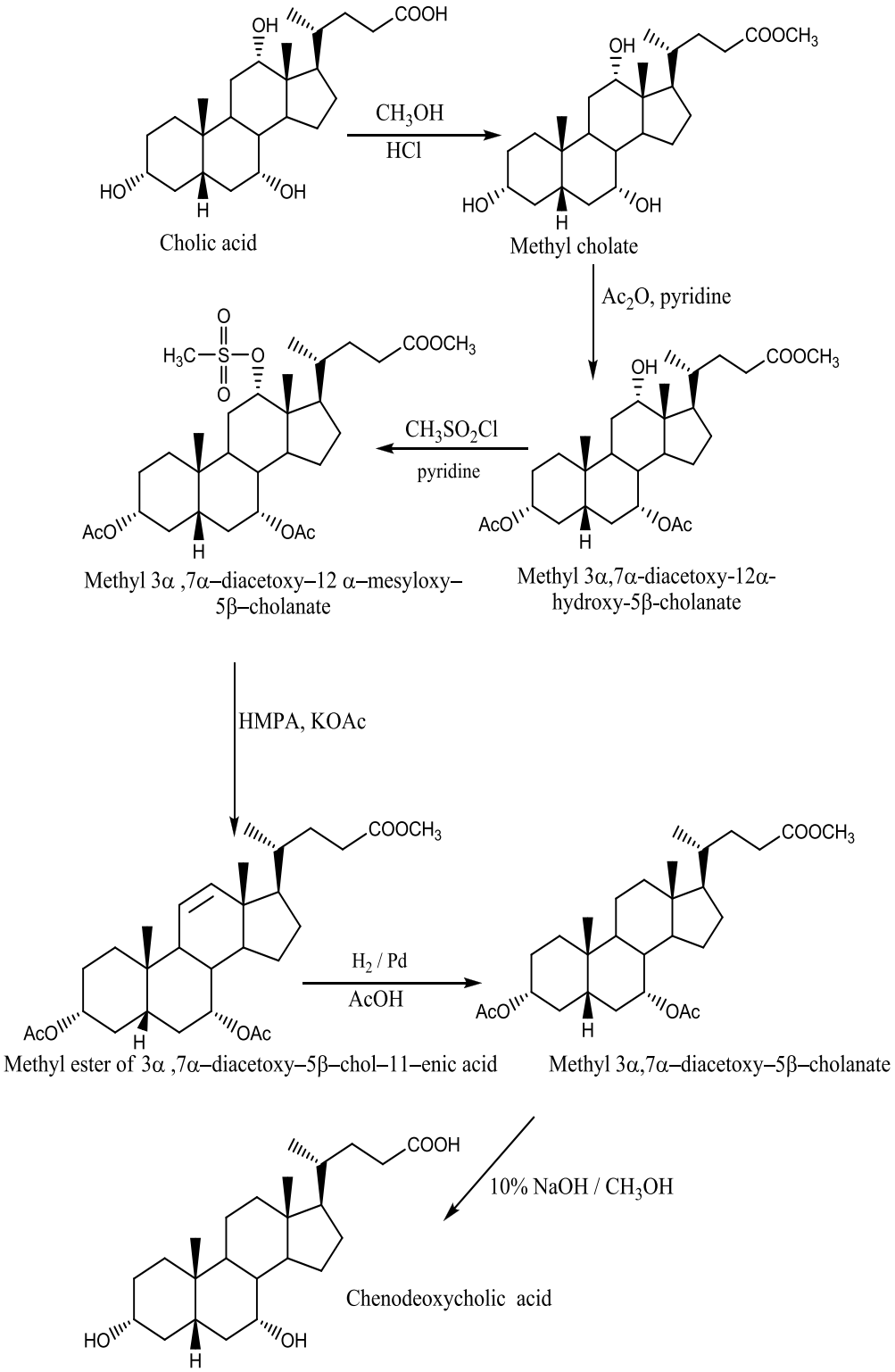


Scheme 4: The conversion of methyl 3α,7α−diacetoxy−12−keto-5β−cholanate to chenodeoxycholic acid.[8]

The cholic acid is reacted with methanol in the presence of hydrochloric acid as the catalyst and gives the methylcholate The resulting methylcholate under the influence of acetic anhydride in pyridine is converted into methyl 3α,7α−diacetoxy−12α−hydroxy−5β−cholanate, which further produces the methyl 3α,7α−diacetoxy−12α−mesyloxy−5β−cholanate under the action of methanesulfonyl chloride in pyridine.[8]

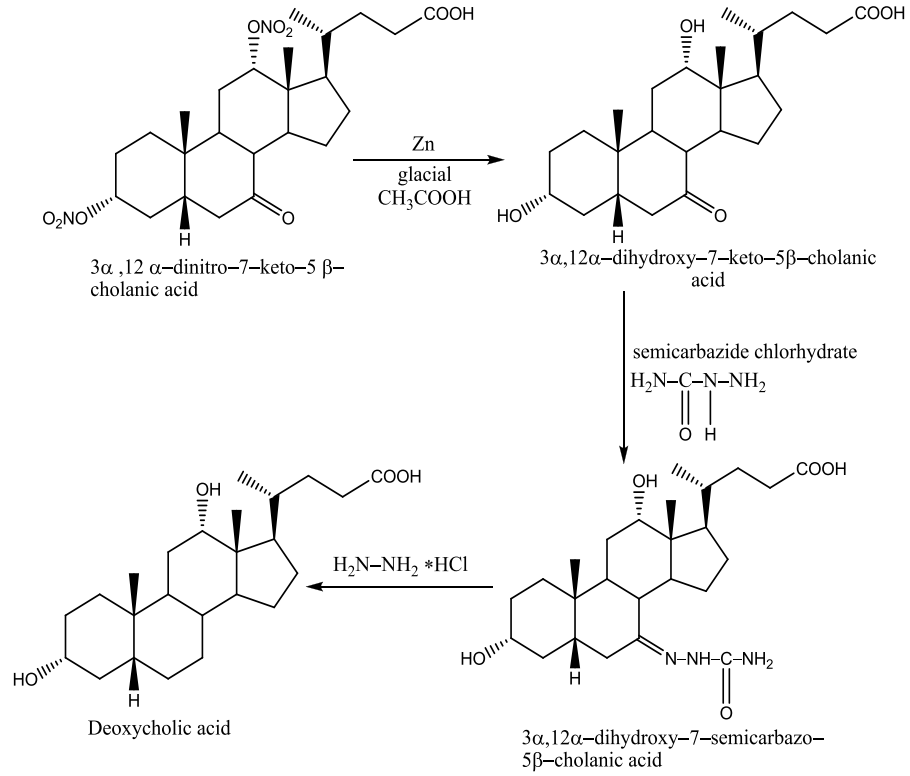
Then, the methyl 3α,7α−diacetoxy−12α−mesyloxy−5β−cholanate under the influence of hexamethyl phosphorus triamide in presence of potassium acetate gives the methyl ester of 3α,7α−diacetoxy−5β−chol−11−enic acid. It is a key intermediate in the synthesis of chenodeoxycholic acid.

The resulting methyl ester of 3α,7α−diacetoxy−5β−chol−11−enic acid by the catalytic hydrogenation in the presence of palladium in acetic acid gives the methyl 3α,7α−diacetoxy−5β−cholanate, which ultimately converted to the chenodeoxycholic acid by total hydrolysis using 10% sodium hydroxide in methanol for 15 hours. Recrystallization from a mixture of ethyl acetate and heptanes gives the pure product in 80% (Scheme 5).[8]



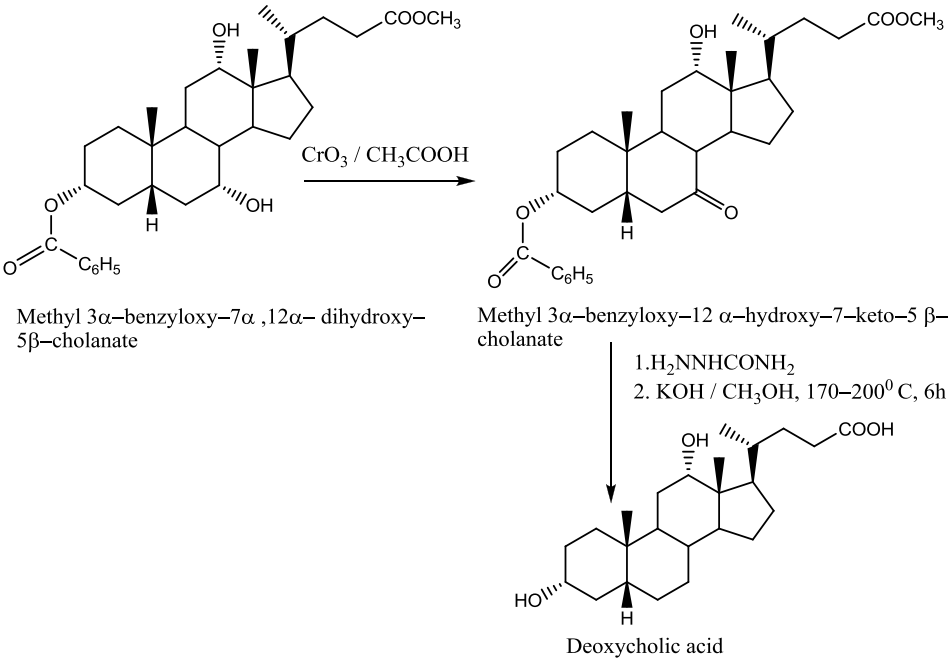
Scheme 5: The synthesis of chenodeoxycholic acid via the appropriate –olefin.[8]

Dinitroestar of 3α,12α−dihydroxy−7−keto−5β−cholanic acid is converted to 3α,12α−dihydroxy−7−keto−5β−cholanic acid by zinc in glacial acetic acid. The resulting 3α,12α−dihydroxy−7−keto−5β−cholanic acid with the corresponding semicarbazide chlorhydrate yields the corresponding 3α, 12α−dihydroxy−7−semicarbazo−5β−cholanic acid. Reduction of 3α,12α−dihydroxy−7−semicarbazo−5β−cholanic acid with hydrazine hydrate at high pH gives the desired deoxycholic acid in 72% yield (Scheme 6).[8]



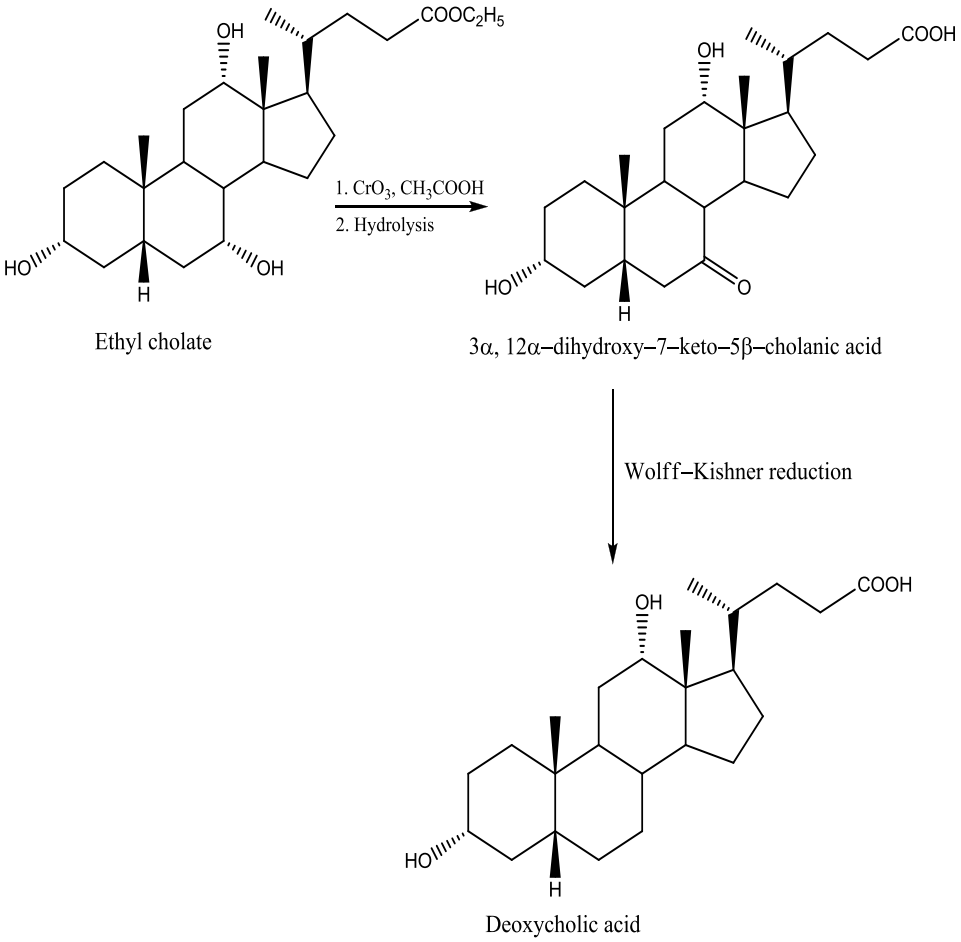
Scheme 6: The synthesis of deoxycholic acid from dinitro ester of 3α,12α−dihydroxy−7−keto−5β−cholanic acid.[8]

Methyl 3α−benzyloxy−7α, 12α−dihydroxy−5β−cholanate is transformed by the action of chromium trioxide in acetic acid to the methyl 3α−benzyloxy−12α−hydroxy−7−keto−5β−cholanate, which is eventually converted to deoxycholic acid by the action of semicarbazide and potassium hydroxide in methanol at a temperature of 170-200^{0}C for 6 hours (Scheme 7).[8]



Scheme 7: Conversion of methyl 3α−benzyloxy−7α,12α−dihydroxy−5β−cholanate to deoxycholic acid.[8]

Ethyl cholate is converted to 3α, 12α−dihydroxy−7−keto−5β−cholanic acid under the influence of chromium trioxide in acetic acid and the hydrolysis reaction. Reduction of 3α,12α−dihydroxy−7−keto−5β−cholanic acid gives deoxycholic acid (Scheme 8).[8]



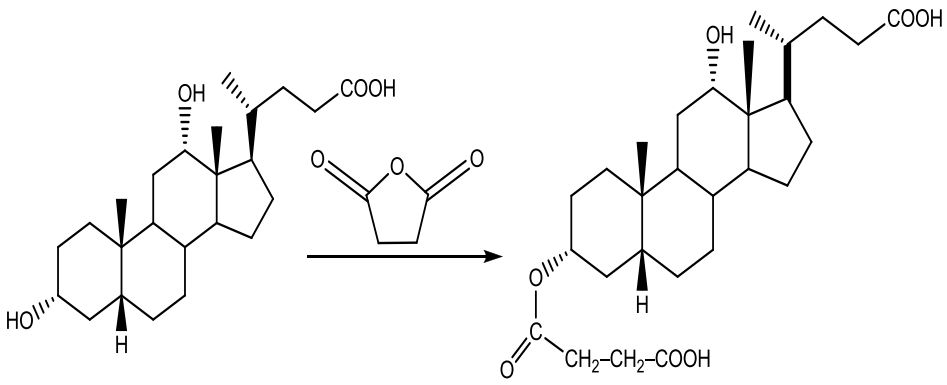
Ethyl cholate

3α, 12α–dihydroxy–7–keto–5β–cholanic acid

Deoxycholic acid

Scheme 8: The synthesis of deoxycholic acid from ethyl cholate.[8]

Reaction of succinyl anhydride with deoxycholic acid results in the formation of the 3α−succinoyloxy derivative of deoxycholic acid (Scheme 9).[8]

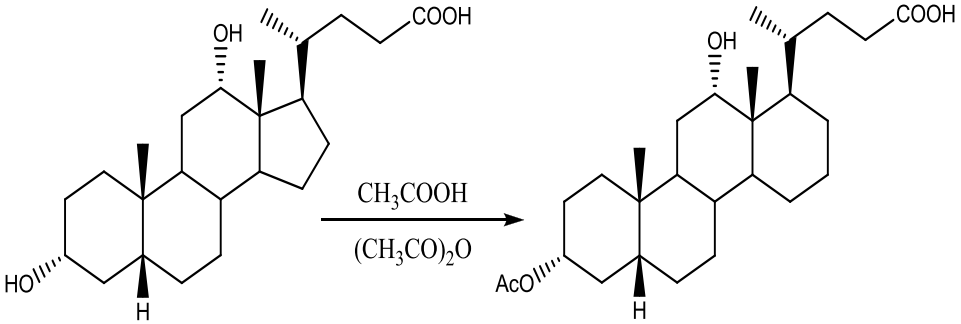


Deoxycholic acid

3α–succinoyloxy derivative of deoxycholic acid

Scheme 9: Synthesis of the 3α−succinoyloxy derivative of deoxycholic acid.[8]

Deoxycholic acid is converted to 3α−acetoxy−12α−hydroxy−5β−cholanic acid by means of acetic acid and its acetic anhydride (Scheme 10).[8]



Deoxycholic acid — 3α–acetoxy–12α–hydroxy–5β–cholanic acid

Scheme 10: Selective 3α−acetylation of deoxycholic acid.[8]

Biomedical application of bile acids

Bile acids as therapeutic agents have the potential to produce a beneficial effect on the sexually transmitted diseases, primary biliary cirrhosis, primary sclerosing cholangitis, stones in the gall bladder, disorders of gastrointestinal tract, cystic fibrosis and cancer. Bile acids decrease the amount of cholesterol that is excreted in bile.[6] Chenodeoxycholic acid reduces the activity of HMG-CoA reductase, the rate-limiting enzyme in the formation of cholesterol. Ursodeoxycholic acid increases the amount of hepatic cholesterol converted into bile acids.[7] It was recently discovered that deoxycholic acid causes fragmentation of a Golgi apparatus and fragments of these organelles were found in tissue biopsies of patients suffering from ulcerative colitis and cancer of colon. Bile acids also activate the secretion of salt and water from the colon. Unlike deoxycholic acid and lithocholic acid, ursodeoxycholic acid is used to treat inflammatory liver diseases such as primaty biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC).[6,7] Ursodeoxycholic acid has potential as a hemoprotective agent. The oral ursodeoxycholic acid is rapidly absorbed into the small intestine, resulting in a low concentration of this acid that reaches the colon.[9] Disulfate C-7 and C-3,7 derivatives of ursodeoxycholic acid inhibit intestinal absorption, thereby improving the availability of this acid in the colon. Unlike natural bile acids, these derivatives are mainly excreted in feces in an unchanged form and are subject to a minimal conversion to toxic lithocholic acid.[7],[9] The sulphate derivatives of ursodeoxycholic acid are more effective hemoprotective agents than the natural ursodeoxycholic acid. During the treatment with uesodeoxycholic acid, there is a change in relative concentrations of bile acids−ursodeoxycholic acid becomes the main component of the bile. Ursodeoxycholic acid inhibits intestinal absorption of cholesterol and its secretion into the gallbladder.[9] The exact mechanism of action in cholestatic liver disease has yet not been explained. Three basic mechanisms are likely be involved: suppression of hepatotoxicity induced by bile acids, cytoprotective effect on hepatocytes and modification of the immune system. It is used to dissolve gallstones. For the action of this drug, it is crucial that the function of the liver is good, that the function of the gallbladder is also good and that the gallstones consist exclusively of cholesterol. Namely, gallstone is sometimes composed of calcium carbonate and in this case the therapy with ursodeoxoic acid is not successful. Calcification of gallstones is possible during therapy. In rare cases, a soft stool was observed in patients.[9]

Bile acids have been implicated in both the causation and prevention of cancer. The mechanism by which fat is carcinogenic to the colon is unclear, but it may arise from the ability of secondary bile acids to act as tumor promoters.[7]

It is also known that bile acids achieve their effects mostly by nuclear receptors, which they primarily bind to farnesoid X receptors, but also the constitutive androgen receptor (CAR).[10] Nuclear receptors provide the network of mechanisms of negative and positive feedback, primarily in order to protect the liver and intestinal cells from the accumulation of bile acids, preventing their synthesis and retrieval in the cells and at the same time including detoxication and export systems of bile acids. Nuclear farnesoid X receptor (FXR) and the membrane Takeda G−protein−coupled teceptor 5 (TGR 5) are also known to improve glucose and insuline sensitivity in obese and diabetic mice for the activation of bile acids.[10] The most effective receptor for the maintenance of homeostasis of bile acids in the body is FXR. Except the regulation of metabolic processes, FXR is significantly involved in the processes of inflammation and carcinogenesi.[10] Activation of FKR can suppress carcinogenicity in the liver. From natural bile acids, only litocholic acid acts as a vitamin D receptor agonist (VDR).[10,11] A somewhat higher affinity for vitamin D receptors show derivatives of lithocholic acid, 3−keto lithocholic acid and LCA-acetate and LCA-propionate. VDR has a protective effects on the action of lithocholic acid, which is carried out by the activation of the CYP 3A4 enzyme, which performs the hydroxylation of lithocholic acid and enzyme SULT 2A1, which catalyses the sulphation of hydroxy derivatives of lithocholic acid.[11] The activation of VDR in enterocytes leads to increase in the expression of MRP3 transporter, which performs the efflux of lithocholic acid and its metabolites from the cells, preventing their intracellular accumulation.[11,12] Despite the low concentration of

VDR in the liver, it was found that the VDR activation with calcitriol in primary human hepatocytes leads to the induction of metabolic enzymes CYP 3A, CYP 2B, and CYP 2C, as well as in the suppression of CYP 7A1, that is, inhibition of bile acid biosynthesis in the liver. The PXR receptor plays a role in the maintenance of the bile acid homeostasis, so that by its activation comes to induction of cytochrome, which converts the bile acids into hydrophobic derivatives and increases the expression of enzymes, which conjugate hydroxylated metabolites of bile acids.[12,13]

This nuclear receptor is a biological sensor of bile acids, which is activated by increasing their concentration in the organism and transcriptionally regulates the expression of gene involved in the synthesis, transport and metabolism of bile acids.[14] FXR induces SHP, which further inhibits the transcription of the key CYP 7A1 gene in the synthesis of bile acids and CYP 8B1 gene, whose expression is determined by the ratio of cholic and chenodeoxycholic acids.[14,15,16] The level of expression of FXR in the liver was reduced in diabetic animals. FXR activation via SHP leads to a reduction in gene expression for phosphoenolpyruvate carboxycinase (PEPCK) and glucose-6-phosphatase (G6Pase), enzymes involved in the gluconeogenesis process.[10,14] Bile acids facilitate the uptake of lipids together with the fat-soluble vitamins A, D, E and K from the intestine. Bile acids also control the intestinal microbial flora and play a role in the elimination of cholesterol from the body. Also, bile acids are increasingly being appreciated as signaling molecules that inform cells and organs concerning the fasting/feeding state, thereby regulating processes ranging from bile acids and metabolism of lipids to glucose and energy homeostasis.[14]

CONCLUSION

In this paper we analyzed the biosynthesis and various chemical synthesis of bile acids, then the biomedical application of bile acids and the manifestation of their role by binding to the corresponding nuclear receptors.

Bile acids as absorption promoters have the potential to aid intestinal, buccal, transdermal, ocular, nasal, rectal and pulmonary absorption. Bile acids as therapeutic agents have the potential to produce beneficial effects in sexually transmitted diseases, primary biliary cirrhosis, primary sclerosing cholangitis, gallstones, digestive tract diseases, cystic fibrosis and cancer. Ursodeoxycholic acid possesses cholesthetic and antiprotective properties and it is used in the treatment of hepatobiliary symptoms of cystic fibrosis. It has been proven that ursodeoxocholic acid normalizes the function of the liver, tests and prevents the progression of fibrosis. Deoxycholic acid has the ability to change intracellular signaling and expression of the gene by using the activity of protein kinase C. Protein kinase C is an enzyme that is very responsible for phosphorylation of proteins, which regulates growth, differentiation and apoptosis of the cells. In addition to secondary bile acids, conjugated and unconjugated bile acids have the ability to activate the protein kinase C. The derivatives of ursodeoxycholic acid and chenodeoxycholic acid have shown antiproliferative effect and they are able to induce apoptosis in carcinogenic cells. These anti-chancergenic properties create the possibility that bile acid derivatives may be suitable leading compounds in the synthesis of new agents for preventional of cancer. It is suggested that natural and synthetic bile acid derivatives are used as new therapeutic agents, and not only as auxiliary agents in some known active substances in pharmaceutical agents.

ACKNOWLEDGMENTS

Great thanks to Momir Mikov for his assistance in preparing the research. This work has been supported by the Ministry of Education, Science and Technology of Republic of Serbia.

CONFLICT OF INTEREST

The authors have no conflicts of interest that are directly relevant to the content of this manuscript.

REFERENCE

1. Kuhajda K, Kandrac J, Kevresan S, Mikov M, Fawcett JP. Structure and origin of bile acids: An overview. In: Mikov M, Fawcett JP, editors. Chemistry, Biosynthesis, Analysis, Chemical and Metabolic Transformations and Pharmacology. Geneva: Mediset−Publishers, 2007; 17−31.
2. Sarenac T, Mikov M. Biosynthesis and Biotransformation of Bile Acids. Hospital Pharmacology of International Multydisciplinary Journal, 2017; 4(1): 469-485.
3. Kevresan S, Kuhajda K, Kandrac J, Fawcett JP, Mikov M. Biosynthesis of bile acids in mammalian liver. In: Mikov M, Fawcett JP, editors. Chemistry, Biosynthesis, Analysis, Chemical and Metabolic Transformations and Pharmacology, Geneva; Mediset−Publishers, 2007; 37−49.
4. Chiang J.Y.L. Bile acids: regulation of synthesis. J Lipid Res, 2009; 50(10): 1955-66.
5. Moghimipour E., Ameri A. and Handali S. Absorption-enhancing effects of bile salts. Molecules, 2015; 20(8): 14451-73.
6. Monte M.J., Marin J.J.G., Antelo A., Vazquez-Tato J. Bile acids: Chemistry, physiology and pathophysiology. World J Gastroenterol, 2009; 15(7): 804-16.
7. Rosenthal M.D., Glew R.H. Medical biochemistry – Human metabolism in health and disease. John Wiley J. & Sons, Inc., Publication, 2009.
8. Kuhajda K, Kevresan S, Kandrac J, Fawcett JP, Mikov M. Chemical and metabolic transformations of selected bile acids. In: Mikov M, Fawcett JP, editors. Chemistry, Biosynthesis, Analysis, Chemical and Metabolic Transformations and Pharmacology, Geneva; Mediset−Publishers, 2007; 89−167.

9. Mikov M, Fawcett JP, Kuhajda K, Kevresan S. Pharmacology of Bile Acids and their Derivatives Absorption Promoters and Therapeutic Agents. In: Mikov M, Fawcett JP, editors. Chemistry, Biosynthesis, Analysis, Chemical and Metabolic Transformations and Pharmacology, Geneva; Mediset−Publishers, 2007; 177−20.
10. Chiang JY. 2002. Bile acid regulation of gene expression: roles of nuclear hormone receptors. Endocr Rev, 23: 443–463.
11. McKenna NJ, Evans RM, O'Malley BW. Nuclear receptor signaling: a home for nuclear receptor and coregulator signaling research. Nucl Recept Signal, 2014; 12: 1−6.
12. Eloranta JJ, Kullak-Ublick GA. The role of FXR in disorders of bile acid homeostasis. Physiology (Bethesda), 2008; 23: 286 – 295.
13. Katsuma S, Hirasawa A, Tsujimoto G. Bile acids promote glucagon-like peptide-1 secretion through TGR5 in a murine enteroendocrine cell line STC-1. Biochem Biophys Res Commun, 2005; 329: 386–90.
14. Jonker JW, Liddle C, Downes M. FXR and PXR: potential therapeutic targets in cholestasis. J Steroid Biochem Mol Biol, 2012; 130: 147–158.
15. Jacinto S, Fang S. Essential roles of bile acid receptors FXR and TGR5 as metabolic regulators. Anim Cells Syst, 2014; 18: 359–364.
16. Russell DW. The enzymes, regulation and genetics of bile acid synthesis. Annu Rev Biochem, 2003; 72: 137–174.