The Role of Bile Acids in the Human Body and in the Development of Diseases

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Abstract: Bile acids are specific and quantitatively important organic components of bile, which are synthesized by hepatocytes from cholesterol and are involved in the osmotic process that ensures the outflow of bile. Bile acids include many varieties of amphipathic acid steroids. These are molecules that play a major role in the digestion of fats and the intestinal absorption of hydrophobic compounds and are also involved in the regulation of many functions of the liver, cholangiocytes, and extrahepatic tissues, acting essentially as hormones. The biological effects are realized through variable membrane or nuclear receptors. Hepatic synthesis, intestinal modifications, intestinal peristalsis and permeability, and receptor activity can affect the quantitative and qualitative bile acids composition significantly leading to extrahepatic pathologies. The complexity of bile acids receptors and the effects of cross-activations makes interpretation of the results of the studies rather difficult. In spite, this is a very perspective direction for pharmacology.

Keywords: bile acids; bile acids receptors; pathogenesis

1. Introduction

Bile acids (BAs) are cholesterol metabolites that are produced exclusively in the liver in a complex multistep process involving cytosolic, mitochondrial, and peroxisomal enzymes [1]. The widespread occurrence of BAs and their derivatives throughout the animal kingdom emphasizes the wide variety of biological functions that they perform in the body. In addition to their “classical” functions (formation of bile, absorption of food lipids in the intestine, proteolytic degradation of food proteins, antimicrobial activity, maintenance of homeostasis), it has been established that bile acids perform hormone-like functions in the control of glucose, lipid, and energy metabolism, in cell proliferation, in the control of detoxification reactions, as well as in the modulation of the immune system [2].

The identification of BAs receptors in the tissue of the cardiovascular system and the recognition of BAs as vasoactive ligands that regulate vascular tone and myocardial contractility in disease have become the reason for the relevance of studying the role of BAs in the regulation of cardiovascular function [3]. It is assumed that in liver diseases (for example, cirrhosis), several mechanisms and ligands, including BAs, induce systemic and internal vasodilation, which causes hyperdynamic circulation. In addition, farnesoid
X receptor (FXR) activation may play a role in the development of atherosclerosis. Therefore, the study of the effect of BAs on the cardiovascular system is likely to provide new mechanistic ideas about their regulatory role.

In addition, BAs also play a certain physiological role in the central nervous system [4]. BAs are readily bioavailable when administered orally, subcutaneously, or intravenously, can cross the blood-brain barrier, are relatively non-toxic, and have been approved by the US Food and Drug Administration for therapeutic use in humans [5].

The composition of the BAs pool is a function of the microbial metabolism of bile acids in the intestine. Disruptions to the microbiota form a pool of BAs and modulate the activity of receptors activated by bile acid, even outside the gastrointestinal tract, triggering various metabolic axes and altering the metabolism of the host. BAs, in turn, can also regulate the composition of the gut microbiome at the highest taxonomic levels [6].

The gastric mucosa, colon, and hepatocytes are affected by BAs [7]. However, their toxicity to the mucous membrane of the respiratory tract is not well understood [8]. Patients with a range of respiratory diseases have been shown to have higher BAs concentrations in their bronchoalveolar lavage [9]. In the study [7], it was shown that BAs present in the lungs can cause damage to the epithelium of the airways, which may be a mechanism of lung damage.

In this review, the role of BAs in the regulation of inflammatory reactions, cardiovascular and nervous systems, pathogenesis of liver diseases and the effect on the development of the tumor process, the interaction of BAs with intestinal microbiota, and aspects of the participation of BAs in the pathogenesis of intestinal and pulmonary diseases are considered in detail.

An analysis of the literature was carried out using the PubMed, Mendeley, and Scopus databases. The depth of the literary search was 10 years using additional sources.

2. The Role of Bile Acids in the Regulation of Inflammatory Reactions

BA receptors, such as FXR, G protein-coupled bile acid receptor 1 (GPBAR1), vitamin D receptor (VDR), and liver X receptor (LXR), are widely represented in immune cells, monocytes and macrophages, dendritic cells, natural killer cells, and natural killer T cells, and to a lesser extent in T and B lymphocytes. By interacting with these receptors, BAs can influence the course of inflammatory reactions. FXR/small heterodimer partner (SHP) activation blocks the c-Jun N-terminal kinase (JNK) cascade and prevents the binding of nuclear factor kappa B (NF-κB) to the promoters of genes encoding proinflammatory cytokines, chemokines, and inducible NO synthase.

FXR stimulates the binding of the nuclear receptor co-repressor 1 to the promoter of proinflammatory genes, which makes it difficult for NF-κB to interact with them [10]. Under conditions of FXR activation and stimulation of toll-like receptor-4/9 by the corresponding ligands, that is, lipopolysaccharides and CpG regions of bacterial and viral DNA, the inflammatory response of intestinal macrophages is suppressed [11,12]. Probably, the anti-inflammatory effect of more amphiphilic BAs, characterized by a higher affinity for FXR, contributes to the maintenance of the tolerogenic phenotype of intestinal and hepatic macrophages and makes a significant contribution to the suppression of the inflammatory response [12].

In contrast, GPBAR1 activation entails JNK activation with an increase in the expression of genes encoding proinflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) [13]. Stimulation of GPBAR1 leads to an increase in the cAMP content in the cell and activation of protein kinase A, mTOR, and nuclear factor FOXO1, which leads to a decrease in the expression of various chemokines. Another cascade involves phosphorylation of the cAMP response element-binding protein and increased expression of the anti-inflammatory cytokine interleukin-10 (IL-10) [12].

Intestine and liver macrophages express GPBAR1 in large amounts, suggesting the important role of non-polar BAs (deoxycholic acid, DCA; tauroliothocholic acid, tauro-LCA) in suppressing the inflammatory process in the colon and liver, especially in conditions of increased concentration of non-polar BAs [13,14]. The phenotype of intestinal and hepatic
macrophages (M1 or M2) may depend largely on the BA spectrum in the intestinal lumen and portal blood [14].

GPBAR1 is also widely present in the endothelium, especially in the sinusoid endothelium [14]. Here, the role of non-polar BAs in the regulation of NO production and the intensity of hepatic blood flow is of particular importance [15].

In the endothelium, GPBAR1 also inhibits the binding of NF-κB to the promoter of target genes, causing inhibition of the production of vascular-cellular adhesion molecule-1 and TNF-α, inhibiting adhesion of circulating monocytes to endothelial cells [15].

A low degree of GPBAR1 expression is associated with a more pronounced reaction of damage and inflammation in the liver. In GPBAR1 knockout mice, alcohol-induced liver damage is more pronounced, and the negative influence of intestinal dysbiosis is more pronounced [12]. In the GPBAR1 knockout mouse model, the development of prolonged cholestasis, an increased inflammatory response, and severe liver damage was noted in response to partial hepatectomy [16]. In the mouse model of xenobiotic-induced sclerosing cholangitis, the liver injury response was less severe when GPBAR1 was highly expressed [17]. Studies have also shown that stimulation of GPBAR1 helps to reduce the degree of damage to the intestinal mucosa and stimulates regeneration [18].

The VDR signaling pathway plays an important role in the regulation of inflammatory responses, cell proliferation, and apoptosis, as well as in the control of glycolipid and energy metabolism [19]. Animal studies have shown that VDRs are involved in gut immune regulation and barrier function and reduce inflammatory responses [20]. Moreover, some studies have demonstrated the important role of BAs signaling through the VDR in adaptive immunity [21,22], especially in relation to inflammatory bowel disease. The pathophysiological significance of VDR was demonstrated in an experiment where mice lacking VDR were more vulnerable to dextran sulfate-induced colitis [2].

Liver X receptors (LXRx and LXRβ) are members of the family of nuclear transcription factor receptors that play an important role in the transcriptional control of lipid metabolism.

The significance of LXR in the biology of macrophages is relevant in the context of atherosclerosis, which is currently recognized as a chronic inflammatory disease, as well as a disorder of lipid metabolism [23]. The accumulation of large amounts of cholesterol in conditions of hypercholesterolemia is a critical step in the transformation of macrophages into foam cells in the early stages of atherogenesis [24]. LXRs are able to lower cellular cholesterol levels by promoting cholesterol efflux through the activation of the ATP-binding cassette family of transporters, which leads to an increase in reverse cholesterol transport. In addition, macrophage LXRs contribute to the reverse cholesterol transport pathway through a mechanism that includes the induction of a subset of apolipoproteins capable of serving as acceptors for cholesterol remodeling enzymes and lipoproteins [25].

The study of the course of the inflammatory processes in conditions of not only increased but also decreased content of non-polar BA is of great importance.

3. The Effect of Bile Acids on the Cardiovascular System

GPBAR1 is widely present in the vascular endothelium and smooth myocytes. A feature of the effects of GPBAR1 stimulation is a systemic vasodilating effect due to an increase in the activity of NO synthase and cystathionine γ-lyase, producing NO and H2S in the endothelium of arterioles and venules [12]. The vasodilating effect is associated with more pronounced lipophilicity of BAs. The vasodilating effect of BAs, independent of GPBAR1 stimulation and NO release by the endothelium, has also been described. Lipophilic BAs likely contribute to a decrease in the affinity of α1-adrenoreceptors for catecholamines due to the activation of lipid peroxidation and a decrease in the plasticity of smooth muscle cell membranes [26].

GPBAR1, expressed by macrophages, appears to play an important role in suppressing inflammation in atherosclerotic plaques and visceral adipose tissue, as well as in promoting lipid transport in adipose tissue [27,28].
The effects of the stimulation of FXR expressed by vascular smooth muscle cells by primary BAs are described; they lead to an improvement in the serum lipid profile and a decrease in vascular tone [29].

Dysfunction of the heart in liver diseases is associated with increased BAs in the blood. The features of such damage have been studied by ligating the common bile duct in rodents [30]. Cardiomyocyte mitochondria perform numerous functions, including energy production, cell growth, calcium transport, regulation of cell death, and production of reactive oxygen species. Many of these functions are impaired by exposure to toxins and diseases. Consequences of mitochondrial dysfunction in the heart include myocardial infarction and ischemia/reperfusion injury, cardiomyopathies, and arrhythmias, and mitochondrial abnormalities have also been described in the pathogenesis of heart failure [31]. Mitochondrial dysfunction and apoptosis of cardiomyocytes have been observed; these mechanisms likely contribute to the formation of the so-called cirrhotic cardiomyopathy [30,32]. Under conditions of obstructive jaundice, the development of bradycardia caused by the negative chronotropic effect of cholic acid (CA), is characteristic [33]. Several studies suggest that more lipophilic BAs (LCA, DCA, and chenodeoxycholic acid, CDCA) can disrupt mitochondrial function by reducing membrane potential, inducing the formation of mitochondrial permeability transition pores, and the deployment of the programmed cell death cascade [30,34,35]. The more hydrophilic glyco- and tauro-conjugates of these BAs exhibited less damaging effects. Ursodeoxycholic acid (UDCA) and its conjugates had the lowest mitochondrial toxicity index [30]. Figure 1 schematically shows the interaction of BAs with various cellular molecules.

![Figure 1](image)

**Figure 1.** Interaction of bile acids with various cellular molecules: non-receptor-mediated interaction of bile acid with big potassium, calcium-activated channels, which leads to K+ outflow, hyperpolarization, and relaxation of vascular smooth muscles (1) and interaction of bile acid with nuclear receptors (2). In the cytoplasm, bile acid binding to FXR triggers dimerization with RXR, which leads to translocation of FXR into the nucleus, where FXR binds to regulatory elements of the target gene. Downward (red) and upward (blue) arrows indicate down and up-regulation of molecules, respectively. MSX2 and osterix are osteogenic transcription factors. Interaction of bile acid with GPCR, which can lead to a negative chronotropic response (for M$_2$R) in cardiac myocytes and the generation of NO (for M$_3$R and GPBAR1) in endothelial cells (3). AT2R: type 2 angiotensin receptor; BKCa: large channels activated by potassium and calcium; CD11b: cluster of differentiation 11b; ET-1: endothelin-1; interleukin-1 and -6; M$_2$R: muscarinic receptor subtype 2; M$_3$R: muscarinic receptor subtype 3; MSX2: homeobox muscle segment 2; NOS3: nitric oxide synthase 3. Figure adapted with permission from Ref. [3] 2011, Khurana, S. et al.
Elevated serum bile acids reduce cardiac fatty acid oxidation both in vivo and ex vivo probably due to suppressed expression of proliferator-activated receptor-γ coactivator 1α (PGC1α), a transcriptional activator of mitochondrial biogenesis, respiratory capacity, oxidative phosphorylation, and fatty acid β-oxidation [36]. In isolated rat heart mitochondria, the most lipophilic BAs (LCA, DCA, and CDCA) showed the most potent inhibition of respiration, respiratory control ratio, and membrane potential and caused the induction of the mitochondrial permeability, while the glycochenodeoxycholic acid possessed the lowest toxicity [37]. These results indicate that at toxicologically relevant concentrations, most bile acids (mainly the most lipophilic) alter mitochondrial bioenergetics. The impairment of cardiac mitochondrial function may be an important cause of the observed cardiac alterations during cholestasis.

Studies on atrial myocardial preparations revealed that an increased concentration of CA can increase the excitability of cells and induce rhythm disturbances. In isolated cardiac myocytes, tauro-CA caused spontaneous depolarization and increased the intensity of the Na⁺/Ca²⁺ flow [38].

4. The Influence of Bile Acids on the Hypothalamic–Pituitary–Adrenal Axis

Steroid-producing cells are particularly susceptible to the effects of BAs. The adrenal cortex cells express at least 3 types of BA receptors, namely, FXR, GPBAR1, and sphingosine-1-phosphate receptor 2 (S1PR2). In an experiment, under the conditions of ligation of the common bile duct, oral administration of CDCA significantly increased the activity of steroidogenesis enzymes and the content of corticosterone. Tauro-CDCA has a stimulating effect on the S1PR2-ERK-SF-1 signaling pathway in adrenal cortex cells and on cortisol secretion [39]. At the same time, in cholestatic diseases, there are signs of suppression of the hypothalamic–pituitary–adrenal axis, which is probably associated with increased BAs in the blood. Decreased adrenal function is likely to have an aggravating effect on adaptive responses in these patients. Studies on the subcellular fraction and hepatoma cell culture have shown that the effect of CDCA (simulating cholestasis conditions) reduces the activity of 5β-reductase at the transcriptional and post-transcriptional levels, altering the clearance of steroid hormones. The activity of progesterone, testosterone, cortisol, and aldosterone depends on the activity of this enzyme. BAs suppress the enzyme 11β-hydroxysteroid dehydrogenase, which converts cortisol into cortisone, which probably contributes to sodium retention [40]. Patients with cholestasis show decreased urinary excretion of 3α, 5β-tetrahydrocortisol, and decreased adrenal mass. A low-fat diet helps reduce the degree of choleemia and increases the activity of 5β-reductase in the liver; however, in real practice, this measure is not applicable [41]. The function of cortisol receptors on hepatocytes is of great importance in the regulation of BAs metabolism. Experiments in mice with a defect in the cortisol receptor showed a decrease in sodium taurocholate cotransporting polypeptide (NTCP) activity and BA import into the hepatocyte, reduced content of BAs in bile, frequent formation of gallstones, the development of steatorrhea, and weight loss. Choleemia that develops as a result of NTCP inhibition stimulates heat production in brown adipose tissues. Similar changes in the metabolism of BAs and clinical manifestations can be observed in chronic insufficiency of the adrenal cortex (Addison’s disease) due to insufficient production of glucocorticoids [42].

5. The Role of Bile Acids in the Nervous System

Cells of the central nervous system express receptors that interact with which BAs and include nuclear receptors FXR, VDR, glucocorticoid receptor (GR), membrane receptors GPBAR1, M2/3, and S1PR2 [43,44].

In the central nervous system, the function of FXR is not well understood (Figure 2).
The chemical structure of BAs is very similar to that of neurosteroids. Neurosteroids are predominantly produced in neurons and glial cells of the cerebral cortex, subcortical white matter, and hippocampus. The type A GABA (GABA_A) receptor, the main channel of inhibitory impulses in the central nervous system, is the main target of neurosteroids. Neurosteroids also modulate the functions of N-methyl-D-aspartic acid (NMDA), the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate acid receptor, as well as the kainate, σ-receptor, glycine, serotonin, nicotinic and muscarinic receptors. Neurosteroids have

![Figure 2. Possible primary signaling pathways (GPBAR1 and FXR) and the potential role of endogenous bile acids in models of neurodegenerative disorders. BA—bile acids, C—cholesterol, FXR—farnesoid X receptor, GPBAR1—G protein-coupled bile acid receptor 1.](image-url)
a pronounced anticonvulsant, sedative, antinociceptive, and antidepressant effect, and affect the mechanisms of learning and memory [55]. These substances also interact with GPBAR1 expressed on astrocytes and neurons; as a result of adenylyl cyclase activation, an increase in the intracellular Ca\(^{2+}\) content and the production of reactive oxygen species are observed [56]. BAs are also able to modulate the function of GABA\(_A\) and NMDA receptors, acting as their antagonists. The maximum antagonism with respect to GABA\(_A\) and NMDA receptors was observed in CDCA, followed by DCA, and CA. UDCA acts on GABA\(_A\) receptors while decreasing drowsiness by disinhibiting the histaminergic system [57,58]. Glyco- and tauro-derived UDCA acids exhibit a neuroprotective effect by inhibiting excessive stimulation of glutamate receptors and associated excitotoxic reactions in the hippocampal tissue [59]. The same highly hydrophilic conjugated BAs protect the endothelium of the blood–brain barrier from oxidative damage [60], while hydrophobic secondary ones, damage interendothelial contacts [61]. A high total BAs content in the blood has been shown to change the physical properties of endothelial membranes in vitro, which leads to the development of arterial hypotension leading up to refractoriness to the administration of vasopressors [26].

UDCA and its conjugate with taurine through interaction with GPBAR1 have anti-inflammatory effects on astrocytes and microglia, counteracting the activation of NF-κB and decreasing the production of NO and vascular adhesion molecules [62]. In models of neurodegenerative diseases such as Huntington’s disease, Alzheimer’s disease, Parkinson’s disease, acute ischemia, and hemorrhagic stroke, Tuaro-UDCA blocks endoplasmic reticulum stress and prevents neuronal apoptosis [5]. A decrease in the level of BAs or their intermediates in the brain is associated with an increased risk of developing Alzheimer’s disease and Parkinson’s disease [63]. A placebo-controlled phase II study is currently underway to examine the efficacy of UDCA at a dose of 30 mg/kg per day in the treatment of parkinsonism. The theoretical basis for the use of BAs in this study is its potentially beneficial effect on mitochondrial function; it involves performing a functional magnetic resonance imaging of the brain with the isotope of phosphorus 31P to assess the state of ATP metabolism [64].

The issue of the degree of BAs penetration from the bloodstream into the brain, and vice versa, has been insufficiently studied. The permeability of the blood–brain barrier for BAs under physiological conditions has been assessed mainly in animals and suggests that less hydrophilic BAs can penetrate by diffusion, and their content in the brain under physiological conditions correlates with serum BA concentration [65]. Conjugated BAs characterized by a larger molecule and pronounced polarity can be transported by active transport.

In the exchange of BAs, the ependyma of the choroid plexus may play a special role and expresses the apical bile salt transporter (ABST) transporter (mainly in the hypothalamus and the cortex of the frontal lobes) [66–69]. ABST is present on both the apical and basolateral membranes of the choroid plexus epithelium, which indicates the possibility of bilateral transfer. In addition, on the cells of the endothelium and epithelium of the choroid plexus, other carriers of BAs, namely, multidrug resistance-associated protein 2/4 (MRP2/4), bile salt exporting pump (BSEP), NTCP, have been found and their abundance is approximately 2% of that in the liver [68,70].

The effect of BA on brain cells in liver diseases is of great interest. Experiments involving ligation of the common bile duct in animals, against the background of a decrease in the total BA content in the brain tissue revealed a dramatic increase in the proportion of LCA (≈87%) with toxic potential, which, from the point of view of the authors, explains the origin of encephalopathy in cholestasis [71]. Several researchers suggest that cells that are devoid of BA excretion systems may suffer the most from BA overload [71]. Under these conditions, the most hydrophobic BAs can exhibit a detergent effect on membranes [72]. In cholestatic liver diseases (primary biliary cholangitis, primary sclerosing cholangitis, etc.), BAs are found in the brain tissue, which is traditionally explained by their excessive content in the blood and penetration through the blood–brain barrier [70].
In the model of acute liver failure, a multi-fold increase in the level of BAs in the plasma results in an increase in the content of BAs in the frontal cortex (which may indicate their local synthesis or increased permeability of the blood–brain barrier). Additionally, it also shows an increased expression of NTCP and FXR in the cortex. Artificial blockade of FXR reduces the rate of progression of neurological disorders [66]. In the model of acute hepatic encephalopathy, activation of GPBAR1 is accompanied by a decrease in the secretion of chemokine molecules by neurons and the sensitivity of macrophages of nervous tissue, microglia, to proinflammatory stimuli, which is considered a mechanism for suppressing neuroinflammation [66]. The most important problem is the development of pruritus in cholestatic liver diseases. Because a clear relationship between the concentration of BAs and the intensity of itching has not been established, their pathogenetic significance is questioned. However, therapeutic measures aimed at reducing the degree of cholestasis are effective in some patients. Recently, a Mas-related G-protein coupled receptor member X4 has been described, with which BAs can interact and which is expressed in the dorsal ganglia together with the type 1 histamine receptor; activation of Mas-related G-protein coupled receptor member X4 provokes itching [73].

During the cycle of enterohepatic circulation, BAs can influence the brain by activating peripheral receptors FXR and GPBAR1. The FGF19 messenger molecule, formed during the interaction of BA with FXR in the intestine, is transported across the blood–brain barrier and interacts with the FGF4 receptor/β-klotho co-facto [74]. β-Klotho is selectively expressed in the suprachiasmatic, arcuate, and paraventricular nuclei of the hypothalamus, area postrema, and the nucleus of the solitary pathway [74].

The interaction of secondary BAs with GPBAR1, expressed at the endings of peripheral nerves, may contribute to the development of neuropathic pain and the pathogenesis of functional intestinal disorders [75].

6. Aspects of the Involvement of Bile Acids in the Pathogenesis of Intestinal Disease

6.1. Bile Acids and Intestinal Microbiota

Microbiota of the gastrointestinal tract can be considered a component of the innate immune defense. Stimulation of FXR with bile acids activates the expression of genes for angiogenin (Ang1) and nitric oxide synthase (iNOS), as well as increases the production of antimicrobial peptides cathelicidins by the epithelium through the cascade of extracellular protein kinase (ERK 1/2) [53].

The role of BA in the regulation of the microbial population is significant; reduced BA content is associated with excessive bacterial growth and inflammation [76]. Excessive bacterial growth is accompanied by more intensive deconjugation of primary BA, as a result of which their ability to form micelles decreases and the risk of steatorrhea development increases. In addition, unconjugated BAs are more passively absorbed along the small intestine, bypassing the stage of interaction with FXR expressed in more distal regions; accordingly, the regulatory influence of FXR is significantly reduced [77].

BA can influence the expression of microbial genes encoding virulence factors. In the presence of bile, the expression of the region containing genes of the pathogenicity island of enterohemorrhagic E. coli O157:H7 is reduced. As the concentration of bile in the distal small intestine decreases, the bacterium begins to show its virulence again [78]. Adaptive changes in gene expression that contribute to the survival of a microorganism in an aggressive environment have been shown for Listeria monocytogenes [79]. The expression of Salmonella enterica island of pathogenicity genes required for invasion of the ileal epithelium is also inhibited by BA [80]. Some genes that regulate the degree of virulence of Shigella, Salmonella, Vibrio cholerae, can be activated in the presence of bile salts, which probably serve as a signal of the presence of a favorable intestinal environment for the invasion of these bacteria [81,82]. Changes in gene expression and protein synthesis in the presence of BAs are described in Campylobacter jejuni and Enterococcus faecalis [83,84]. The regulatory action of BAs on bacteria occurs due to interaction with specific receptors of the bacterial membrane and activation of signaling cascades that regulate gene expression [85].
Tauro-CA interacts with the CspC receptor of Clostridium difficile spores and activates their germination, while CDCA has the opposite effect [86,87].

In the colon, less polar BAs (DCA, CDCA, and LCA), to a certain extent likely have an antimicrobial effect due to their ability to diffuse through bacterial membranes [88]. Protonated BAs freely diffuse through the lipid bilayer. Bile acid molecules penetrate the membrane in the form of dimers with a hydrophilic α-part inside and a hydrophobic β-part outside. The bacterial defense mechanism that prevents this process is the maintenance of a higher pH, which leads to the dissociation of protonated BAs resulting in a negative charge [88]. Unconjugated CDCA and DCA, which increase membrane permeability and disrupt the operation of the proton pump have shown a particularly high bactericidal effect against Staphylococcus aureus [89]. The symbiosis of bacteria producing hydrolases and oxidases, as well as the degree of production of short-chain BAs, can affect the spectrum of BAs and the degree of their protonation. The effect of probiotics on the spectrum of BAs and stimulation of the corresponding receptors in the intestine and outside it should be further studied [90].

Microbiota and dietary habits, in turn, significantly affect the total pool and composition of BAs. Mice grown under sterile conditions showed a significant increase in the pool of bile acids due to the synthesis of primary BAs and more active absorption by ABST. This is associated with insufficient stimulation of FXR in the ileum due to the absence of the stage of microbial dehydroxylation of the primary BA β-muricholic acid conjugated with taurine, which is not an FXR agonist [76]. Reduced stimulation of GPBAR1 and decreased production of GLP-1 are associated with an increase in the proportion of primary BAs that have not undergone dehydroxylation, which contributes to an increase in the volume of the gallbladder and the formation of gallstones [91]. People that follow the “Western” style of nutrition show the predominance of secondary BAs in the total pool of BAs, which may explain their increased risk for cancer [92].

Activation of GPBAR1 and FXR contributes to the maintenance of immunological tolerance at the intestinal level and shifts the polarization of macrophages towards the anti-inflammatory M2 phenotype, which produces high concentrations of IL-10. The result of increased production of IL-10 is an increase in the content of FoxP3⁺ in Treg cells and a decrease in the migration of monocytes into the lamina propria of the colon [12]. By acting on GPBAR1 and FXR, BAs indirectly regulate leukocyte migration and differentiation of macrophages in the distal ileum and colon; however, the role of certain types of BAs in this regard is not well understood. In mouse models of colitis, FXR activation has been shown to inhibit the expression of NF-κB-dependent genes (TNF-α, IL-1β, IL-6, COX-2, and iNOS genes). The anti-inflammatory effect of FXR manifests through SHP, as well as the stabilization of the nuclear co-repressor NCoR on the NF-κB-sensitive element of the IL-1β gene promoter. Reduced FXR expression is associated with the development of colitis in rodent models as well as in Crohn’s disease [93].

An important aspect of the development of diarrhea in non-inflammatory bowel diseases can be malabsorption of BAs, the signs of which are found in about a quarter to a third of patients who are diagnosed with irritable bowel syndrome with diarrhea or functional diarrhea. The main reason for the development of diarrhea in these cases is decreased ABST function; entry of excessive BAs in the colon stimulates the secretion of chlorides by colonocytes [94]. Confirmatory tests include tests using taurine-75Se-homocholic acid or the assessment of 7α-hydroxy-4-cholesten-3-one in blood serum, reflecting the activity of the classical cascade of BA synthesis [95,96]. As seen within mice, BAs also contribute to the development of visceral hypersensitivity due to stimulation of FXR, the NF-κB cascade, and nerve growth factor (NGF) release from mast cells, as well as increased expression of TRPV1 in the spinal ganglia [97]. Gastrointestinal malabsorption is detected in a significant proportion of patients with microscopic colitis [96]. The treatment plan for such patients includes BA adsorbents [94,96].

The use of FXR ligands seems to be a promising treatment for enterocolitis. 6-ethyl-CDCA, a synthetic ligand of FXR, reduces the degree of macrophage activation
by lipopolysaccharide. In vivo application of 6-ethyl-CDCA contributed to a decrease in the degree of activation of immune cells and organ damage [93].

6.2. Bile Acids and Colon Tumors

As seen in the study of the effects of DCA and UDCA, depending on the degree of polarity, BAs can differently affect the phases of the cell cycle of the cells of the intestinal epithelium [98]. Ever since the first experiments in mice, secondary BAs, especially DCA, have been considered potential carcinogens [99]. DCA activates the EGFR/MAPK cascade and increases cell survival by activating the signaling molecules AKT, ERK1/2, JNK1,2 COX2, PGE2, and beta-catenin, and may contribute to the progression of colon cancer. The mechanism of action of DCA is not clear; it may manifest through the stimulation of NADP-oxidase, lipid peroxidation due to mitochondrial damage, activation of EGFR due to membrane reorganization, or interaction with FXR [98,100]. The most hydrophobic BAs (particularly, DCA) modify the membrane protein caveolin-1, which is accompanied by dysfunction of various receptors. In particular, ERK1/2 activation is considered a manifestation of caveolar or membrane stress [101].

Subjects at high risk of developing colorectal cancer showed a higher content of DCA and 7α-dehydroxylating bacteria in their feces. High-fat content in food helps to increase the level of DCA in the intestine [102]. Exposure to UDCA and tauro-UDCA is associated with the suppression of colon carcinogenesis. UDCA inhibits the formation of intracellular reactive oxygen species and cell growth, as well as the inflammatory cascade in experimental colitis [103,104].

Thus, DCA and UDCA seem to have different effects on the same oncogenic signaling pathways and must be studied further [98,105]. The findings from several studies are somewhat inconsistent and can be attributed to the peculiarities of the organization of the experiments. In the human colon cancer cell line HCT116, increased DCA and CDCA has been shown to induce apoptosis of cells within a few hours after exposure. Their chemical modifications (in particular, chio-, lago-, nor-DCA), as well as homo-, iso-UDCA, which are less hydrophobic, delay apoptosis. BAs conjugated with glycine or taurine only slow down cell growth [106].

6.3. The Gastrointestinal Tract after Cholecystectomy

It is difficult to construct a biological model of BA metabolism after the removal of the gallbladder due to insufficient knowledge of the adaptive mechanisms. Some data indicate that in such patients, BAs accumulate in the proximal small intestine because of the continuous flow of bile, which does not depend on the release of cholecystokinin [107]. A small study assessing the effects of duodenal bile on an empty stomach showed that after cholecystectomy, the BA content in relation to bilirubin increases, and cholesterol decreases by 27%; such changes reflect an increase in the enterohepatic circulation of BA. The synthesis of CA is reduced by 37%, likely as the result of inhibition by the feedback mechanism. The kinetics of BA stabilizes three months after the removal of the gallbladder [108]. The concentration of BAs in the blood is likely determined by intestinal peristalsis and no longer depends on the rhythm of nutrition and contractions of the gallbladder [107]. After cholecystectomy, the serum BA level more than doubles, while there are no pronounced increases in the level of FGF19, which is normally produced in the gallbladder in large quantities [109].

Several studies have shown that cholecystectomy is an independent risk factor for the development and progression of non-alcoholic fatty liver disease (after standardization of data on traditional metabolic risk factors) One of the proposed explanations is the violation of entero-hepatic circulation of BAs, as well as the metabolism of triglycerides due to the increased supply of free BAs from adipose tissue to the liver the influence of BA and is the most important mediator in the reverse regulation of BA synthesis in the liver [109]. Cases of non-alcoholic steatohepatitis after cholecystectomy can also be explained by significant and progressive changes in the composition of the intestinal microbiota (an increase in the
population of *Bacteroides ovatus*, *Prevotella copri*, and *Fusobacterium varium*, and decrease in that of *Clostridium prausnitzii* and *Roseburia faecalis*. There exists conflicting data and some studies suggest no effect of cholecystectomy on the progression of non-alcoholic fatty liver disease [109].

A meta-analysis of 10 cohort studies showed that cholecystectomy was associated with an increased risk of colon cancer (hazard ratio 1.30; 95% CI 1.07–1.58) [110]. Another study showed that cholecystectomy was associated with a tendency of the formation of recurrent adenomatous polyps [111,112].

7. Possible Effects of Bile Acids on the Growth of Tumor Cells

Patients with colorectal cancer show an increased content of DCA in bile, feces, and serum [92]. The possible involvement of DCA in the development of hepatocellular carcinoma against the background of obesity, tumors of the Vater papilla, and other localizations, have been discussed in several studies; as an important condition for the implementation of the negative effect of DCA is the phenomenon of cellular aging [113,114]. The Western diet high in saturated fat promotes the preferential conjugation of BAs with taurine, which acts as an additional source of organic sulfur for sulfate-reducing pathobiont bacteria, such as *Bilophila wadsworthia*, that play a role in the pathogenesis of colitis and colorectal cancer [115,116].

8. The Role of Bile Acids in the Pathogenesis of Liver Diseases

Liver diseases are associated with alterations in the qualitative and quantitative composition of the BA pool. Extrahepatic manifestations, such as muscle hypotrophy, changes in vascular tone, etc., are probably associated with changes in the signaling cascades of BAs. Due to the diversity and variability of the course of liver diseases, many aspects remain insufficiently studied. Tauro-CA, which predominates in the liver under physiological conditions, has shown a protective effect on biliary epithelial cells through activation of the signaling pathway of phosphoinositide 3-kinase (PI3K)/kinase AKT, vascular endothelial growth factor (VEGF), cAMP, and regression damage [117].

Changes in the synthesis of primary BAs and their transport in liver diseases can be explained by oxidative stress and damage to the cytoskeleton with impaired expression of BA transporters on the membrane, changes in blood flow, and other factors [118]. One of the characteristic changes is a change in the activity of enzymes that control the exchange of xenobiotics (constitutive androstane receptor (CAR), pregnane X receptor (PXR)) along the three zones of the hepatic acinus [119]. A significant contribution to the change in the BA spectrum is made by the change in the intestinal microbiota. For example, it has been shown that in liver cirrhosis, the total BA content in feces is reduced, while the proportion of primary BAs is increased, which reflects the inhibition of the conversion of primary BA salts into secondary salts. Such changes develop against the background of an increased content of potentially pathogenic Enterobacteriaceae and a decrease in the population of bacteria producing 7α-dehydroxylase (*Lachnospiraceae, Ruminococcaceae, Blautia*). A significant correlation was shown between the content of these microorganisms and the ratio of primary and secondary BAs (CDCA for *Enterobacteriaceae*, DCA and DCA/CA for *Ruminococcaceae*, and LCA/CDCA for *Blautia*) [120].

A decrease in the total pool of BAs has been described in liver cirrhosis, which probably contributes to the development of bacterial overgrowth in the small intestine and intestinal dysbiosis. The production of proinflammatory cytokines and other mediators of inflammation by the intestinal microbiota, in turn, contribute to the suppression of the synthesis of new BAs. The pathogenesis of complications of liver cirrhosis and portal hypertension are directly related to an increased intake of lipopolysaccharide from the intestine [121].

The study of BA metabolism in cholestatic liver diseases and non-alcoholic fatty liver disease (NAFLD) attracts the most attention. Models for the reproduction of cholestatic liver diseases in animals include those with ligation of the common bile duct, supplemented
by vagotomy, ligation of the hepatic artery, and toxic effects (in particular, the effect of carbon tetrachloride). In the model of bile outflow obstruction, damage to cholangiocytes with an increase in their proliferation is reproduced. Vagotomy, the effect of toxins, and ischemia stimulate a violation of proliferative activity and the ability of cells to survive an increase in the propensity for apoptosis and a decrease in ductal secretion [117].

Under conditions of cholestasis, protective mechanisms that protect the hepatocyte from overloading with bile acids are triggered—the activity of NTCP and MRP2 decreases, and the activity of MRP3 increases. BSEP function can undergo multidirectional changes, depending on the type of liver damage. For example, in drug-induced cholestasis due to damage to the cytoskeleton, BSEP expression is sharply reduced, usually in conjunction with the expression of the conjugated bilirubin transporter MRP2 [118]. Adaptive changes in cholestasis also include a decrease in the abundance of ABST in the proximal renal tubules and an increase in MRP2 at the apical membrane, which promotes the excretion of BAs in the urine; however, the development of cholemic nephropathy may reduce the relative contribution of this mechanism [122].

The importance of an alternative pathway for BA production significantly increases under conditions of cholestasis due to the activation of FXR/SHP, CAR, and PXR, leading to inhibition of CYP7A1 [119,123,124]. In animals, under conditions of experimental cholestasis caused by ligation of the common bile duct, suppression of CYP27A1 activity and an increase in the relative proportion of CA were noted [125].

One of the key aspects of the pathogenesis of cholestatic liver diseases is the aging of biliary epithelial cells, which is expressed by morphological and molecular genetic changes, reflecting a decrease in the ability to proliferate and functional activity, and an increased tendency to apoptosis and tumor transformation [126]. Aging cholangiocytes secrete proinflammatory cytokines and chemokines that activate hepatic stellate cells, which promotes fibrogenesis and increases the risk of tumor growth [127]. Such changes may partly reflect the general aging process, and also be due to the effects of lipopolysaccharide and other damaging factors, particularly, carcinogens [126,128]. One of the manifestations of dystrophic changes in the biliary epithelium may be a decrease in the secretion of bicarbonates, which inhibit the penetration of BAs to the cell surface [129]. In primary biliary cholangitis, the expression of the anion exchanger AE2 and the secretion of bicarbonate are reduced in cholangiocytes [130]. Animal models show a decrease in bicarbonate secretion, corroborating laboratory and histological features of primary biliary cholangitis, including the appearance of anti-mitochondrial autoantibodies [131]. Mutations in the CFTR gene, against the background of which the secretion of bicarbonate is impaired, can also contribute to the development of cholestasis [132].

Cytokines can also have a significant effect on BA metabolism in hepatocytes. TNFα, produced by Kupffer cells, through interaction with the TNF receptor, activates the MAPK/JNK cascade, which leads to phosphorylation of HNF4α and suppression of the transcription of the CYP7A1 and CYP8B1 genes [133]. At the same time, the profibrogenic cytokine TGFβ1 produced during inflammatory reactions activates the promoter of CYP7A1 [134] CYP7A1 transcription in cholestatic diseases also suppresses insulin (signaling of the receptor which enhances BA) and the hepatocyte growth factor produced during inflammation. These cellular signaling pathways can be considered as an epigenetic mechanism for the protection of cells from BA overload in cholestasis [123,135].

The functional state of ABST determines the degree of absorption of BAs in the intestine and is likely to contribute to the course of cholestatic diseases. A study using cholecintigraphy with a taurine-conjugated 75Se-homocholic acid (75SeHCAT) showed that in primary biliary cholangitis, the absorption of BAs in the ileum is increased, which probably contributes to additional damage to liver cells, and with the appointment of UDCA, the degree of absorption of BAs decreased [136]. Preclinical studies have shown that FXR and PPAR agonists, ASBT antagonists, and a UDCA derivative, nor-UDCA, are promising for the treatment of primary sclerosing cholangitis [137,138].
In pediatric practice, progressing familial intrahepatic cholestasis syndromes 2, 3, and 5 (PFIC 2/3/5) are classic examples of cholestatic syndromes reflecting hereditary defects in BA transport. PFIC 2 occurs due to the low activity of BSEP; it is characterized by the low activity of \( \beta \)-glutamyl transpeptidase in the blood clot, which is involved in the export of BAs to bile. PFIC 3 occurs due to the low activity of MDR3 and a deficiency of phospholipids in bile, as a result of which BAs free from micelles attack the cells of the biliary epithelium, and crystallization of cholesterol is also observed. PFIC 5 is mediated by FXR inactivation with secondary suppression of BSEP and is characterized by the development of severe cholestasis [139]. The cause of the development of cholestatic syndrome in cystic fibrosis is a violation of the secretion of bicarbonate, as well as an obstructive component [140]. Regardless of the origin, cholestatic syndromes in infancy can lead to the common outcome of inflammatory cholangiopathy and extrahepatic biliary atresia [141].

In chronic cholestatic liver diseases, the risk of developing hepatocellular and cholangiocellular carcinoma increases, which is probably associated with the activation of proliferative processes under the influence of BA [142]. The damage caused by DCA has been shown, in an animal model, to stimulate the secretion of proinflammatory cytokines and protumorigenic factors by stellate cells. Thus, the so-called secretory phenotype associated with aging is realized. Experiments on animals have shown that DCA largely predisposes to hepatocellular carcinoma development [113].

In mouse models, it has been shown that tauro-CA and S1PR2 can promote the development of cholangiocellular cancer through the activation of EGFR, the ERK1/2/Akt-NF-\( \kappa \)B signaling cascade, and COX-2. The interaction of conjugated bile acids with S1PR2 promotes the invasive growth of cholangiocarcinoma in the cell line [143]. The protumorigenic effect of DCA has also been shown [144]. Impairment of FXR function has also been shown to contribute to the spontaneous development of liver tumors [145].

BAs play an essential role in the pathogenesis of non-alcoholic fatty liver disease; however, many aspects of this phenomenon remain debated. It is assumed that the defect in the MAFG gene increases the relative content of CA and the absorption of cholesterol and BAs in the intestine, which contributes to the development of dyslipidemia [146].

Clinical studies (in particular, PIVENS and FLINT) have shown that the use of nuclear receptor agonists can lead to multidirectional effects, including undesirable ones. There is a paradoxical discrepancy in the indicators of steatosis, inflammation, fibrosis, and the development of insulin resistance, dyslipidemia, and obesity. Achievement of the desired effect may likely require the development of tissue-specific ligands or partial agonists of nuclear receptors [147].

9. Potential Role of Bile Acids in the Development of Lung Diseases

Gastroesophageal reflux and microaspiration can damage the airway epithelium and cause fibrosis. In the human epithelial cell line BEAS-2B, it was shown that LCA, even at a low concentration (>10 \( \mu \)mol/L), causes death at a significantly higher concentration DCA, CDCA, and CA (30 \( \mu \)mol/L). Exposure to BA resulted in a significant release of IL-8 and IL-6 from BEAS-2B cells [7]. BAs suppress the synthesis of inositol phosphate under the influence of acetylcholine in the smooth muscle cells of the respiratory tract rich in M3 receptors. A lung transplant revealed that BAs suppress the reactivity of bronchial smooth muscle cells in response to acetylcholine [148]. The negative effect of BAs can reduce bronchial clearance and contribute to the development of respiratory tract infections [149]. In cystic fibrosis, the effect of BA increases the tolerance to macrolides and polymyxin antibiotics. BA and CDCA promote the formation of Pseudomonas aeruginosa biofilms. Microbiome analysis of sputum samples in children with cystic fibrosis showed increased colonization of P. aeruginosa and other proteobacterial pathogens during bile aspiration [150]. The possible role of BAs entering the respiratory tract as part of gastroesophageal reflux in the pathogenesis of interstitial lung diseases is being studied [151].
10. Conclusions

Over the past decades, the interest of hepatologists in BAs has grown markedly [152]. The reason lies in the discovery of the role of BA in many different physiological processes. BAs comprise a group of molecular compounds with similar but not identical chemical structures. They have a variety of physical properties and different biological characteristics. While their most famous role is in the digestion and absorption of fat, they play an important role in several other functions. Table 1 summarizes the diverse biological processes in which BAs are involved.

Table 1. The role of bile acids in biological processes associated with the development of diseases.

| BA Type                                | Effect                                                                 | Probable Mechanism                                                                 | Ref. |
|----------------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------|------|
| DCA, LCA in vitro                      | Mesenterial arterial dilatation                                        | Endothelial S1PR2 stimulation, ↑ Ca\(^{2+}\) intracellular concentration and ↓ NO production | [153,154] |
| BA (not specified) or CDCA in serum    | ↓ in mean arterial pressure and peripheral vascular resistance in cirrhosis. Could be involved in splanchnic hyperaemia and hyperdynamic syndrome | Endothelial FXR stimulation with ↑ eNOS and ↓ endothelin-1 and angiotensin-II receptor expression; ↓ vascular response to noradrenaline with DCA being the most potent inhibitor | [155–161] |
| Fasting BAs level in serum             | Reversible association with atherosclerosis severity and the presence and severity of coronary artery disease, especially myocardial infarction | TGR5 stimulation with anti-inflammatory effect. Excess cholesterol excretion by secreting large amounts of BA into intestine. Activation of FXR (in animal models) | [162–164] |
| CDCA derivatives (oral administration) | Significantly ↓ aortic plaque formation and ↓ aortic expression of inflammatory factors (IL-6, IL-1, etc.) in apolipoprotein E-deficiency | Activation of FXR | [165] |
| Elevated serum BAs level in cirrhosis  | Cirrhotic cardiomyopathy                                              | Reduced fluidity of the myocardial membrane, resulting in adrenergic dysfunction and the inability to produce cAMP; ↓ myocardium contractility, apoptosis of cardiomyocytes, promoting myocardial ischemia/reperfusion injury, ↑ production of NO mediated by intracellular Ca\(^{2+}\) signaling | [161,166] |
| CA in cirrhosis/DCA and LCA in vitro and portal blood | Bradycardia                                                            | Altered cardiac membrane fluidity and decreased beta-adrenergic receptor signalling. DCA and LCA act as muscarinic antagonists | [166–169] |
| Non-UDCA/UDCA ratio in serum           | Independent predictor of atrial fibrillation                          | ↑ portion of non-UDCA can change slow inward Na\(^{+}\) and Ca\(^{2+}\) currents and outward K\(^{+}\) currents, ↑ the duration of the action potential in cardiomyocytes predisposing to re-entry type arrhythmia | [38,170,171] |
| Supraphysiological tauro-CA concentration in vitro and in intestine | A role in progressing of heart failure                                | Depolarization of the resting potential and inducing posterior depolarization of cells (reduced contractility and pacemaker activity). Decrease protein expression in heart tissue. | [172–174] |
| ↑ ratio of secondary BAs to primary BAs in intestine | –                                                                     | Indirect influence of the intestinal flora on the severity of HF hydrophobic BAs significantly alter mitochondrial bioenergetics | [37,172,175] |
| BA Type                                      | Effect                                                                 | Probable Mechanism                                                                                                                                                                                                 | Ref.          |
|---------------------------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Intestinal microbiota modifications         |                                                                        |                                                                                              |               |
| Primary bile acids per os                   | Prevention of overgrowth of aerobic and anaerobic bacteria in the ileum and cecum and of bacterial translocation | FXRα activation resulting in up-regulation of genes involved in mucosal defense in the ileum. Direct antimicrobial effects in high concentration of conjugated BAs | [176,177]    |
| ↑ CA per os                                 | ↑ in *Firmicutes*, especially groups capable of 7α-dehydroxylation, and ↓ of *Bacteroidetes* | Due to sustaining of 7α-dehydroxylation bacteria and antagonistic effect on other bacterial communities (↑ production of an antimicrobial compounds by these members, or use of BAs as an electron acceptor in metabolic pathways providing a net energy gain)/BA induce (bai) operon | [76,178,179] |
| Primary bile acids (tauro-CA) in intestine  | Recovery of microbiota after dysbiosis induced by antibiotics or toxins | Provide homing signals to gut bacteria and promote germination of spores. This mechanism can be exploited by pathogens such as *Clostridium difficile*, germinating into a vegetative form | [120,180]    |
| More hydrophobic bile acids (having two rather than three hydroxy groups) in intestine | Inhibition of bacterial overgrowth | Impair the membrane integrity. FXR activates genes involved in enteric protection (ANG1, iNOS). Induce ERK 1/2 pathway which activates the VDR and the synthesis of antimicrobial peptides cathelicidins | [85,181,182] |
| Metabolic effects                           |                                                                        |                                                                                              |               |
| Dehydroxylated BAs in intestine             | Significant reduction in host weight gain, plasma cholesterol, and liver triglycerides | Activation transcription of key genes involved in lipid metabolism (PPARγ, ANGPTL 4), cholesterol metabolism (ABCG 5/8), gastrointestinal homeostasis (REG 3γ), and circadian rhythm (DBP, PER1/2) in the liver or small intestine (probably through the FXRα activation) | [183]         |
| ↑ energy expenditure                       | ↑ in brown adipose tissue and muscle | TGRS can stimulate glucagon-like protein 1, improving glucose tolerance and activating thyroid hormone | [184,185]    |
| BAs in intestine                            | Improve glucose homeostasis and triglyceride control aspects of metabolic syndrome in animal models |                                                                                              | [186]         |
| Decreased concentration of BAs in intestine (in acid-binding resins application) | Stimulate the conversion of cholesterol to bile acids | Activation of FXRα | [187]         |
| BAs or their synthetic derivatives per os   | ↓ serum triglycerides and total cholesterol, inhibition of the atherosclerosis in a dose-dependent manner. |                                                                                              | [188]         |
| CA and other FXRα agonists per os           | ↑ serum HDL and phospholipids but decreased ApoA-1 (controversial results) | FXRα induction leading to ↓ SREBP1c (through SHP and LXRα/LXRβ) and triglyceride synthesis and VLDL level. FXRα induction leading to SR-B1 activation ↑ total and serum HDL cholesterol suggesting that reverse cholesterol transport is disrupted. Probable role of epigenetic mechanisms. | [189–191]    |
| BA Type                              | Effect                                      | Probable Mechanism                                                                                                                                                                                                 | Ref.   |
|-------------------------------------|---------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------|
| **Role in fatty liver disease**     |                                             |                                                                                           |        |
| Glycine-conjugated BAs              | Positive correlation with macrovesicular steatosis score | Inhibition of CYP8B1 and stimulation of CYP7B1 expression in NASH livers (suggests a shift to alternative pathway of BAs synthesis)                                                                              | [192]  |
| Oral CA and UDCA                    | Improvement in hepatic steatosis            | Under the study                                                                                                                                      | [193]  |
| **Role in cholestatic liver disease**|                                             |                                                                                           |        |
| Accumulation of hydrophobic bile acids DCA and CDCA in the liver | Cholestatic liver injury                    | Membrane desorganisation stimulates production of reactive oxygen species and activation of NF-κB, resulting in insertion of transporter molecules into the canalicular membrane and NTCP into the basolateral membrane. Inhibition of mitochondrial membrane permeability transition, and possibly, stimulation of a survival pathway. Counteraction with the action of toxic BAs reduces endoplasmic reticulum stress. TUDC initiates differentiation of multipotent mesenchymal stem cells. α5β1 integrins probably serve as sensors for TUDC with the downstream activation of focal adhesion kinase, c-SRC, the epidermal growth factor receptor and activation of the mitogen-activated protein kinases, ERKs and p38. | [194]  |
| Total BAs in fetal serum in intrahepatic cholestasis of pregnancy | Association with ventricular arrhythmia in pregnant women | Modulation of the composition of mixed phospholipid-rich micelles, possibly, decrease in the concentration of hydrophobic bile acids in the cholangiocytes. Stimulation of Ca(2+)- and protein kinase C-alpha-dependent mechanisms and/or activation of p38 (MAPK) and extracellular signal-regulated kinases (ERK) resulting in insertion of transporter molecules into the canalicular membrane and NTCP into the basolateral membrane. Inhibition of mitochondrial membrane permeability transition, and possibly, stimulation of a survival pathway. Counteraction with the action of toxic BAs reduces endoplasmic reticulum stress. TUDC initiates differentiation of multipotent mesenchymal stem cells. α5β1 integrins probably serve as sensors for TUDC with the downstream activation of focal adhesion kinase, c-SRC, the epidermal growth factor receptor and activation of the mitogen-activated protein kinases, ERKs and p38. | [195]  |
| Oral UDCA/tauro-UDCA                | Protection of cholangiocytes against cytotoxicity of hydrophobic bile acids, stimulation of hepatobiliary secretion, and protection of hepatocytes against BAs-induced apoptosis |                                                                                           | [196,197] |
| Obeticholic acid (a selective potent FXR agonist, structural CDCA analog) | Anticholestatic and antifibrotic properties in primary biliary cholangitis not responding to first-line treatment; ↓ portal pressure without a ↓ in mean arterial pressure. Protective cardiopulmonary effect in both cholestatic cirrhotic rat models. Ileal barrier function improvement, reduced bacterial translocation. | FXR activation with decreased BAs synthesis. Increased intrahepatic eNOS activity. Interaction with Kupffer cells and expression of IL-1 and TNFα with concomitant repression of CYP7A1 in hepatocytes. | [198–203] |
| **Role in carcinogenesis**          |                                             |                                                                                           |        |
| Accumulation DCA and CDCA in the liver | Hepatocellular carcinoma development         | Stimulates production of reactive oxygen species and activation of RAS and NF-κB, proinflammatory or tumorogenic factors in the liver with subsequent downregulating of FXR and SHP—an important tumor suppressor. | [204–206] |
Table 1. Cont.

| BA Type                           | Effect                                                                 | Probable Mechanism                                                                 | Ref.        |
|-----------------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------|-------------|
| ↑ levels of DCA, LCA in stool     | Pro-carcinogenic potential in the colon                               | Generation of cancer stem cells probably through Wnt/β-catenin signaling           | [207]       |
| Tauro-CA in the colon             | Pro-carcinogenic potential in the colon                               | Genotoxic effects are under investigation. Metabolism of taurine conjugated BAs by gut microbes generates a genotoxic hydrogen sulfide | [208]       |
| BAs in duodenal refluxate         | Esophageal dysplasia, squamous cell carcinoma and adenocarcinoma       | Expression of COX2 and p53 in esophageal proliferating cells                      | [209,210]  |
| Altered colonial BA               | Association with several disease states, including recurrent *C. difficile* infection (with cases of CDI pouchitis) | A permissive environment in which the bacterium may thrive stimulate germination of *C. difficile* spores. CDCA, LCA, and UDCA inhibit germination of spores | [211,212]  |
| Oral UDCA                         | May protect against DNA damage induced by hydrophobic bile acids such as DCA in the metaplastic mucosa of patients with Barrett’s esophagus | UDCA counters the DNA damaging effects of DCA                                     | [213]       |
| Repeated microaspiration of CDCA, DCA, and LCA | Fibrotic changes in alveolar wall                                      | Stimulation of fibrogenic mediator expression and activating TGF-β1/SMAD3 signaling and FXR | [150]       |
| BAs in the lung tissue in cystic fibrosis | Association with inflammation and restructuring of the lung microbiota with a dominance of *Proteobacteria* | Tissue damage, bactericidal effect.                                               | [214]       |

**Bowel diseases**

**Esophageal diseases**

**Lung disease**

Abbreviation: ABCG 5/8—ATP-binding cassette sub-family G member 5/5; ANGPTL 4—angiopoietin-related protein 4; ANGI—angiogenin gene 1; BA—bile acids; BSEP—bile salt exporting pump, CA—cholic acid; cAMP—cyclic adenosine monophosphate; CDCA—chenodeoxycholic acid; COX2—cyclooxygenase-2; c-SRC—proto-oncogene; CYP7B1—cytochrome P450 family 7 subfamily B member 1; CYP8B1—cytochrome P450 family 8b; family 8, subfamily B, polypeptide 1; DBP—D-box binding PAR BZIP transcription factor; DCA—deoxycholic acid; DNA—deoxyribonucleic acid; ERK—1/2 extracellular signal-regulated kinase 1/2; eNOS—endothelial nitric oxide synthase; iNOS—inducible nitric oxide synthase; HF—heart failure; FXR—farnesoid X receptor; IL-1—interleukin 1; IL-6—interleukin 6; LCA—lithocholic acid; LXR—liver X receptor; MAPK—mitogen-activated protein kinase; MRP2—multidrug resistance-associated protein 2; NASH—non-alcoholic steatohepatitis; NF-κB—nuclear factor-kappa B; NO—nitric oxide; NTCP—Na+ taurocholate cotransporting polypeptide; PER1/2—period circadian protein homolog 1/2; PPARγ—peroxisome proliferator-activated receptor γ; RAS—from “Rat sarcoma virus”, is a family of related proteins; REG 3γ—regenerating islet-derived protein 3γ; SHP—small heterodimer partner; SMAD3—mothers against decapentaplegic homolog 3; S1PR2—sphingosine-1-phosphate receptor 2; TGR5—G protein-coupled bile acid receptor 5; TGF-β1—transforming growth factor-beta 1; TNFα—tumor necrosis factor-alpha; TUDC—tauroursodeoxycholate; UDCA—ursodeoxycholic acid; VDR—vitamin D receptor. Designation: ↑—increase; ↓—decrease.

In recent years, the importance of BAs has been demonstrated not only for the regulation of metabolism but also for the function and plasticity of immune cells. By interacting with receptors FXR, GPBAR1, VDR, and LXR, FAs can influence the course of inflammatory reactions. The relevance of these identified bile acids for inflammatory liver disease has not yet been studied, and future studies need to determine whether less common DCA or lithocholic acid derivatives come into contact with liver parenchymal and immune cells.

Moreover, BA signaling plays a vital role through receptor-dependent (FXR, VDR, GPBAR1, S1PR, M) and channel-mediated mechanisms in different cell types. In particular, with regard to the cardiac system, most studies have shown that BA signaling affects...
cardiac function, and cardiac dysfunction in liver disease is common. Further research in this area will allow for a more detailed description of the complex interactions between BA and their receptors in order to provide a pharmacological basis for the clinical treatment of related diseases.

Activation of the hypothalamus–pituitary–adrenal gland axis and increased release of cortisol are critical for a successful stress response, but this homeostatic mechanism is impaired in liver disease. In cirrhosis, an impaired adrenal response to adrenocorticotropic hormone increases mortality with impaired hemodynamics [41].

BAs are known to be secreted into the intestine, approximately 90% are reabsorbed in the portal system via the enterohepatic bloodstream and recirculated to hepatocytes [215]. However, in painful conditions, when reuptake is impaired, bile acids are released into the circulation, which can cause various pathological effects. Recent studies have shown that bile acids and bile acid signaling can influence a variety of neuropathological conditions.

The composition of the human gut microbiota can vary with diet, age, antibiotics, and disease. Bile acids appear to be the main regulator of the gut microbiota. In connection with a study by Kakiyama et al. a link has been suggested between liver health, fecal bile acid concentration, and gut microbiota composition [120]. In this study, fecal bile acid levels and community structure of the microbiome, as determined by quantification of the 16S ribosomal gene, were compared with control patients and patients with early and advanced cirrhosis. As cirrhosis progresses, it has been found that the bacterial dysbiosis seen in cirrhosis [216] is associated with low levels of bile acids entering the intestine [120]. This dysbiosis was characterized by a significant reduction in the number of Gram-positive members of the normal microbiota, such as Blautia, Ruminococcaceae [217]. An increase in pro-inflammatory and potentially pathogenic taxa of Enterobacteriaceae with the development of cirrhosis has been observed in patients with cirrhosis and decreased fecal BAs [120]. Thus, the size and composition of the bile acid pool appear to be important factors in the regulation of the structure of the human intestinal microbial community.

Due to their amphipathic characteristics, bile acids can behave like detergent molecules, which in many cases is the main cause of bile acid damage when they accumulate in the liver and other organs [218]. Elevated intracellular bile acid concentrations, such as those found in cholestasis, are associated with oxidative stress and apoptosis in both adult and fetal liver.

Finally, there is a link between bile acids and cell proliferation. Several types of bile acids have been shown to modulate DNA synthesis during liver regeneration after partial hepatectomy in rodents, and the regenerative process depends on bile acid signaling through the nuclear receptor FXR. The teratogenic [219] and carcinogenic [220] effects of more hydrophobic bile acids have been reported. Thus, bile acids have been suggested to play a role in the etiology of cancer at various sites—the colon, esophagus, or even non-digestive tissues such as the breast [221]. Moreover, it has recently been shown that mice lacking FXR spontaneously develop liver tumors [222].

Thus, the studies carried out in the past three decades have convincingly shown that the role of BAs is not limited to their participation only in digestion processes. Their role in various pathological processes is obvious, both as an etiological factor and as mediators of individual links of pathogenesis. However, based on the physicochemical and biological characteristics of BAs, it can be assumed that the list of their participation in pathological processes is far from complete and will be supplemented with the accumulation of scientific facts. These facts will make it possible to expand the indications for their use in clinical practice both in the form of independent drugs and in combination with other drugs acting at the cellular level or manifesting their effects at the molecular level through receptor-mediated cell mechanisms. There is no doubt that as knowledge of the physiological role of bile acids in the human body deepens, new concepts will appear that explain the reasons for the emergence and formation of a number of pathological processes, which are still unclear until today [223].
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