Physiology and Physical Chemistry of Bile Acids

Maria Chiara di Gregorio 1*, Jacopo Cautela 2 and Luciano Galantini 2*

1 Department of Molecular Chemistry and Materials Science, Weizmann Institute of Science, Rehovot 7610001, Israel
2 Department of Chemistry, Sapienza University of Rome, 00185 Rome, Italy; jacopo.cautela@uniroma1.it
* Correspondence: maria-chiara.di-gregorio@weizmann.ac.il (M.C.d.G.); luciano.galantini@uniroma1.it (L.G.)

Abstract: Bile acids (BAs) are facial amphiphiles synthesized in the body of all vertebrates. They undergo the enterohepatic circulation: they are produced in the liver, stored in the gallbladder, released in the intestine, taken into the bloodstream and lastly re-absorbed in the liver. During this pathway, BAs are modified in their molecular structure by the action of enzymes and bacteria. Such transformations allow them to acquire the chemical-physical properties needed for fulfilling several activities including metabolic regulation, antimicrobial functions and solubilization of lipids in digestion. The versatility of BAs in the physiological functions has inspired their use in many biomedical applications, making them important tools for active molecule delivery, metabolic disease treatments and emulsification processes in food and drug industries. Moreover, moving over the borders of the biological field, BAs have been largely investigated as building blocks for the construction of supramolecular aggregates having peculiar structural, mechanical, chemical and optical properties. The review starts with a biological analysis of the BAs functions before progressively switching to a general overview of BAs in pharmacology and medicine applications. Lastly the focus moves to the BAs use in material science.

Keywords: bile acids; physiological functions; bile acid derivatives; pharmacological application; material science applications; self-assembly; surfactants

1. Introduction

Bile acids (BAs) constitute an important class of biological molecules produced in the metabolism of all vertebrates. In mammals, they exhibit the so-called C24 structure: 24 carbon atoms form a steroid nucleus (three six-member rings indicated as A, B, C and a five-member ring indicated as D) and a five-carbon side chain with a carboxyl group at the C-24 position.

The A and B rings are linked in cis configuration, inducing an overall bent shape. Such a structural feature delineates a concave and convex side of the steroidal backbone where OH groups in α orientation (up to three) and two methyl groups in β orientation, respectively, point out. Therefore, two opposite faces with hydrophilic and hydrophobic properties can be distinguished. Figure 1a,b) Further variations of the molecular structure can be observed at C-3 carbon due to hydroxyl, sulfate or glucuronate substituents [1,2]. C-6 and C-24 glucuronide conjugates were also found in humans [2]. Other C-24 substituents are glycine or taurine [3–6]. Recently Dorrestein et al. reported new amino acid C-24 substituted cholic acid (CA) namely phenylalanocholic, tyrosocholic and leucococholic acid [7]. BA actions generally occur in conditions where they are deprotonated; for this reason, many authors refer to them as bile salts instead of acids. In this review the term BA will be used keeping in mind that we refer mostly to their salt form.

According to the order in which they are produced in the human body, BAs are differently named. CA and chenodeoxycholic (CDCA) acids—3 and 2 OH groups, respectively—are first synthesized by the hepatocyte and thus named primary BAs. Subsequently CA and CDCA are conjugated to glycine or taurine, giving rise to glycocholic...
taurocholic (TCA), acids and glycochenodeoxycholic (GCDCA), taurochenodeoxycholic (TCDCDA) acids, respectively. Further metabolization leads to the secondary BAs, deoxycholic (DCA) and lithocholic (LCA) acids, that present two and one OH groups, respectively (Figure 1c,d). The increase in the hydrophobic character, moving from primary to secondary BAs, affects the BA chemical–physical and physiological properties, making them differently active in the diverse parts of the enterohepatic circuit.

Generally speaking, five major physiological roles can be distinguished in BA activity: (1) regulation of cholesterol homeostasis; (2) deterrence for the formation of gallstones and kidney stones; (3) emulsification of dietary lipids and absorption of fat-soluble vitamins; (4) antimicrobial activity; (5) regulation function.

These functions will be described in the next paragraphs, following the BA physiological pathway—from biosynthesis to elimination/recirculation.

BAs are produced in the liver and stored in the gallbladder. Subsequently they are secreted through the biliary tract in the intestine, absorbed in the intestinal epithelium to pass into the portal circulation and return to the liver. The overall process is named enterohepatic circulation. [8] A small part of BAs escapes this cycle being secreted through the feces. The daily loss of BAs is compensated by new liver production.

Figure 1. (a) Planar representation of the general molecular structure of bile acids (BAs). Letters, numbers and labels R indicate the rings of the steroid skeleton, the carbon atoms and the functional groups, respectively. (b) Chair representation of the general molecular structure of BAs. Brackets indicate the hydrophobic and hydrophilic faces. (c) Molecular structures of BAs showing different hydroxyl groups on the steroid backbone. (d) Molecular structures of the amino acid conjugated BAs.

2. Synthesis in the Liver and Storage in the Gallbladder: BAs in Cholesterol Metabolism

BAs are produced in their primary forms (CA and CDCA) in the liver, adopting cholesterol as starting substrate and the activity of 16 enzymes. Such enzymes catalyze 17 different reactions. In humans, the synthesis takes place in multiple intracellular compartments such as the cytosol, endoplasmic reticulum, mitochondria and peroxisomes.

A living organism can exploit two different synthetic routes for the BA synthesis [9].
The route, that is quantitively more important for adult humans, is known as “classic or neutral path” and provides for more than 90% of the BA needs. Such a synthetic pathway starts with the hydroxylation of the sterol ring on C7 mediated by the cholesterol 7α-hydroxylase (CYP7A1). Subsequently the intermediate is immediately modified on the lateral chain by the sterol 27-hydroxylase (CYP27) for the CDCA synthesis or, in the case of the CA synthesis, is further hydroxylated on C-12 by the 12α-hydroxylase (CYP8B1) before the CYP27 catalyzed step. In this pathway, the CYP7A1 activity is the kinetic key that determines the overall rate of the metabolic pathway. On the other hand, the CYP8B1 activity, modulating the hydrophilicity composition of the steroid nucleus, controls the CA and CDCA production ratio.

The second biosynthetic route, named “acidic path”, leads to the production of CDCA in humans and it is dominant in human neonates. In this pathway the chemical modifications of the cholesterol substrate involve first the lateral chain where a hydroxyl group is introduced on C27 by the CYP27 activity. Subsequently the modification of the sterol part is performed by the oxysterol 7α-hydroxylase (CYP7B1). A minority fraction of C25- and C24-hydroxycholesterols generated by the corresponding hydroxylases can also enter the acidic pathway to form BAs. Although most of the hydroxycholesterols are produced in the liver, hydroxycholesterols generated in extra hepatic tissues, such as lungs and brain, may be transported to the liver and be also involved in this BAs biosynthetic route. After their synthesis, CA and CDCA are conjugated to taurine and glycine by the activity of two enzymes, bile acid-CoA synthase and bile acid-CoAmino acid N-acyltransferase. The conjugation makes the produced BA more hydrophilic and more acidic on the side chain: the pKa decreases from ~5.0 to ~3.9 and <2 for glycine and taurine conjugates, respectively. The amount of synthesized BA is regulated by control mechanisms that operate at transcriptional level, where the transcription factors are nuclear receptors. An exceeding amount of BA triggers a negative feedback mechanism, starting with the BAs binding to the hepatic farnesoid X receptor (FXR) and ending with the inhibition of the genes expressing the CYP7A1 and CYP8B1 enzymes involved in the biosynthesis of BA [10,11]. The activation of FXR affects not only the synthesis itself but it also regulates the level of the BA in the intestine and biliary tree. Indeed, in order to assure concurrently an efficient lipid absorption and a sustainable hepatic level of BA, the FXR increases the expression of the transporters which mediate the efflux of the BA into the biliary canaliculi. At the same time, it suppresses the expression of the importer NTCP, thus reducing the BA reabsorption from the blood into the hepatocytes [12]. Besides the effect in the liver, reabsorbed BAs can bind also the intestinal FXR in the distal ileum, activating it. The activated FXR stimulates in turn the expression of the fibroblast growth factor 19 (FGF19) and its release into the portal blood. Once it reaches the hepatocyte plasma membrane, FGF19 binds the FGF receptor 4 (FGFR4)/β-klotho complex, triggering a signaling cascade that results in the suppression of the CYP7A1 mRNA and thus the suppression of the CYP7A1 expression [13,14].

BA production utilizes a consistent amount of the cholesterol pool (about 500 mg per day), thus turning out to be one of the main mechanisms for cholesterol regulation in the human body. [15] Consistently, hypercholesterolemia is often treated by Bas sequestrants [16–19]. It has been observed that certain animals when fed with hypercholesterolic diet manage to keep normal the plasma cholesterol level, thanks to a compensating mechanism that increases the production of BAs [20]. BAs sequestrants [16] are generally formed by cationic polyelectrolytes, which are able to bind the BAs through both electrostatic and hydrophobic attractive interactions and as such to remove them from the enterohepatic circulation. Sequestration stimulation increased conversion of cholesterol into BAs in the liver, thereby leading to the lowering of the LDL (low-density lipoproteins, “bad”) cholesterol in the blood, and simultaneously to an increase in the HDL (high-density lipoproteins, “good”) cholesterol and triglycerides [21,22]. BA sequestrants are also used in the medical treatment of BA related diseases, such as BA diarrhea caused by BAs in the large intestine or colon due to the malabsorption of BA in the small intestine (secondary BA
diarrhea) or BA overproduction resulting from defective feedback inhibition of the biosynthesis of BAs in the liver (primary BA diarrhea) [23–26]. In the treatment, sequestrants bind BAs, hinder them from contact with the colonic mucosa, thereby decreasing the BA level in the colon [27–29]. BA sequestrants can also reduce glucose levels in patients with type 2 diabetes mellitus, although the mechanism of action still remains unclear [30]. Moreover, BAs malabsorption reduces the amount of BA in the small intestine inducing fat maldigestion and consequent steatorrhea as occurring in patients with short bowel syndrome [31]. Consequently, the maldigested fatty acids in the small intestine complex the luminal Ca, lowering the fraction of Ca available for the dietary oxalate precipitation. In turn, the oxalate remains as free ions and is hyperabsorbed by the colon, leading to hyperoxaluria and increasing the possibility of kidney stone formation. Oral therapies based on natural and synthetic conjugated bile salts were observed to decrease fecal fat and urinary oxalate excretion in patients with short bowel syndrome [32,33].

A further important role of BAs towards cholesterol concerns the solubilization activity in the bile. Cholesterol is majorly eliminated through the secretion in bile. Bile is a solution produced in the liver that is composed by 95% of water. Free cholesterol is insoluble in aqueous solutions. However, in bile due to the presence of BAs (about 0.7%) and lipids like lecithin, cholesterol is easily solubilized through the formation of mixed micelles. Such a process avoids the cholesterol supersaturation and in turn the formation of gallstones. The interaction between cholesterol and BAs has been analyzed both from a chemical and medical point of view. In the first case, several studies analyzed the structure, stability and parameter formation of BAs–cholesterol-based micelles and crystals [34–36]. In the latter case, CDCA was proved in the 1970s as successful molecule for dissolution of cholesterol gallstones [37–40]. However, its use was lately abandoned because of the occurrence of side effects. The more hydrophilic ursodeoxycholic acid (UDCA) and its taurine conjugate started to be investigated as alternative treatment for cholelithiasis and their use in oral therapy is still ongoing, albeit restricted to a specific target group of patients (e.g., patients having gallstones due to temporary and non-genetic causes) [41]. The combined efficiency of UDCA and polyunsaturated fatty acids in dissolving cholesterol gallstones in mice was recently reported by Lee et al. [42].

After the synthesis, conjugated BAs are transferred into bile, passing through the hepatocyte’s membrane to the canaliculi via the biliary tree. The bile in the canaliculi converge in a series of ducts that eventually terminate into the common hepatic duct. Via the hepatic duct, the bile reaches the gallbladder, where it is stored or is delivered directly to the intestinal lumen [43].

3. From the Gallbladder to the Intestine: Lipid Solubilization and Absorption

After a meal, the cholecystokinin hormone is released and its presence is the signal for the gallbladder to release bile. At this point the aminoacidic conjugation is functional for the BA activities since it allows for the transits to the small intestine via the biliary tree. Indeed, being completely ionized at the pH of biliary tract and small intestine, conjugated BAs cannot diffuse through the cell membranes, thus assuring consistent intraluminal concentration in the intestine for lipid digestion. Moreover, the conjugated BAs are less prone than unconjugated BAs to precipitate in presence of high concentration of Ca²⁺ ions. In the distal small intestine, bacteria break the conjugation with the aminoacidic of a fraction of conjugated BAs. Deconjugation is completed in the colon where further modifications as dihydroxylation and epimerization occur to give rise to secondary BAs, i.e., DCA, LCA and UDCA. Recently, anaerobic in vitro reconstitution experiments showed that six enzymes are sufficient for the conversion of cholic acid into DCA [44].

At any time, a portion of 85–90% of BAs is present in the small intestine. Here BAs have several roles in the digestion of lipids, ranging from emulsification to transport (Figure 2a) [45,46]. Lipid digestion starts in the stomach where the food is initially broken down by the mechanical action of peristalsis and by the chemical activity of gastric juices. Subsequently the digestion continues in the duodenum where the partially digested food
mixes with digestive enzymes from the pancreas—pancreatic lipase—and BAs. At this stage, the ingested lipids are in the form of oil-in-water emulsion stabilized by different surface-active substances such as proteins and phospholipids. In order to hydrolyze lipids into simpler and absorbable molecules, lipase and its co-factor co-lipase have to anchor on the droplet surface. The first crucial role of BAs is to increase the bioavailability of the lipid substrates to the enzyme by displacing the different stabilizers at the water–oil interface. Subsequently BAs indirectly help the positioning of lipase on the lipidic substrate by favoring the interfacial adsorption of co-lipase. After the lipase activity, lipids are decomposed in free fatty acids and monoglycerides. These products remain at the oil–water droplet interface until BAs englobe them in mixed micelles, thereby providing their removal and transport through the intestinal mucus.

The fundamental understanding of these mechanisms is supported by a large collection of literature that by means of microscopic, spectroscopic and rheological techniques, (i) analyzed the displacement mechanism of BAs with respect to a large number of proteins and lipids (Figure 2b), (ii) demonstrated the improved activity of lipase in presence of BAs, (iii) elucidated the mechanism of lipid transport through the intestinal mucus [45,47–49]. Besides clarifying the physiological mechanism, such knowledges turn out to be essential for food and drug industry in order to engineer efficient strategies for drugs, dietary lipids and sugars uptake in the gastrointestinal tract [50–53].

Figure 2. (a) Schematic representation of the BA functions and self-assembly during the lipid digestion and transport in the intestine (adapted from Macierzanka, A.; Torcello-Gómez, A.; Jungnickel, C.; Maldonado-Valderrama, J. Bile Salts in Digestion and Transport of Lipids. Adv. Colloid Interface Sci. 2019, 274, 102045. [46] with permission from (2019) Elsevier). (b) Transmission Electron Microscopy images of oil-in-water emulsions stabilized by two surfactants with interest in food and drug industry, namely Pluronic F68 and Lecithin (left top). Transmission Electron Microscopy images of the surfactant-emulsion transformation upon BA (left center) and BA + lipase addition (left bottom). Scheme representing the disposition of surfactant-BA-lipase at the oil/water interface (right). Reproduced from Torcello-Gómez, A.; Maldonado-Valderrama, J.; Martín-Rodríguez, A.; McClements, D.J. Physicochemical Properties and Digestibility of Emulsified Lipids in Simulated Intestinal Fluids: Influence of Interfacial Characteristics. Soft Matter 2011, 7, 6167–6177. [53] with permission from The Royal Society of Chemistry.

4. Antimicrobial Activity

BAs and gut microbiota have a mutual interaction. As aforementioned, the molecular structures of primary BAs are modified by the gut bacteria to give rise to secondary BAs or other BA forms that escape the enterohepatic circulation. Nevertheless, also BAs influence the microbiota composition [54,55]. Concerning the latter point, it has been for example observed that low levels of BAs in the gut induce an overgrowth of bacteria and potential pathogens, increasing the occurrence of inflammations and bacterial translocation. This is due to the fact that BAs have relevant antimicrobial activities. The BAs antimicrobial activity can be mainly related to two different action mechanisms. The first one refers to the detergent properties of BAs and their ability to penetrate and break membranes...
In vitro experiments proved that BAs can provoke hemolysis in erythrocytes due to BA-induced membrane damages [56]. Similarly, cells were observed to shrivel under BAs exposure and release intracellular materials [57–59]. Fast and drastic decomposition of membrane proteins occurs at high BA concentrations [60]. Sub micellar BA concentrations can also alter membrane permeability by interacting with membrane-bounded enzymes/proteins, by changing the transmembrane flux of divalent cations or by inducing hydrophobicity and external charge modification of the cells [61]. Antimicrobial activity due to detergent properties is particularly strong in unconjugated BAs [62]. Indeed, unconjugated BAs can passively penetrate through the lipid bilayer by the “flip-flop” mechanism and access the cells [63]. The kinetic of the penetration process is strongly affected by the number of hydroxyl groups, becoming more efficient as the number of hydroxyl group decreases. Consistently antimicrobial activity of DCA was proved in vitro to be an order of magnitude higher than that of CA. On the other hand, conjugated BAs are strong acids and are fully ionized at physiological pHs. In the absence of a specific transport system, this feature inhibits the BA penetration through the membrane, favoring instead the BA adhesion on the external part of the bilayers. In vitro studies showed that such adhesion varies the membrane surface properties that, although destabilizing cell integrity, induce less membrane damage than the unconjugated analogues. Despite the in vitro results, in vivo experiments suggested relevant antibacterial properties related to the presence of conjugated BAs. It was for example observed that events that decrease conjugated BA secretion in animals, such as liver cirrhosis or bile duct ligation, induce an increase in the bacterial growth (Figure 3d–f). Similarly, upon feeding of conjugated BAs and bile in BAs-deficient intestines, overgrowth of bacteria was suppressed. Such contradiction was solved by Inagaki and coworkers in 2006 who showed an alternative antibacterial mechanism of BAs [64]. It was proved that conjugated BAs are natural ligands of the nuclear receptor farnesoid X (FXR) that in turn activate the expression of genes whose products (e.g., nitric oxide) stop bacterial overgrowth. Such a mechanism occurs in the distal small intestine that turns out to host a poor fraction of microbes (about $10^4$ to $10^5$ colony-forming units/mL), a high concentration of conjugated BAs (about 10 mM during digestion time) and an FXR level three times higher than the epithelium of the proximal small intestine.

Moreover Kang et al. recently discovered that the bile acid 7a-dehydroxyxylating gut bacteria, responsible for the biotransformation of primary BAs into secondary BAs, secrete tryptophan and proline-based antibiotics. Such antibiotics are able to obstruct bacterial pathogens causing diarrhea and colitis and their efficiency is enhanced in presence of DCA and LCA [65]. Commensal gut bacteria were also demonstrated to have a regulating function towards liver cancer by using BAs as signaling molecules. Indeed, BAs through the portal vein reach the liver sinusoidal endothelial cells and regulate the accumulation of natural killer T cells, which in turn inhibits the liver tumor growth. It was found in particular that the accumulation of the natural killer T cells was favored by primary BAs and disfavored by secondary ones [66].

To conclude this paragraph, it has to be emphasized that the enteric flora in the human body can have protecting functions, by for example eliciting immune responses, but can be also responsible for pathologies such as inflammatory bowel disease and cancers [67,68]. Therefore, the resistance of bacteria to the bile toxicity turns out to be one of the key mechanisms used by the human body to select probiotic strains that can positively perform in the gastrointestinal tract. The functions showed in the physiological environment can be modified/amplified by covalently or not-covalently combining the natural BAs with other moieties/molecules. The huge possibilities offered by modern organic chemistry has made the BAs functionalization more and more complex. Novel synthetic procedures have allowed for precise control on stereospecific substitutions, polymerization processes, introduction of differently charged groups and derivatization of concurrent and multiple positions on the original molecular structure.
The BA ability to penetrate membranes has been boosted up in derivatives, enabling for preparation of active molecule carriers where the BA derivatives (BADs) can work both as monomer (e.g., by the specific interaction with proteins membrane) or in aggregates (e.g., by the formation of drugs including transfersomes, vesicles, micelles, gels). BAs emulsification properties have been investigated to formulate new drugs for treatment of obesity and other diseases related to slow fat assimilation and high levels of cholesterol (e.g., lithiasis). Starting from the regulatory functions of BAs, BADs have also been developed to interfere in several physiological pathways (e.g., glucose, lipid and energy metabolism) for the treatment of metabolic syndromes.

5. Functionalized BAs in Medicine

In the light of their biological origin and the specific interaction with several physiological pathways, BA and BADs have naturally become the protagonist of many biomedical and pharmaceutical studies [69]. For example, antimicrobial activity of natural BAs has been used in traditional Chinese Medicine in environments different to the physiological one, e.g., in treatment of skin laceration or for reduction in swelling, pain and fever [70].

Both natural BAs and a large number of BADs have been proved efficient against many bacteria, parasites, fungi and to induce apoptosis in different types of cancerogenic cells. To mention some examples, it has been known for more than a decade that LCA induces apoptosis in neuroblastoma [71], breast cancer [72], prostate cancer [73] cells, although recently its selective effects on nephroblastoma and sarcoma cell-lines was questioned [74]. UDCA turned out to both favor and block apoptotic processes in different types of cells, according to the dosage and administration time. At low dose, UDCA efficiency has been proved in blocking lung cancer cell migration and propagation of colon and liver cancer cells. Better performance and lesser occurrence of side-effects have been shown when UDCA is used in combination with other anticancer drugs [75]. BA molecules have also been used as a platform for the synthesis of BA-based anticancer drugs recently overviewed [76]. Synthetic C24 aminoacid conjugated BA such as CDCA and UDCA acids have been reported to induce apoptosis in several human cancer cells like calf pulmonary endothelial cancer cells [77], hepatocellular carcinoma cells [78,79], breast carcinoma cells [80,81], leukemic T cells [82], prostate [83], colon [84] and gastric cancer cells. Piperazinil derivatives of CDCA and UDCA has been proved to be active anticancer drugs [85]. Heparin containing C24 modified DCA was reported to be able to limit migration and adhesion of cancer cells to extracellular matrix and to inhibit formation of metastasis [86,87]. Functionalization at C3, C7 and C12 with groups containing positive trimethyl ammonium heads was observed to show enhanced cytotoxicity compared to the precursor BA [88]. C24 substituted CA derivatives containing phenyl, benzothiazole, and four methylphenyl groups via aminoacid linkers showed good activity against breast and glioblastoma cancer cell lines [89]. Recently dihydroartemisinin–UDCA derivatives were reported to improve the cytotoxicity of dihydroartemisinin towards leukemia cells [90] and hepatocellular carcinoma [91]. A deoxycholic acid–Camptothecin conjugate [92] was recently proved by Xiao et al. to enhance the targeted delivery of anticancer molecules in liver by exploiting the specific BA-BA receptors interaction. A series of nucleoside [93] and platinum(II) [94] -BADs were screened to test the cytotoxic activity in different tumor cell lines. A bioconjugate of 4-nitro-3-(trifluoromethyl)aniline with UDCA was proposed by Navacchia et al. as photochemotherapeutic agent thanks to its ability to release the antimicrobial and antioxidant agent NO upon visible light input [95]. Different moieties were introduced on the BAs scaffold to inhibit the activity of Tyrosyl-DNA phosphodiesterase 1 that is an enzyme involved in removing DNA damage caused by the anticancer topoisomerase 1 poison drugs [96,97].

Antimicrobial activity is mainly based on the ability of BAs to damage membranes resulting from their amphiphilic steroidal structure [98]. In addition, BAs can hinder bioenergetics processes by intracellular acidification, reducing proton motive forces, DNA damaging and protein denaturation [99]. Based on the antimicrobial activity of natural
BAs, BADs have been synthesized to be used as antifouling agents [100]. Moreover, a class of BA-based antibiotics termed Ceragenins have been prepared by covalently attaching amines to BAs, inspired by the molecular structure of squalamine, a naturally occurring aminosterol with potent antimicrobial activity, isolated from shark liver [101–103]. Similar molecules have been linked as pendants to polymers able to locally cluster the facial amphiphilicity of these cationic steroid antibiotics, thereby enhancing interactions with bacterial membranes [104–106]. To date, BAs are actually used both as precursor and co-agent in drug formulation. BA-drug conjugates have been synthesized to make the drug target liver and to enhance its intestinal absorption, by exploiting the ability of the conjugate to enter the enterohepatic circulation exploiting the BA transport system. Based on these principles, BA-based nanocarriers and BADs have been synthesized to target the apical sodium-dependent BA transporter with inhibitors [107], antiviral [108] and anticancer [109] drugs. Moreover, drugs against hepatitis C virus and anticancer cytostatic drugs have been specifically targeted to the liver upon conjugation with BAs [110,111]. With the emergence of the COVID-19 pandemic, natural and synthetic BAs derivatives have also been investigated as anti-SARS-CoV2–2 agents [112,113].

![Figure 3. (a) Direct antimicrobial mechanism of natural BA: detergent effect of BA on the bacterial membrane. Transmission Electron Microscopy images of *S. aureus* before (b) and after (c) the interaction with glycocholic acid (GCA) (Sannasiddappa, T.H.; Lund P. A.; Clarke S. R. In Vitro Antibacterial Activity of Unconjugated and Conjugated Bile Salts on *Staphylococcus aureus*. Front. Microbiol. 2017, 8, 1581 [99] copyright © 2021 Sannasiddappa, Lund, Clarke (CCBY)) (d) Indirect antimicrobial mechanism of natural BA: BAs activate the farnesoid X receptor (FXR) that in turn induces](image-url)
the expression of genes producing toxic molecules for bacteria (Inagaki, T.; Moschetta, A.; Lee, Y.K.; Peng, L.; Zhao, G.; Downes, M.; Yu, R.T.; Shelton, J.M.; Richardson, J.A.; Repa, J.J.; et al. Regulation of Antibacterial Defense in the Small Intestine by the Nuclear Bile Acid Receptor. Proc. Natl. Acad. Sci. USA 2006, 103, 3920–3925. [64], Copyright (2006) National Academy of Sciences, U.S.A.). (e) Transverse sections of terminal ileum of mice immunostained with anti-occludin antiserum (top) and hematoxylin and eosin (H&E, bottom), scale bar 50 µm. Micrographs of control mice (left) are contraposed to micrographs of FXR knockout mice (right). (f) Lymphatic vessel section of FXR knockout mice, scale bar 2µm. Arrows point to traces of edema and dilated lymphatic vessels that are induced by bacteria. (g) Copolymers of cholic acid (CA) and polyethylene glycol self-assemble into rods that are able to penetrate the bacterial membrane Scanning Electron Microscopy images of E.coli without (h) and with (i) BA polymer treatment (adapted with permission from Rahman, M. A.; Jui, M. S.; Bam, M.; Cha, Y.; Luat, E.; Alabresm, A.; Nagarkatti, M.; Decho, A. W.; Tang, C. Facial Amphiphilicity-Induced Polymer Nanostructures for Antimicrobial Applications ACS Appl. Mater. Interfaces 2020, 12, 21221–21230 [105]. Copyright (2020) American Chemical Society).

6. BA-Based Polymers

BAs can be used in the preparation of polymers with a main interest in drug delivery [114]. The presence of the carboxylic and hydroxyl groups on their molecule allows them to anchor polymer chains or to join into BA-based chains. BA containing polymers have been extensively investigated and recently overviewed by Zhu and co-workers [115]. According to the former approach, BAs can be used as templates onto which polymers are grown, by exploiting the hydroxyl and the carboxylic groups as junctions for polymer chains, thereby providing star polymers [116]. The star polymers self-assemble into micelles with a hollow-core [117] able to encapsulate large drug loads, which depends on the number of BA hydroxyl groups (i.e., the number of polymer branches) (Figure 4a,b). The doxorubicin-loading ability of star polymers formed by poly(allyl glycidyl ether) and poly(ethylene glycol) grafted from the CA was recently analyzed, showing that a particularly high loading is achieved by exploiting electrostatic interactions. In addition, a remarkable cellular internalization was observed for the loaded carrier [118]. BAs can be also introduced as pendant groups in block copolymers and thereby used to tune their properties and functionalities such as pH- and thermo- responsiveness and self-healing properties (Figure 4c,d) [119,120]. The investigation of the aggregates formed by these macromolecules has been promoted for their potential in drug and gene delivery applications [119,121–123].

Polymers formed by BAs as repeating units in the main chain, have also been synthesized with branched or linear architectures [124], mainly studied for their elastomeric and shape memory properties [125]. CA has also been introduced as pendants in the hydrophobic diblock copolymers containing a glucosamine-based hydrophilic block, for bio-related applications. It was demonstrated that the self-assembly of the block copolymer could be tuned by changing the length of the blocks to provide micelle with optimal drug loading ability [126]. Recently a block copolymer containing a dextran block linked to semi-rigid deoxycholic acid-oligo ethylene glycol polyester, was investigated, which showed a rich self-assembly involving star-shaped and wormlike micelles and vesicles depending on the dextran block length [127].

7. BA Lipid Mixtures

BAs and lipids can form mixed micelles exploited to solubilize hydrophobic drugs and to improve their bioavailability [50,128] BA containing liposomes, sometimes named bilosomes, can be also prepared by intercalating BAs in the liposome lecithin bilayer. Bilosomes are preferentially used to deliver oral administrated drugs and vaccines due to their ability to stand acid conditions, enzyme attack and bile salt degradation in the gastrointestinal track compared to pure liposomes. They have also been observed to increase the absorption of oral administrated insulin [129] and to facilitate transdermal drug delivery [130].
8. BA Polymer Mixtures

Biocompatible polymers are versatile systems widely exploited in applications. Based on their composition and sample conditions they can be available as solids, free chains, covalently crosslinked nano- and micro-gels or self-assembled nanoparticles, thus providing a platform adaptable for performances in several fields including drug delivery, tissue engineering, sensors, and catalysis. Interactions of BAs with cationic polymers are crucial for sequestration in the treatment of BA malabsorption or hypercholesterolemia. However, there is room for improvement of the currently used sequestrants of water-insoluble cationic hydrogels that have poor patient compliance [28,29] and recently some reports on new polymeric BA sequestrants have appeared in the literature [131,132]. Block copolymers able to strongly interact both electrostatically and hydrophobically with BAs have been proposed as compelling alternative sequestrants [133,134]. Investigations on the interaction between BAs and poloxamers have recently demonstrated that BAs can be adsorbed on the corona of block copolymer micelles, thereby promoting block copolymers as alternative BA sequestrants [135–137]. Similar Pluronic/BA mixed micelles were proven to be appealing drug-delivery vehicles and to efficiently load drugs like Clozapine [138] and Doxorubicin [139,140]. Because the BAs are anionic surfactants, it is expected that cationic block copolymers provide better BA binding and sequestration. Therefore, in a recent paper the co-assembly in dilute aqueous solution was reported in mixtures of diblock copolymer constituted of one poly(N-isopropyl acryl amide) (PNIPAM) block and a cationic polymer block of poly(3-acrylamidopropyl)-trimethylammonium chloride (PAMPTMA(+)) and the oppositely charged BA surfactant sodium deoxycholate. Two kinds of mixed aggregates were observed to form at room temperature having a globular morphology or a longitudinally striped tape-like architecture, which have a roughly neutral zeta potential at all compositions of the mixtures (Figure 4e–g) [141]. It was also found that the loss of water-solubility of PNIPAM with increasing temperature induces pronounced aggregation at a transition temperature, to provide aggregates with an interior containing dehydrated PNIPAM and a remarkably positive or negative charge depending on the mixture composition, thereby promoting the block copolymer–BA complex as versatile smart material for nanotechnological application. It was also demonstrated that precipitation of the complexes occurs at large fraction of BA as those encountered by sequestrants in the gastrointestinal track [142]. A thermoresponsive BAD was observed to interact with the same catanionic block copolymer to form a complex, for which an intriguing thermoresponse was revealed by scattering techniques and circular dichroism measurements [143].

Polymeric carriers for the oral administration of drugs are expected to interact with BAs, which may affect the drug solubilization and absorption. With this motivation, the interaction in mixtures of sodium taurocholate and widely used hydrophilic model polymers such as hydroxypropyl methylcellulose and polyvinylpyrrolidone, was investigated, revealing that the formation of mixed BA/polymer aggregates occurs in the mixtures, which could significantly affect the drug solubilization in the gut when hydrophilic polymers are used as dispersant [144].
Figure 4. (a) Star-shaped block copolymers are able to load the drug Doxorubicin (Dox) through hydrophobic interaction (yellow box) or electrostatic interaction with (blue frame) or without (red frame) oleic acid (OA) as cosurfactant. (b) TEM micrographs of the star-polymer micelles before (upper panel) and after (lower panel) Dox loading. Adapted with permission from Cunningham, A. J.; Robinson, M.; Banquy, X.; Leblond, J.; Zhu, X. X. Bile Acid-Based Drug Delivery Systems for Enhanced Doxorubicin Encapsulation: Comparing Hydrophobic and Ionic Interactions in Drug Loading and Release Mol. Pharm. 2018, 15, 1266–1276. [118] Copyright 2018 American Chemical Society (c) Block-copolymer formed by cholic acid and β-cyclodextrin residues assembling into a self-healing gel; schematic representation showing the interplay among the residues in the gel matrix (top). (d) Optical (left) and rheological (right) evidence of the gel break and self-healing process (adapted with permission from Jia, Y. G.; Zhu, X. X. Self-Healing Supramolecular Hydrogel Made of Polymers Bearing Cholic Acid and β-Cyclodextrin Pendants. Chem Mater 2015, 27, 1, 387–393. [120] Copyright (2015) American Chemical Society). (e) The block copolymer PNIPAM120-b-PAMPTMA(+)30 when mixed with CA self-assembles into tape-like complexes where single stripes present recurring spacing. (f,g) Cryo TEM images of the tape-like aggregates (adapted from Schillén, K.; Galantini, L.; Du, G.; Del Giudice, A.; Alfredsson, V.; Carnerup, A. M.; Pavel, N. V.; Masci, G.; Nyström, B. Block Copolymers as Bile Salt Sequestrants: Intriguing Structures Formed in a Mixture of an Oppositely Charged Amphiphilic Block Copolymer and Bile Salt. Phys. Chem. Chem. Phys. 2019, 21, 12518–12529. [141] Published by the PCCP Owner Societies).

9. Self-Assembly of Natural and Chemically Modified BAs

BA salts, here simply referred to as BAs, are soluble in water and provide self-assembly. Unlike conventional surfactants with the typical head–tail amphiphilic structure these salts have a rigid molecular structure with, in the majority of the cases, a well-defined facial amphiphilicity, resulting in a more complex self-assembly. As a matter of fact, it is well established that aggregation of BAs is driven by the interplay of hydrophobic interactions and hydrogen bonds involving hydroxyl, amide and carboxylic groups and provide aggregates with merged hydrophobic and the hydrophilic domains. The issue is still debated among several self-assembly models including the stepwise mechanism from
globular primary micelles to secondary elongated ones [145,146], micellar disks [147] or helical aggregates [148,149].

In water, BAs form micelles with low aggregation number (2–20) in an associated process that is often observed to be gradual and without a sharp critical micellar concentration. Reported critical micellar concentrations decrease relative to a decrease in the number of hydroxyl groups (increasing hydrophobicity) according with the order cholate < deoxycholate [150–152], but also strongly depend on their positions and orientations with ursodeoxycholate that have hydroxyl groups in β-orientation presenting a lower cmc than the cholate and deoxycholate.

A decrease in the repulsions among the charged heads of deprotonated BAs can be induced by increasing the ionic strength or by decreasing the pH (for carboxylate BAs), thus promoting unidirectional growth of the micelles. Fibrils form because of the growth that can lead to gelation. For example, it is well known that DCA forms gels in water upon lowering pH around neutrality [4,153], with specific features induced by the used acid [154] or the presence of additives [155,156]. Gelation is also promoted by increasing the electrolyte concentration in DC, glycodeoxycholic (GDCA), LCA, and taurodeoxycholic (TDCA) acid salt solutions [149,157]. In such gels, the chirality of the building blocks is extended also at supramolecular level [158] where the helical structures of the fibrils, analogous to those observed in some BA crystal, [148,149,159], are observed.

Multivalent cations like Ca$^{2+}$ can crosslink BA charge heads promoting micellar growth and gelation for cholate and GDCA. Crosslinking and formation of nanohelices can be induced on CA solution also by other multivalent cations, like those of transition metals [160,161] and lanthanides [162–164]. Similarly, gels can be formed by LCA upon addition of alkaline earth, lanthanide, and transition-metal ions, [165] and by DCA in the presence of europium nitrate [166].

Electrolyte-induced wormlike micelle growth and gelation is also observed in lecithin/BA aqueous mixtures [167,168]. A similar growth, but with a different mechanism is observed in lecithin/BA mixtures in oil, where reverse micelles of lecithin turn wormlike upon inclusion of the BAs in their interior [169,170].

The various self-assembly behavior of natural BA includes the formation of tubular aggregates, provided by LCA at strong alkaline conditions (pH = 12) [171,172]. It was shown by Fang and coworkers that pH variation can induce a switch of the tubules from spiral to a straight shape by changing pH [173]. The same authors demonstrated that LCA can form ribbon-like J or tubular H aggregates when mixed with cyanine dyes [174], and mixed tubules with TLC that can reversibly open/close by controlling the hydration (Figure 5a) [175].

It is important to remark that BAs are chiral molecules, and can selectively interact with enantiomers of additives both in monomeric and micellar form. This ability was reported for the interaction of monomers and micelles of DCA [176], GCA, and TCA [177] with the enantiomeric conformers of bilirubin-IXa, and recently for CA and DCA with binaphthyl enantiomers [178]. BA micellar self-assembly was extensively investigated in the past and exhaustively described in a recent review [4]. In addition, it is worthy to stress that, in the light of the use of BAs in the formulation of drugs, the effect of active molecules on the self-assembly of BAs, as recently reported for CA and DCA in the presence of the antibiotic drug ceftriaxone, is a particularly relevant topic [179].

Beside the drug-conjugated derivatives employed in medicine and the polymeric molecules, a broad family of molecules can be synthesized starting from BAs, to provide an expanded set of self-assembling biomaterials [6]. Derivatives can be prepared with dispersing ability of diverse materials like proteins [180] or carbon nanotubes (Figure 5b) [181]. In addition, BAs can be used as substrates to prepare an ensemble of stereoidal building blocks for the fabrication of unconventional supramolecular nanostructures. Typically, fibers or ribbons are formed together with more complex tubular nano- and micro-aggregates with diameters ranging from a few nanometers to half a micron. Tubules are reported to form in aqueous systems of C-3 substituted BA with various residues such as
aromatic organic groups [6,182–188] or amino acids [189–192], and sugars [193,194], often via stimuli-responsive self-assembly, triggered by pH [182,183] or temperature [184,195]. Interesting systems of tubules with tunable charge or diameter have been implemented by mixtures of cationic and anionic derivatives [196,197] or precursor and derivative [198]. In addition, it was recently demonstrated that BA derivative tubules are suitable elements for higher order self-assembly, providing supracolloidal non-obvious aggregates when mixed with microgels, with relevant potential in the preparation of new functional materials (Figure 5c) [199].

Keeping the same substituent, the ability to form tubules was reported to be lost for aminoacid substituted derivatives obtained from more hydrophilic BA precursors [191,192], whereas for organic aromatic substituent, tubules with remarkably different sizes were observed to form by BA differing for number, positions and orientations of the hydroxyl groups [184–186,195]. Spectroscopies, such as circular dichroism, show that the substituents are strongly involved in intermolecular interactions in the aggregates thereby demonstrating their relevance in the self-assembly of the derivatives. The ability to form tubules in sugar substituted derivatives is lost when glucose instead of mannose [200] is used as substituent, thereby remarking the key role of the substituent and its specific interactions in the aggregation. Recently, selectively C-3 and C-12 substituted CA derivatives were investigated, highlighting crucial effects of position and orientation of the substituent on the self-assembly: both systems showed thermoresponsive assembly at similar critical temperature, probably due to the nature of the substituent, but involving morphologically different structures according to the position and stereochemistry of the substituting residue [201] (Figure 5d). Exploiting the cross-linking action of cations [202], stable gels of helical ribbons closed into hollow cylinders have been reported to form by calcium ions and phenylalanine substituted deoxycholate at high pH [203].

Several BAs functionalized at the carboxylic groups to form different species like hydrazide [204] and aminoacid [205] esters [206] and conjugate [207,208] have also been widely investigated for their organo- or hydro-gelation properties. The importance of the hydrophobic/hydrophilic balance of the derivatives on their gelation ability was clearly illustrated. Very interestingly, the gelling ability enhancement in the mixture of cationic and anionic derivatives has also been disclosed highlighting the relevant contribution to the gelation of electrostatic attraction between the derivatives charge heads [209].
Figure 5. (a) Co-assembled lithocholate/taurilithocholate tubes (optical microscopy image, top left) are longitudinally unzipped into flat structures (Atomic Force Microscopy image, top right) by capillary force upon dehydration on substrates. The process of unzipping is proved by optical microscopy images (center) and schematized (bottom) (adapted with permission from Zhang, X.; Bera, T.; Liang, W.; Fang, J. Longitudinal Zipping/Unzipping of Self-Assembled Organic Tubes J. Phys. Chem. B, 2011, 115, 14445–14449. [175] Copyright (2011) American Chemical Society). (b) BA or BA derivatives facially interact with carbon nanotubes’ surface, enabling their dispersion in water solution (scheme, top). Atomic Force Microscopy images of BA derivative dispersed carbon nanotubes in water (bottom right). Graph reporting the carbon nanotubes dispersion efficiency upon addition of BA derivatives, natural BA and conventional head–tail surfactant SDS (dark grey, light grey, black bars, respectively, bottom right) (adapted with permission from Gubitosi, M.; Trillo, J. V.; Alfarovargas, A.; Pavel, N. V.; Gazzoli, D.; Sennato, S.; Jover, A.; Meijide, F.; Galantini, L. Characterization of Carbon Nanotube Dispersions in Solutions of Bile Salts and Derivatives Containing Aromatic Substituents J. Phys. Chem. B 2014, 118, 1012–1021. [181] Copyright (2014) American Chemical Society). (c) BA derivative-based scrolls having negative (top left, red frame) and positive charge (bottom left, blue frame) interact with positive and negatively charged microgels, respectively, giving rise to electrostatically stabilized supracolloidal aggregates (right) (from Cautela, J.; Latanzni, V.; Månsson, L.; Galantini, L.; Crassous, J. J. Sphere–Tubule Superstructures through Supramolecular and Supracolloidal Assembly Pathways Small 2018, 14, 1803215. [199] Copyright (2018) Wiley). (d) Thermoresponsive cholic acid derivatives functionalized with a tert-butyl phenyl amide residue on C-3 (top left) and C-12 (top right). Microscopy images of the structures forming at lower and higher temperatures than the critical transition temperatures for the C-3 (bottom left) and C-12 (bottom right) derivatives (from Galantini, L.; Leggio, C.; Jover, A.; Meijide, F.; Pavel, N.V.; Soto Tellini, V.H.; Vázquez Tato, J.; Di Leonardo, R.; Ruocco, G. Kinetics of Formation of Supramolecular Tubules of a Sodium Cholate Derivative. Soft Matter 2009, 5, 3018–3025.[[184] permission conveyed through Copyright Clearance Center, Inc. Cautela, J.; Severoni, E.; Redondo-Gómez, C.; di Gregorio, M.C.; Del Giudice, A.; Sennato, S.; Angelini, R.; D’Abramo, M.;
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10. Conclusions

BAs are natural molecules ubiquitously found in vertebrates. In humans, they are produced in the hepatocytes from cholesterol modification and, through a cyclic path named enterohepatic circulation, are transported from liver to intestine, lately being transferred to the blood stream by which they are re-absorbed from the liver. The unusual amphiphilic structures allow BAs to exhibit detergent functions towards different compounds, e.g., solubilization of cholesterol, fat dietary lipids and penetration/breaking of membranes. The latter feature, expressed towards bacteria, makes BAs important antibacterial elements that are able to regulate the strength of the gut microbiota. Furthermore, BAs work in the body as hormones, being signaling molecules for the expression of genes and regulators of different metabolic paths. The physiological roles of BAs briefly summarized here and comprehensively overviewed by other specialist reports [210–214], opened the field for an extensive investigation of BAs and BADs use in biomedical applications including antimicrobics, anti-cholesterol drugs, regulator of dietary lipid uptake and drug carriers in co-formulations with other molecules (e.g., lipids and polymers). The application possibilities broaden even more when adopting BADs. BADs have been shown to be suitable building blocks for self-assembly structures showing a wide range of properties (e.g., gelling ability, stimuli responsiveness, self-healing). Such aggregates have been reported to be useful both in biological fields and material science. These aspects are going continuously growing, opening up unexpected scenarios in the preparation of different kinds of organic and inorganic nanomaterials [4].

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Abbreviations

| Abbreviation | Term |
|--------------|------|
| BA           | Bile acid |
| CA           | Cholic acid |
| CDCA         | Chenodeoxycholic acid |
| GCA          | Glycocholic acid |
| TCA          | Taurocholic acid |
| TCDCDA       | Taurochenodeoxycholic acid |
| GCDCDA       | Glycochenodeoxycholic acid |
| DCA          | Deoxycholic acid |
| LCA          | Lithocholic acid |
| CYP7A1       | Cholesterol 7α-hydroxylase |
| CYP27        | Sterol 27-hydroxylase |
| CYP8B1       | 12α-hydroxylase |
| CYP7B1       | Oxysterol 7α-hydroxylase |
| BAD          | Bile acid derivative |
| PNIPAM       | Poly(N-isopropyl acryl amide) |
| PAMPTMA      | Poly((3-acrylamido-propyl)-trimethylammonium chloride |
| GDCA         | Glycodeoxycholic acid |
| TDCA         | Taurodeoxycholic acid |

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