The role of bile acids in carcinogenesis

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Abstract
Bile acids are soluble derivatives of cholesterol produced in the liver that subsequently undergo bacterial transformation yielding a diverse array of metabolites. The bulk of bile acid synthesis takes place in the liver yielding primary bile acids; however, other tissues have also the capacity to generate bile acids (e.g. ovaries). Hepatic bile acids are then transported to bile and are subsequently released into the intestines. In the large intestine, a fraction of primary bile acids is converted to secondary bile acids by gut bacteria. The majority of the intestinal bile acids undergo reuptake and return to the liver. A small fraction of secondary and primary bile acids remains in the circulation and exert receptor-mediated and pure chemical effects (e.g. acidic bile in oesophageal cancer) on cancer cells. In this review, we assess how changes to bile acid biosynthesis, bile acid flux and local bile acid concentration modulate the behavior of different cancers. Here, we present in-depth the involvement of bile acids in oesophageal, gastric, hepatocellular, pancreatic, colorectal, breast, prostate, ovarian cancer. Previous studies often used bile acids in supraphysiological concentration, sometimes in concentrations 1000 times higher than the highest reported tissue or serum concentrations likely eliciting unspecific effects, a practice that we advocate against in this review. Furthermore, we show that, although bile acids were classically considered as pro-carcinogenic agents (e.g. oesophageal cancer), the dogma that switch, as lower concentrations of bile acids that correspond to their serum or tissue reference concentration possess anticancer activity in a subset of cancers. Differences in the response of cancers to bile acids lie in the differential expression of bile acid receptors between cancers (e.g. FXR vs. TGR5). UDCA, a bile acid that is sold as a generic medication against cholestasis or biliary surge, and its conjugates were identified with almost purely anticancer features suggesting a possibility for drug repurposing. Taken together, bile acids were considered as tumor inducers or tumor promoter molecules; nevertheless, in certain cancers, like breast cancer, bile acids in their reference concentrations may act as tumor suppressors suggesting a Janus-faced nature of bile acids in carcinogenesis.

Keywords Bile acid · Primary bile acid · Secondary bile acid · Bile acid biosynthesis · Bile acid receptors · Bile acid transporters · Microbiome · CA · CDCA · DCA · LCA · UDCA · Carcinogenesis · TGR5 · S1PR2 · Muscarinic receptor CHRM2 · Muscarinic receptor CHRM3 · FXR · PXR · CAR · VDR · LXR · SHP · Oesophageal carcinoma · Gastric cancer · Hepatocellular carcinoma · Pancreatic adenocarcinoma · Colorectal carcinoma · Breast cancer · Prostate cancer · Ovarian cancer · Epithelial–mesenchymal transition · Oxidative stress · Warburg metabolism

Abbreviations
AKT Serine/threonine kinase 1
AMPK AMP-activated protein kinase
AP-1 Activator protein-1
APE1 Apurinic/apyrimidinic endodeoxyribonuclease 1
ATG5 Autophagy related 5
BA Bile acids
Bai Bile acid inducible operon
Bax Bcl-2-associated X protein
Bcl-2 B-cell lymphoma 2
BE Barrett’s esophagus

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| **Beclin-1/BECN1** | Coiled-coil myosin-like | **FAS** | Fas Cell Surface Death Receptor |
| **BIRC7/Livin** | Baculoviral IAP repeat-containing protein 7 | **FGF19** | Fibroblast growth factor 19 |
| **BSEP/ABCB11** | ATP-dependent cassette transporter | **FGF15** | Fibroblast growth factor 15 |
| **BSH** | Bile salt hydrolases | **FGFR4** | Fibroblast growth factor receptor 4 |
| **BRCA1** | Breast cancer type 1 susceptibility protein | **FLK1/KDR** | Fetal liver kinase 1/ Kinase |
| **CA** | Cholic acid | **FXR/ NR1H4** | Farnesoid X receptor |
| **CAR/NR1H3** | Cyclic adenosine monophosphate | **FXREs** | FXR response elements |
| **CHRM2/3** | Constitutive androstane receptor | **GADD153** | Growth arrest- and DNA damage-inducible gene 153 |
| **CDCA** | Chenodeoxycholic acid | **GBC** | Gallbladder cancer |
| **CDX1/2** | Caudal type homeobox 1/2 | **GERD** | Gastroesophageal reflux disease |
| **C/EBPα** | CCAAT/enhancer-binding protein alpha | **GCDCA** | Glycochenodeoxycholic acid |
| **CHRM2/3** | Muscarinic receptor 2/3 | **GCDA** | Glycochenodeoxychololate acid |
| **C-Myc** | Myc-related translation/ localization regulatory factor | **GCDC** | Glycocylcholic acid |
| **COX2** | Cyclooxygenase-2 | **GDC** | Glycodeoxycholic acid |
| **CRC** | Colorectal carcinoma | **GLCA** | Glycolithocholic acid |
| **CREB** | CAMP response element-binding protein | **GPBAR1/TGR5** | G-protein-coupled bile acid receptor/ |
| **CSC** | Cancer stem cells | **HCC** | Takeda-G-protein-receptor-5 |
| **CYP** | Cytochrome P450 | **HDCA** | Glycoursodeoxycholic acid |
| **CYP7A1** | Cholesterol 7α-hydroxylase | **HNF4α** | Hepatocellular carcinoma |
| **CYP7B1** | 25-Hydroxycholesterol 7α-hydroxylase | **HSC** | Hepatic stellate cells |
| **CYP8B1** | Sterol 12α-hydroxylase | **I-BABP** | Intestinal BA-binding protein |
| **CYP27A1** | Sterol 27-hydroxylase | **IGFBP2** | Insulin-like growth factor binding protein 2 |
| **CYP3A4** | Cytochrome P450 family 3 subfamily | **IKKβ/IKBKB** | Inhibitor Of Nuclear Factor kappa B Kinase Subunit Beta |
| **DC** | Deoxycholate | **IKB** | interleukin 1 |
| **DCA** | Deoxycholic acid | **IL6** | interleukin 6 |
| **Dlc1** | Deleted in Liver Cancer 1 | **IL8/CXCL8** | interleukin 8 |
| **DNA-PK** | DNA-dependent protein kinase | **iNOS** | inducible nitric oxide synthase |
| **DR5** | Death receptor 5 | **JAK2** | Janus kinase 2 |
| **EAC** | Oesophageal adenocarcinoma | **JNK** | C-Jun N-terminal kinase |
| **EGF** | Epidermal growth factor | **JUN** | Jun Proto-Oncogene AP-1 |
| **EGFR** | Epithelial growth factor receptor | **KLF4** | Transcription Factor Subunit |
| **EMT** | Epithelial–mesenchymal transition | **LBD** | Kruppel Like Factor 4 |
| **EPHA2** | EPH Receptor A2 | **LCA** | Ligand-binding domain |
| **ER** | Estrogen receptor | **LCT** | Lithocholytaurine |
| **ERK** | Extracellular signal-regulated kinase | **Lod** | Limit of detection |
| **FAK/PTK2** | Focal adhesion kinase | | |
| Abbreviation | Description |
|--------------|-------------|
| LRH-1/NR5A2  | Liver receptor homolog-1 |
| LXRα/β/NR1H3-2 | Liver X receptor |
| mACHR | Muscarinic acetylcholine receptor |
| MAPK/MEK | Mitogen-activated protein kinase |
| MCA | Muricholic acid |
| MCL1 | Induced myeloid leukemia cell differentiation protein |
| MDM2 | Mouse double minute 2 |
| MDM4 | Double Minute 4 |
| MDR1/ABCB1 | Multidrug resistance protein 1 |
| MMP2 | Matrix metalloproteinase 2 |
| MMP9 | Matrix metalloproteinase 9 |
| MRP2/ABCC2 | Multidrug resistance-associated protein 2 |
| MRP3/ABCC3 | Multidrug resistance-associated protein 3 |
| MRP4/ABCC4 | Multidrug resistance-associated protein 4 |
| MSK1/RPS6KA5 | Nuclear mitogen- and stress-activated protein kinase 1 |
| mTOR | Mammalian target of rapamycin |
| mTORC1 | Mammalian target of rapamycin complex 1 |
| MUC2 | Mucin 2 |
| MUC4 | Mucin 4 |
| MUTYH | MutY DNA Glycosylase |
| MYC | Myc proto-oncogene protein |
| NB | Neuroblastoma |
| NDRG2 | N-Myc downstream regulated gene 2 |
| ND | Not detected |
| NF-κB | Nuclear factor kappa-light-chain-enhancer of activated B cells |
| NOX5 | NADPH Oxidase 5 |
| NR | Nuclear receptor |
| NRF2/NFE2L2 | Nuclear factor erythroid 2-related factor 2 |
| NR4A1/Nur77/TR3/NGFIB | Nuclear receptor subfamily 4 group A member 1 |
| NSCLC | Non-small cell lung cancer |
| NTCP/SLC10A1 | Sodium/taurocholate cotransporting polypeptide |
| OATP1A2/SLCO1A2 | Solute carrier organic anion transporter family member 1A2 |
| OATP1B/SLCO1B | Solute carrier organic anion transporter family |
| OGG1 | 8-Oxoguanine DNA glycosylase |
| PGC-1α | Peroxisome proliferator-activated receptor gamma coactivator 1 alpha |
| PGE2 | Prostaglandin E2 |
| PI3K | Phosphatidylinositol 3-kinase |
| PKA | Protein kinase A |
| PKC | Protein kinase C |
| PLA2 | Phospholipase A2 |
| Prx2 | Peroxisiredoxin II |
| PXR/ NR1H2 | Pregnane X receptor |
| PTEN | Phosphatase and tensin homolog |
| p38/MAPK14 | P38 MAP kinase |
| Rac1 | Rac family small GTPase 1 |
| Raf1 | Proto-oncogene, serine/threonine kinase |
| RhoA | Ras homolog family member A |
| RNS | Reactive nitrogen species |
| ROS | Reactive oxygen species |
| RXR | Retinoid X receptor |
| S1PR2 | Sphingosine-1-phosphate receptor 2 |
| SLC51A/B or OSTα/β | Solute carrier family members |
| SLC10A1/NTCP | Solute carrier family 10 |
| SLC10A2/ASBT | Sodium-dependent bile acid transporter |
| SRC-1/NC0A1 | Steroid receptor coactivator 1 |
| SHP/ NR5O2 | Small heterodimer partner |
| SLC51A/B or OSTα/β | Solute carrier family members |
| SRC-1/NC0A1 | Steroid receptor coactivator 1 |
| SphK2 | Sphingosine kinase 2 |
| SREBF | Sterol regulatory element-binding factor |
| SphK2 | Sphingosine kinase 2 |
| STAT3 | Signal transducer and activator of transcription 3 |
| SULT | Sulfotransferase |
| TCA | Taurocholic acid |
| TCDC | Taurochenoatecholic acid |
| TCDDA | Taurochenodeoxycholic acid |
Background

Bile acids (BAs) belong to cholesterol-derived sterols. Due to the side chain carboxyl group and hydroxylation of their steroid ring they are more polar than cholesterol. They have an amphipatic character for which they are known as natural detergents. Majority of cholesterol is excreted by bile acids that are prone to enterohepatic circulation between the gallbladder and the liver. Cholesterol absorption in the intestine and cholesterol secretion into the bile both require bile salts, which are, together with enterohepatic circulation of BAs, crucial for balancing the plasma cholesterol level [1].

BAs are also signaling molecules. They deorphanized the farnesoid X nuclear receptor (FXR) which is now known as a ligand-inducible transcription factor responsive to BAs [2]. It is important to note that BAs are metabolized in a similar manner as xenobiotics, contributing to the cross-talk between the endogenous and xenobiotic metabolism in the liver through nuclear receptors Pregnane X receptor (PXR), constitutive androstane receptor (CAR) and others [3]. While their synthesis takes place exclusively in the liver, the homeostasis and excretion involve multiple organs and compartments in the body. After discovering their signaling role, BAs have been considered as pro-carcinogenic molecules [4–6]. However, recent studies have provided evidence that in certain cancers, BAs can have antineoplastic features (e.g. breast cancer [7–11]). This novel, context-dependent, dualistic finding prompted us to thoroughly assess the involvement of BAs in carcinogenesis and cancer progression.

Bile acid biosynthesis

The excess of free cholesterol is toxic to cells and needs to be excreted, primarily through conversion to more polar BAs. The introduction of a hydroxyl group in cholesterol reduces the half-life and directs the oxidized molecule to excretion [12]. BA synthesis is thus the main cholesterol detoxification pathway where multiple cytochrome P450 (CYP) enzymes are involved in the classical or alternative pathways (Fig. 1). The two major primary BAs in humans are cholic acid (CA) and chenodeoxycholic acid (CDCA). They are synthesized in the liver and secreted into the gallbladder as glycine or taurine conjugates [13]. The BA composition in mice substantially differs from the humans which has to be taken into account when using mouse as a model for BA related diseases. The mouse Cyp2c70 metabolizes CDCA to more hydrophilic primary muricholic acids (MCAs) [14].

The first enzyme of the classical BA synthesis pathway is cholesterol 7α-hydroxylase (CYP7A1), leading to 7α-cholesterol in a rate-limiting reaction step, followed by several enzymatic conversions. This enzyme is prone to the negative feedback regulation by BAs and FXR [2]. Sterol 12α-hydroxylase (CYP8B1) lies at the branching point that leads to CA. Sterol 27-hydroxylase (CYP27A1) is needed for both CA and CDCA. In the alternative pathway, cholesterol is first metabolized by CYP27A1 to form 27-hydroxycholesterol that is a substrate for 25-hydroxycholesterol 7α-hydroxylase (CYP7B1) and later other enzymes [15]. The alternative pathway leads majorly to CDCA. The ratio of CA to CDCA is determined by the expression level of CYP8B1, which transforms a di-hydroxylated BA to tri-hydroxylated BA. The alternative pathway is estimated to account for about 10% of cholesterol conversion [16]. Of importance, there are major differences in individual BA synthesis genes in mouse and in humans which may be due also to different biological roles of human and mouse BA species (reviewed in [15]).

Bacterial metabolism of bile acids, production of secondary bile acids

Hepatocytes secrete BAs to the bile canaliculi. By fusing with each other bile canaliculi form bile ducts, which eventually form the hepatic duct that runs to the gallbladder. The gallbladder empties to the duodenum upon feeding and, hence, releases BAs to the gastrointestinal tract. Primary BAs emulsify dietary fats and activate pancreatic
lipases in the small bowel. BAs are then reabsorbed through the enterocytes and get to the liver for reuptake and reuse through the portal circulation. This circle is termed the enterohepatic circulation of BAs. A fraction of the reabsorbed BAs enter the systemic circulation (total BA concentration in the serum is < 5 µM in a healthy individual) and exert hormone-like effects [7, 17–20]. The reference concentrations of the serum, tissue and fecal bile acids are in Tables 1, 2, 3.
Table 1  Reference serum bile acid levels

|          | Cohort size, reference | n = 40 [303] | n = 8 [304] | n = 30 [305] | n = 28 [306] | n = 56 (pooled) serum [7] |
|----------|------------------------|--------------|--------------|--------------|--------------|----------------------------|
|          |                        | Mean ± SEM   | Mean ± SD    | Mean ± SEM   | Mean ± SEM   | Mean                        |
| Primary bile acids | CA                     | 181.5 83.1   | 440 651      | 162.05 40.19 | 153.68 159.64 | 287                        |
|          | GCA                    | 233.0 56.0   | 85 55        | 42.55 13.72  | 72.86 93.69  | 301                        |
|          | TCA                    | 179.7 47.0   | 14 12        | 2.04 0.63    | 18.56 29.4   | 71                         |
|          | CDCA                   | 256.8 56.3   | 380 410      | 1160.64 299.60 | 654.78 660.43 | 563                        |
|          | GCDCA                  | 771.5 111.9  | 450 210      | 975.59 205.81 | 649.19 648.55 | 931                        |
|          | TCDCA                  | 120.2 21.8   | 69 56        | 7.51 1.74    | 54.28 69.18  | 137                        |
| Secondary bile acids | DCA                    | 386.7 66.0   | 320 120      | 593.27 141.09 | 402.76 350.11 | 701                        |
|          | GDCA                   | 246.2 42.5   | 104 44       | 190.78 44.32 | 156.39 149.88 | 415                        |
|          | TDCA                   | 44.9 11.8    | 21 18        | 44.06 8.66   | 24.62 22.68  | 61                         |
|          | LCA                    | 12.8 1.8     | 17 20        | 9.74 1.51    | 94.95 57.21  | 31                         |
|          | GLCA                   | 16.3 4.1     | 17 20        | 25.26 15.82  | 25.26 15.82  | 25                         |
|          | TLCA                   | 23.4 3.6     | 0.33 0.52    | 0.46 0.07    | 22.82 19.29  | 25                         |
|          | UDCA                   | 137.6 25.1   | 43 27        | 208.35 32.94 | 130.83 114.96 | 147                        |
|          | GUDCA                  | 76 40        | 60.92 9.76   | 128.04 178.12 | 330                |                             |
|          | TUDCA                  | 5.0 1.1      | 2.7 2.7      | 6.24 5.63    | 6.24 5.63    | 6.24 5.63                  |

All concentrations are in nM
CA Cholic acid, CDCA Chenodeoxycholic acid, DCA Deoxycholic acid, GCA Glycocholic acid, GCDCA Glycochenodeoxycholic acid, GDCA Glycodeoxycholic acid, GGLCA Glycolithocholic acid, GUDCA Glycoursodeoxycholic acid, LCA lithocholic acid, TCA Taurocholic acid, TCDCA Taurochenodeoxycholic acid, TDCA Taurodeoxycholic acid, TLCA Taurolithocholic acid, TUDCA Tauroursodeoxycholic acid, UDCA Ursodeoxycholic acid

Table 2  Reference fecal bile acid levels

|          | Cohort size, Reference | n = 97 [307] | n = 28 [308] | n = 15 [309] |
|----------|------------------------|--------------|--------------|--------------|
|          |                        | Mean µg/mg ± SD | Median nmol/g | Q1; Q3 | Median ng/mg of dry feces |
| Primary bile acids | CA                     | 56.16 255.46 | 20.19 | 5.03;1304.28 | 0.23 |
|          | GCA                    | 199.35 317.56 | 2.23 | 1.39;3.55 | 0.72 |
|          | TCA                    | 4.14 7.82 | 0.72 | 0.46;2.11 | 0.46;2.11 |
|          | CDCA                   | 29.65 102.48 | 5.17 | 2.56;10.51 | 0.72 |
|          | GCDCA                  | 3.35 10.5 | 1.41 | 0.37;3.58 | 0.37;3.58 |
| Secondary bile acids | DCA                    | 110.41 167.88 | 2.67 | 1.44;6.83 | 2.67 |
|          | GDCA                   | 4.84 12.5 | 1.75 | 0.86;6.63 | 0.86;6.63 |
|          | TDCA                   | 548.75 336.88 | 2339.24 | 1737.09;2782.40 | 3.1 |
|          | LCA                    | 0.18 0.18 | 0.91 | 0.41;1.28 | 0.41;1.28 |
|          | GLCA                   | 4.94 4.46 | 1.03 | 0.36;2.80 | 0.36;2.80 |
|          | TLCA                   | 17.21 8.76 | 8.76;33.48 | 0.1 | 0.1 |
|          | UDCA                   | 0.81 3.88 | 0.65 | 0.38;0.87 | 0.38;0.87 |
|          | GUDCA                  | 0.37 0.71 | 0.07;1.23 | 0.07;1.23 |

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BAs are very powerful surfactants [21]; therefore, bacteria, mostly in the large bowel, need to protect themselves against being disintegrated by BAs. For example, lipopolysaccharides serve as membrane components in Gram-negative bacteria to passively ward off external toxins or BAs [22]. In addition to that, bacteria have a more sophisticated enzymatic system to cope with BAs termed BA conversion [23].

The hydroxyl groups and the tauryl or glycyl conjugate on BAs are crucial elements of the molecular structure of BAs for their strong surfactant properties. Therefore, the removal, modification or substitution of these molecular elements diminishes the potentially toxic features of primary BAs and renders them largely apolar. The dehydroxylated primary BAs are called secondary BAs and the main site for converting primary BAs to secondary BAs is the large bowel [24]. Secondary BAs can be resorbed to the portal circulation and are transported to the liver, where, however, hydroxylation and conjugation needs to be restored for reuse. The main secondary BAs in humans are lithocholic acid (LCA), deoxycholic acid (DCA) and to a lesser extent, ursodeoxycholic acid (UDCA) [24, 25].

Bile salt hydrolases (BSHs) are responsible for the deconjugation of BAs, namely the removal of glycine or taurine by breaking the C24 N-acyl bond. Glycine and taurine can be fed into the metabolism of bacteria to be used as an energy source [23]. BSH activity is common among the bacteria inhabiting the small and the large intestines [23]; both aerobic [26] and anaerobic bacteria can deconjugate bile salts [27]. Namely, among the Gram-positive bacteria BSH was identified in Clostridium [27–30], Enterococcus [27, 31], Bifidobacterium [27, 32, 33], Lactobacillus [34, 35], Streptococcus [36], Eubacterium [37] and Listeria, among Gram-negative bacteria in Bacteroides [30, 38, 39], while among archea Methanobrevibacter smithii and Methanospirillum hungatei [40].

The substituents on the gonane core of BAs can be also modified, the term “secondary BA” typically stands for the removal of 7α or 7β-hydroxyl groups from primary BAs. Clostridiales and Eubacteria were shown to play a major role in dehydroxylation [23, 41–45], although other genre or species were also implicated (e.g. Bacteroidetes, Escherichia) [7, 38, 44, 46, 47]. Although BA deconjugation and dehydroxylation are different processes, they may be linked through regulatory circuits [30]. Other reactions of BAs involve oxidation, and epimerization that can be linked to intestinal Firmicutes (Clostridium, Eubacterium, and Ruminococcus), Bacteroidetes and Escherichia [23, 36, 37, 41, 42, 44, 45, 48]. Bacterial enzymes involved in secondary BA production are assembled in the BA inducible

| Table 3 Reference tissue bile acid levels |
|-----------------------------------------|
| **Gastric juice (µM)** | **Breast cyst fluid (µM)** | **Adipose tissue (ng/g)** | **Liver tissue (nmol/g)** | **Liver tissue (nmol/g)** |
| n=10 [310] | n=12 [261] | n=24 [311] | n=6 [312] | n=10 [313] |
| Mean ± SEM | Min–Max | Median Min–Max | Mean ± SEM | Mean ± SEM |
| **Primary bile acids** | | | | |
| CA | 2.38 ± 1.09 | 3–119 (n = 1, ND) | LOD | 0–11.4 |
| GCA | 0.74 ± 0.65 | 7.5 | 2.6–33.6 |
| TCA | 0.87 ± 0.1 | 12.5 | 4.9–106.9 |
| CDCA | 0.03 ± 0.04 | 4–305 | LOD | LOD |
| GCDCA | 0.55 ± 0.5 | 15.9 | 2.2–67.3 |
| TCDA | 0.57 ± 0.08 | 2.6 | 1.0–3.5 |
| **Secondary bile acids** | | | | |
| DCA | 3.78 ± 0.6 | 17–160 (n = 1, ND) | 9.4 | 0–60.6 |
| GDCA | 0.39 ± 0.2 | 14.9 | 4.8–45.3 |
| TDC | 5.22 ± 0.02 | 4.2 | 1.6–6.0 |
| LCA | 0.12 ± 0.02 | 9–23 (n = 6, ND) | LOD | LOD |
| GLCA | 0.12 ± 0.007 | 8.1 | 2.9–19.0 |
| TLCA | 0.86 ± 0.01 | LOD | LOD |
| UDCA | 0.02 ± 0.02 | LOD | LOD |
| GUDCA | 0.24 ± 0.08 | 2.0 | 0–15.9 |
| TUDCA | 3.58 ± 0.002 | 0.8 | 0.3–1.9 |

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Interactions between BAs and gut microbiota are bidirectional. Microbiota can transform primary BAs and, hence, modulate the composition of the BA pool [49, 50]. Inversely, BAs can influence the composition of the microbiome as well [51–56] and facilitate bacterial translocation to tissues [57], further underlining that notion BAs act as potent drivers of the early intestinal microbiota maturation [58]. Oncobiosis (dysbiosis associated with cancers) [59] can alter the secondary BA pool that may contribute to carcinogenic effects [4, 5, 7, 18]. It is of note that several other non-BA bacterial metabolites are known that play role in carcinogenesis [60–64].

**Bile acid transporters**

The enterohepatic circulation of BAs depends on BA transporters in the gastrointestinal system. Almost 90% of BAs are involved in circulation due to efficient active transport [65]. Different uptake and efflux BAs transporters are present in the hepatic and intestinal cells (Fig. 2). After BAs are synthesized in the liver they are transported into the bile mainly by the ATP-dependent cassette transporter (BSEP) [65], but also minor transporters, the multidrug resistance-associated protein 2 (MRP2, ABCB2) and the multidrug resistance protein 1 (MDR1, ABCB1) [65]. From the intestinal lumen, BAs are uptaken into the intestinal cells by the major apical sodium-dependent bile acid transporter (SLC10A2, ASBT), which transports BAs also across the canalicular membrane in cholangiocytes and renal tubule apical membrane from glomerular filtrate [66]. BAs are then effluxed into the portal circulation by two Solute Carrier.
Family members, SLC51A or OSTα and SLC51B or OSTβ. The bile acids are then taken back up into hepatocytes by the major transporter the solute carrier family 10 (SLC10A1, NTCP), [65].

BAs can enter the systemic circulation via export across the hepatic sinusoidal membrane by OSTα/OSTβ, the multidrug resistance-associated protein 3 (MRP3, ABCC3) and the multidrug resistance-associated protein 4 (MRP4, ABCC4) [67]. The MRP transporters have a role in reducing hepatic BA concentration in cholestatic conditions. MRP3 and MRP4 are also present in cholangiocytes, where they efflux BAs to portal circulation and are part of the cholehepatic shunt together with ASBT [66]. Several transporters are expressed in the kidney, where they participate in BA elimination via urine (Fig. 2) [66, 68, 69]. The Solute Carrier Organic Anion Transporter Family, OATP1B1 or SLCO1B1 and OATP1B3 or SLCO1B3 contribute to the systemic clearance of BAs via liver [70]. Other cells also express BA transporters and can, therefore, uptake BAs from the systemic circulation [68, 69, 71].

### Bile acids as signaling molecules

In addition to their role in digestion, BAs act as signaling molecules. BAs can activate membrane receptors (Fig. 3), such as G protein-coupled bile acid receptor 1 (GPBAR1, also known as TGR5), sphingosine-1-phosphate receptor 2 (S1PR2), muscarinic receptors (CHRM2 and CHRM3) and nuclear receptors (NRs), such as farnesoid X receptor (FXR, NR1H4), PXR (NR1H2), vitamin D receptor (VDR, NR1H1), CAR (NR1H3) and liver X receptor (LXR, NR1H2-3). Each BA can interact with more than one receptor. Receptors are differentially activated by BAs. For example, FXR is activated by CDCA > DCA > LCA > CA [72], while TGR5 is activated by LCA > DCA > CDCA > CA [73, 74], respectively. VDR and PXR are mainly activated by LCA. BAs mediate immune responses [75], gastrointestinal mucosal barrier function, gestation [76], carcinogenesis [11, 18, 56] and metabolic diseases [20]. The activation of BA receptors may lead to the induction of signaling pathways involved in the regulation of several physiological functions, such as glucose, lipid and energy metabolism, as well as, in cancers. Below, we review the mode of action of BA receptors and highlight those receptor-mediated functions that have a key role in regulating the behavior of cancer cells.

#### Cell membrane receptors

**G protein-coupled bile acid receptor 1 (GPBAR1, TGR5)**

TGR5 is a member of the G protein-coupled receptor superfamily, highly expressed in the epithelium of the gallbladder [77], the intestine [74], the brown adipose tissue and the skeletal muscle [20], as well as in the brain [78]. TGR5 is also expressed in human monocytes/macrophages [73]. TGR5 is not expressed by hepatocytes, while Kupffer cells and liver sinusoidal cells can express the receptor [79].

Secondary BAs LCA and DCA are the most potent, natural ligands for TGR5, but the receptor also responds to CDCA and CA [73, 74] and a set of artificial ligands [80–84] (Table 4). Ligand binding to the TGR5 receptor triggers activation of adenylate cyclase leading to the production of cAMP [73, 74, 85] and the downstream activation of extracellular signal-regulated kinase 1/2 (ERK1/2), protein kinase A (PKA), protein kinase B (AKT), mammalian target of rapamycin complex 1 (mTORC1) and Rho kinase [86–89]. TGR5 activation leads to metabolic changes characterized by energy expenditure and β-oxidation [20, 90]. BA-dependent induction of TGR5 has immunomodulating effects. Most studies point to TGR5-dependent immunosuppression [73, 79, 91–94] partly due to the suppression of the Toll-Like Receptor 4—Nuclear factor-κB (TLR4–NF-κB) pathway [91, 93, 94]. In line with that, in a murine model of breast cancer, LCA treatment induced the proportions of tumor-infiltrating lymphocytes through TGR5 [7].

**Sphingosine-1-phosphate receptor 2 (S1PR2)**

Conjugated BAs activate S1PR2 [95–97] that upregulates the expression of sphingosine kinase 2 (SphK2), which in turn enhances the level of sphingosine-1-phosphate in the nucleus. Elevated nuclear sphingosine-1-phosphate inhibits the function
of histone deacetylases resulting in the upregulation of genes encoding nuclear receptors and enzymes involved in lipid and glucose metabolism [98] Similar to TGR5, ligand binding to S1PR2 can activate different downstream signaling pathways, such as ERK, AKT and/or c-Jun N-terminal kinase (JNK1/2) [96, 97, 99, 100]. Glycochenodeoxycholic acid (GCDCA) can trigger apoptosis in hepatocytes through activating S1PR2 [101]. S1PR2 is highly expressed in macrophages [102] and has widespread immunological roles [100, 102, 103].

### Muscarinic receptors (CHRM2 and CHRM3)

Taurine conjugated BAs can activate muscarinic receptors, the cholinergic receptor muscarinic 2 and 3 (CHRM2 and CHRM3). CHRMs are overexpressed in colon cancer cells and stimulate cell proliferation and invasion [104, 105]. Taurolithocholic acid (TLCA) induces cholangiocarcinoma cell growth via muscarinic acetylcholine receptor and EGFR (epithelial growth factor receptor)/ERK1/2 signaling [106].

### Nuclear receptors

**Farnesoid X receptor (FXR, NR1H4)**

FXR is a member of the nuclear hormone receptor superfamily. There are two FXR genes, encoding FXRα and FXRβ of which only FXRα is expressed, FXRβ is present as a non-expressed pseudogene in humans. The FXR receptor heterodimerizes with retinoid X receptor (RXR) and binds to FXR response elements (FXREs) within the regulatory regions of its target genes [107]. BAs are physiological ligands for FXR (with decreasing affinity: CDCA, DCA, LCA, CA) [72]. FXR is expressed mainly in the liver, intestine, kidney and adrenal glands [107].

FXRα controls BA synthesis, transport and detoxification. The activation of FXR receptor by BAs reduces the expression of Cyp7a1 and Cyp8b1, key enzymes of BA biosynthesis pathway. In the liver, FXRα induces the transcription of its target gene encoding small heterodimer partner
(SHP, NR5O2), an orphan nuclear hormone receptor (see in detail later) that lacks a DNA binding domain and acts as a transcriptional repressor [108]. SHP inhibits the expression of Cyp7a1 through the inhibition of the interaction with liver receptor homolog-1 (LRH-1, NR5A2) [109]. In addition to LRH-1, SHP also prevents the function of hepatocyte nuclear factor-4α (HNF4α), a positive regulator of Cyp7a1 and Cyp8b1 [110]. In the intestine, FXRα induces the expression of fibroblast growth factor 19 (FGF19) in humans and its mouse homolog fibroblast growth factor 15 (FGF15). The secreted growth factor via portal blood reaches the liver where it binds to its receptor, fibroblast growth factor receptor 4 (FGFR4) and induces JNK and ERK pathways and causes repression of Cyp7a1, thus reducing BA synthesis [111]. In addition to Cyp7a1, Cyp8b1 is also repressed by FXRα via SHP-dependent mechanism involving HNF4α [110].

FXRα is also a key regulator of BA transport by influencing the expression of BA transporters. FXRα activation suppresses BA reuptake to hepatocytes through repressing the expression of NTCP via SHP dependent mechanism [112]. At the same time, FXRα facilitates the efflux of BAs from hepatocytes into bile by enhancing the expression of BSEP and into the systemic circulation via O斯塔/β transporter [113]. FXRα also upregulates MR2, which promotes BA secretion into the gallbladder. Finally, FXRα regulates the expression of intestinal BA-binding protein (I-BABP) in the ileum which promotes transport of BAs from enterocytes into portal blood [114] whereas limits enterocyte uptake of BAs by reducing ASBT expression. FXRα increases the expression of enzymes involved in the detoxification of BAs, such as cholesterol 25-hydroxylase or cytochrome P450 family 3 subfamily A4 (CYP3A4) [115], dehydroepiandrosterone-sulfotransferase (SULT) 2a1 [116] and uridine 5′-diphosphate-glucuronosyltransferase 2B4 (UGT2B4) [117]. Many studies have reported the relationship between FXR and inflammation. NF-κB activation suppressed FXR-mediated gene expression, indicating that there is a negative crosstalk between the FXR and NF-κB signaling [118].

**Pregnane X receptor (PXR, NR1I2)**

In humans, PXR is mainly expressed in the liver and intestine [119]. Among BAs, the most potent ligand of PXR is LCA, and the oxidized, 3-keto form of LCA. PXR acts as a xenobiotic sensor and regulates the expression of genes involved in the detoxification and metabolism of BAs [120]. Upon ligand binding, PXR binds to the promoter of its target gene as a heterodimer with RXR. Activation of PXR induces the uptake of xenobiotics, their modification by phase I enzymes (CYPs, including CYP3A, CYP2B, CYP2C), conjugation by phase II enzymes, such as glutathione S-transferases, UDP-glucuronosyl-transferases (UGTs) and sulfotransferases, and finally elimination by phase III drug transporters including MDR1, MRP2 and organic anion-transporting polypeptide (OATP2) [120]. The activation of PXR prevents cholesterol gallstone disease by regulating BA biosynthesis and transport [121] and protects the liver against LCA-induced toxicity [122–125]. PXR activation disrupts the interaction between HNF4α and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α, PPARG1C1), which is required for the activation of CYP7A1 gene expression, thus reducing the expression of CYP7A1 and inhibiting the synthesis of BAs [126]. PXR activation is anti-inflammatory [127–129]. PXR activation facilitates lipogenesis, suppressing β-oxidation and ketogenesis and gluconeogenesis [130–132]. Furthermore, PXR through HNF4 and PGC-1α modulates the expression of CYP7A1 [133].

**Constitutive androstane receptor (CAR, NR113)**

CAR is the closest relative to the PXR and is expressed primarily in the liver. First studies identified that CAR has constitutive transcriptional activity in the absence of its ligand [134]. Later, it was reported that the constitutive transcriptional activity of CAR is reversed by androstanone metabolites, which are inverse agonists [135]. CAR can be activated by direct ligand binding and indirect activation by CAR controls the expression of drug-metabolizing enzymes and transporters, thereby supporting the detoxification of xenobiotics [120, 139]. In contrast to PXR, it remains unclear whether BAs can function as natural ligands for CAR; nevertheless, there are reports underscoring the involvement of CAR in BA signaling [111].

**Vitamin D receptor (VDR, NR111)**

In humans, VDR is highly expressed in the kidney, intestine, bone as well as in hepatocytes but expressed at low levels in other tissues [140–142]. LCA is a potent endogenous VDR ligand [143, 144]; hence, VDR can act as an intestinal BA sensor. VDR activation induces expression of CYP3A that metabolizes LCA [143, 145]. In addition, VDR induces the expression of SULT2A1, MRP3 and ASBT to stimulate BA sulfonation, excretion and transport [146–148]. The activated VDR plays a role in the inhibition of BA synthesis via suppression of CYP7A1, thus protecting liver cells during cholestasis [140].

VDR can function as a nuclear receptor and a membrane-bounded receptor. Upon ligand binding, VDR translocates into the nucleus, where it binds to DNA response elements
as a heterodimer with RXR to mediate gene transcription. Plasma membrane-associated VDR receptor activates several signaling cascades to inhibit CYP7A1 transcription [142, 149]. It has been shown that the activation of membrane VDR signaling by LCA in the liver activates MEK1/2ERK1/2 pathway, which stimulates nuclear VDR/RXR heterodimer recruitment of corepressors to inhibit CYP7A1 gene transcription [150]. In biliary epithelial cells, bile salts (CDCA, UDCA) stimulate the expression of cathelicidin, an antimicrobial peptide, via VDR and FXR to control innate immunity [151]. The possible role of VDR in regulating immunity and the role of VDR in different cancer cells and diseases is reviewed in detail elsewhere [152].

Liver X receptor (LXR, NR1H2-3)

LXRs are activated by naturally occurring cholesterol metabolites such as oxysterols and bind to DNA as heterodimers with the RXR [153]. LXRα (NR1H3) and LXRβ (NR1H2) share a high structural homology [154]. LXRβ is ubiquitously expressed, while LXRα is primarily expressed in the liver, the adipose tissue, the intestine and macrophages. Upon ligand activation LXRs regulate gene expression via binding to LXR response elements in the promoter regions of the target genes. LXRα promotes the conversion of cholesterol into BAs through the induction of CYP7A1 expression in the liver. LXRs enhance the efflux of cholesterol from cells [155] and have an anti-inflammatory response in the adipose tissue and macrophages. Upon ligand activation LXRs regulate gene expression via binding to LXR response elements in the promoter regions of the target genes. LXRα promote the conversion of cholesterol into BAs through the induction of CYP7A1 expression in the liver. LXRs enhance the efflux of cholesterol from cells [155] and have an anti-inflammatory response in the adipose tissue and macrophages. Upon ligand activation LXRs regulate gene expression via binding to LXR response elements in the promoter regions of the target genes.

Small heterodimer partner (SHP, NR5O2)

SHP is a unique nuclear receptor that contains a ligand-binding domain but lacks the conserved DNA-binding domain. SHP acts as a transcriptional corepressor regulating different metabolic processes, including lipid, glucose, energy homeostasis and BA synthesis via interaction with multiple transcription factors and nuclear receptors (reviewed in [158]). BAs or FGF19 signaling enhances posttranslational modifications of SHP, which modulates the regulatory function of SHP protein [159, 160]. SHP acts as an inhibitory regulator in Hedgehog/Gli signaling pathway [161].

Effects of bile acids in cancers

The role of BAs was implicated in a wide variety of neoplasias (Fig. 4, Tables 5, 6, 7). When assessing the effects of BAs, one has to keep in mind that the concentrations applied in the experiments need to correspond to the reference concentrations in serum or the compartment in question (e.g. parts of the gastrointestinal tract). However, several reports are using substantially higher concentrations than the reference. These studies need to be considered as ones using “therapeutic” concentrations. In the forthcoming chapters, we will review those neoplasias where BAs were implicated in pathogenesis.

Oesophageal carcinoma

The development of Barrett’s esophagus (BE) and its progression to oesophageal adenocarcinoma (EAC) are linked to gastroesophageal reflux disease (GERD). Conjugated BAs, mainly taurocholic acid (TCA) and glycocholic acid (GCA) are the main BA constituents in GERD refluxate [162]. Conjugated BA levels in the refluxate from patients with advanced BE or EAC are significantly higher than from patients with benign BE [163]. Conjugated BAs, as TCA or taurodeoxycholic acid (TDCA), promote EAC progression [164, 165] (Table 7). Unconjugated BAs, including DCA and CDCA, induce oxidative stress, DNA damage and inflammation contributing to EAC carcinogenesis, while UDCA protects against DCA-induced injury (Tables 5 and 7).

Apparently, numerous BA receptors as TGR5, S1PR2, FXR and VDR are activated in EAC cells in response to BAs in the refluxate [164–167]. In good agreement with that, the inhibition of the FXR receptor suppresses tumor cell viability in vitro and reduced tumor formation in nude mouse xenografts [168]. Furthermore, TGR5 is highly expressed in the EAC and precancerous lesions and is associated with worse overall survival [169] suggesting that these observations can be translated to the human situation.

Acidic bile acids bring about oxidative stress, TDCA can induce NADPH Oxidase 5 (NOX5) through TGR5 [164]. Furthermore, bile acids can induce inflammation through FXR activation [170] and the EGFR–STAT3 (signal transducer and activator of transcription 3)—Apurinic/Apyrimidinic Endodeoxyribonuclease 1 (APE1) pathway [171]. Acidic bile salts can also induce epithelial–mesenchymal transition (EMT) through vascular endothelial growth factor (VEGF) signaling in Barrett’s cells [172]. Interestingly, the activation of the EGFR-DNA-PKs (DNA-dependent protein kinase) pathway by insulin-like growth factor binding protein 2 (IGFBP2) protects EAC cells against acidic bile salt-induced DNA damage [173].

Gastric cancer

Carcinogenesis in gastric cancer is a sequential process that includes chronic superficial gastritis, intestinal metaplasia (IM), atrophic gastritis, intramucosal carcinoma, dysplasia and invasive neoplasia [174]. IM is considered a risk factor for gastric tumorigenesis. The concentrations of
Bile acids (BAs) in gastric juice positively correlate with the degree of intestinal metaplasia [175] and BAs serve a critical multi-pronged role in the induction of intestinal metaplasia. BAs can enhance caudal-related homeobox family 2 (CDX2) and mucin 2 (MUC2) expression via FXR/NF-κB signaling [176, 177] and cyclooxygenase-2 (COX-2) expression via induction of SHP [178], all promoting gastric intestinal metaplasia. Acidic bile salts can induce telomerase activity in a c-Myc-dependent fashion [179, 180], while DCA can induce the metaplastic phenotype of gastric cancer cells [181] (see Tables 6 and 7). TGR5 is a key factor in BA-induced gastric metaplasia via HNF4α [181], EGFR and mitogen-activated protein kinase (MAPK) [182] activation and promotes EMT in gastric carcinoma cells [183]. TGR5 is overexpressed in gastrointestinal adenocarcinomas, and moderate to strong TGR5 staining is associated with decreased patient survival [184]. Nevertheless, there anticarcinogenic effects of bile acids in gastric cancer, as UDCA (Table 5) or DCA in supraphysiological concentrations [185, 186] or 23(S)-mCDCA [187].

**Hepatocellular carcinoma (HCC)**

Several studies have shown that more hydrophobic BAs as LCA, DCA and CDCA, are the main promoters of liver cancer and can contribute to the development of HCC (see in Table 7) [188–192]. Nevertheless, CDCA (> 100 µM) [193, 194], UDCA and Tauroursodeoxycholic acid (TUDCA) inhibit HCC cell growth and induce apoptosis [195–199] (see in Tables 5 and 6). Deregulation of BA homeostasis marked by the expression of hepatic BA transporters (BSEP, OStαβ, MRP2, MDR2-3, NTCP) is diminished leading to increased hepatic BA sequestration and inflammation and reduced FXR signaling [200–203] in liver cirrhosis and non-alcoholic steatohepatitis that are risk factors for the development of HCC. In good agreement with that, metabolomics identified long-term elevated serum BAs in HCC patients.
| Cancer type                    | Cell models        | Concentration | Effects                                                                 | Ref   |
|-------------------------------|--------------------|---------------|-------------------------------------------------------------------------|-------|
| Glioblastoma                  | A172, LN229        | 400–800 µM    | UDCA inhibits cell viability, induces ROS production and endoplasmic reticulum stress, synergizes with proteasome inhibitor Bortezomib | [314] |
| Neuroblastoma                 | SH-SY5Y            | 100 µM        | TUDCA protects against mitochondrial damage, cell death and ROS generation via mitophagy | [315] |
| Pancreatic cancer             | HPAC, Capan1       | 0.2 mM        | UDCA reduces intracellular ROS level and Prx2 expression, as well as suppresses EMT and stem cell formation | [227] |
| Prostate cancer               | DU145              | 0–200 µg/ml   | UDCA inhibits cell growth and induces apoptosis via extrinsic and intrinsic pathways | [274] |
| Melanoma                      | M14, A375          | 0–300 µg/ml   | UDCA inhibits cell proliferation and induces apoptosis via ROS-triggered mitochondrial-associated pathway | [316] |
| Hepatocellular carcinoma (HCC)| Huh-BAT, HepG2     | 750 µM        | UDCA has a synergistic effect on the antitumor activity of sorafenib in HCC cells via activation of ERK and dephosphorylation of STAT3 | [195] |
|                              | HepG2, BEL7402     | 0.1–1 mM      | UDCA inhibits proliferation and induces apoptosis of HCC cell lines by blocking cell cycle and regulating the expression of Bax/ Bcl-2 genes. UDCA suppresses growth of BEL7402 cells in vivo | [196] |
|                              | HepG2              | 0.25–1 mM     | UDCA induces apoptosis via regulating of Bax to Bcl-2 ratio, the expressions of Smac and Livin, and caspase-3 expression and activity | [197] |
|                              | Huh-Bat, SNU761, SNU475 | 200 µM   | UDCA suppresses cell growth and induces DLC1 tumor suppressor protein expression by inhibiting proteasomal DLC1 degradation in an ubiquitin-independent manner | [198] |
|                              | HepG2, SK-Hep1, SNU-423, Hep3B | 100 µM | UDCA switches oxaliplatin-induced necrosis to apoptosis via inhibition of ROS production and activation of the p53-caspase 8 pathway | [199] |
| Oral Squamous Carcinoma       | HSC-3              | 100–400 µg/ml | UDCA induces apoptosis via caspase activation                         | [318] |
| Leukemia                      | T leukemia cell line (Jurkat cell) | 100 µg/ml | TUDCA and UDCA induce a delay in cell cycle progression         | [319] |
| Gastric cancer                | MKN-74             | 200 µM        | UDCA suppresses chenodeoxycholic acid-induced PGE2 production and tumor invasiveness without affecting the COX-2 expression | [320] |
|                              | SNU601, SNU638     | 0.25–1 mM     | UDCA induces apoptosis, which is mediated by lipid raft-dependent death receptor 5 (DR5) expression and activation | [321] |
|                              | SNU601             | 0.6–1 mM      | UDCA induces apoptosis via MEK(MAPK)/ERK pathway. DCA-mediated ERK activation exerts an antiapoptotic activity in this cell line | [322] |
|                              | SNU601             | 0.5–1 mM      | UDCA induces apoptosis via CD95/Fas death receptor, downregulates ATG5 level and prevents autophagic pathway | [323] |
The role of bile acids in carcinogenesis

[204] and children (<5 years of age) with bile salt export pump deficiency developed HCC [205]. FXR activity is a major inhibitor of HCC carcinogenesis. Whole-body FXR-deficient mice spontaneously develop liver tumors [206, 207] in which the activation of the Wnt/β-catenin signaling pathway and oxidative stress were identified as the major drivers [208–210]. Nevertheless, liver-specific FXR deficiency in mice does not induce spontaneous liver tumorigenesis, but may only serve as a tumor initiator [211]. Due to their amphipathic nature, BAs can disrupt the plasma membrane and activate protein kinase C (PKC) and phospholipase A2 (PLA2) inducing the p38-MAPK-p53-NFκB pathway [212, 213]. Inflammation can suppress FXR activity that contributes to bile acid accumulation and carcinogenesis [185, 193, 194, 214].

Interestingly, senescence-associated secretory phenotype has crucial role in promoting obesity-associated HCC development in mice. Administration of high-fat diet to mice induces alterations in the gut microbiota and increases the levels of DCA. Increased DCA level promotes SASP

### Table 5 (continued)

| Cancer type                  | Cell models | Concentration | Effects                                                                 | Ref                |
|------------------------------|-------------|---------------|------------------------------------------------------------------------|--------------------|
| Oesophageal cancer / Barrett’s esophagus | BAR-T, BAR-10 T | 125–250 µM | UDCA increases antioxidant expression and prevents DCA-induced DNA damage and NF-κB activation | [324]              |
|                              | SKGT-4, OE33 | 300 µM       | UDCA inhibits DCA-induced NF-κB, AP-1 activation and COX-2 upregulation | [325]              |
|                              | BE CP-A     | 0.1–0.2 mM   | GUDCA has cytoprotective role by inhibiting oxidative stress           | [326]              |
| Colon cancer                 | HCT116      | 500 µM       | UDCA inhibits DCA-induced apoptosis via modulation of EGFR/Raf-1/ERK signaling | [246]              |
|                              | HCT116      | 500 µM       | UDCA suppresses DCA-induced apoptosis by stimulating AKT-dependent survival signaling | [327]              |
|                              | HCT116      | 500 µM       | UDCA protects colon cancer cells from apoptosis induced by DCA by inhibiting apoptosis formation independently of the survival signals mediated by the PI3K, MAPK, or cAMP pathways | [328]              |
|                              | HCT116      | 400 µM       | UDCA inhibits cell proliferation by suppressing the expression of c-Myc protein and cell cycle regulatory molecules | [329]              |
|                              | HT29, HCT116| 0.2 mM       | UDCA inhibits cell proliferation by regulating ROS production, induces activation of ERK1/2, and inhibits formation of colon cancer stem-like cell | [244]              |
|                              | HCT116      | 300 µM       | UDCA inhibits interlin β1 and blocks DCA-induced NF-κB and AP-1 activation | [330]              |
|                              | HT-29       | 250 µM       | UDCA suppresses cell growth, which is enhanced in the presence of cavelin; UDCA promotes endocytosis and degradation of EGFR receptor | [331]              |
|                              | HCT116, COLO 205 | 50 µg/ml | TUDCA suppresses NF-κB signaling and ameliorates colitis-associated tumorigenesis | [332]              |
| Cholangiocarcinoma           | Mz-ChA-1    | 0.2–200 µM   | TUDCA inhibits cell growth via a signal-transduction pathway involving MAPK p42/44 and PKCα | [333]              |
Table 6 Antitumor effects of bile acids other than UDCA in cancers

| Cancer types                      | Cell lines                                 | Concentration of bile acids | Effects of bile acids                                                                 | Refs. |
|----------------------------------|--------------------------------------------|----------------------------|---------------------------------------------------------------------------------------|-------|
| Breast cancer                    | MCF7, MDA-MB-231                          | LCA (50–200 µM)            | LCA induces TGR5 expression and exhibits anti-proliferative and pro-apoptotic effects. LCA inhibits lipogenesis and reduces ERα expression in MCF7 cells | [10]  |
|                                  | MCF7, 4T1                                  | LCA (0.3 µM)               | LCA inhibits cell proliferation, EMT transition, VEGF production and induces antitumor immune response and elicits changes in metabolism through TGR5 receptor | [7]   |
|                                  | MCF7, 4T1                                  | LCA (0.3 µM)               | LCA induces NRF2/NFE2L2 dependent oxidative/nitrosative stress via TGR5/CAR receptors | [11]  |
|                                  | MCF7                                       | CDCA (50 µM)               | CDCA activates FXR receptor and inhibites Tamoxifen-resistant breast cancer cells proliferation and EGF-induced growth through downregulation of HER2 expression | [268] |
|                                  | MCF7, MDA-MB-231                          | CDCA (30 µM)               | CDCA induces cell death via activation of FXR | [334] |
| Colon cancer / Colorectal carcinoma | Caco-2, HT29C19A                           | LCA (20 µM)                | LCA activates VDR to block inflammatory signals in colon cells | [335] |
|                                  | HCT116                                     | LCA (150–400 µM)           | LCA activates p53 and promotes apoptosis by its binding to MDM4 and MDM2, key negative regulators of p53 | [336] |
|                                  | HCT116                                     | DCA, CDCA (500 µM)         | DCA and CDCA induce apoptosis | [337] |
|                                  | HCT116                                     | DCA (200–250 µM)           | DCA induces apoptosis via AP-1 and C/EBP mediated GADD153 expression | [338] |
|                                  | HCT116                                     | DCA (0.05–0.3 mM)          | DCA in physiologically relevant dose inhibits cell growth and induces apoptosis | [242] |
| Gallbladder cancer (GBC)         | NOZ, GBC-SD, EGH1                          | DCA (50–200 µM)            | DCA functions as a tumor suppressive factor in GBC by interfering with miR-92b-3p maturation | [339] |
| Gastric cancer                   | SGC7901                                    | DCA (0.1–0.3 mM)           | DCA induces apoptosis via the mitochondrial-dependent pathway | [186] |
|                                  | BGC-823                                    | DCA (0.3 mM)               | DCA inhibits the growth of gastric cancer cells via p53 mediated pathway | [185] |
|                                  | SNU-216, MKN45                             | DCA (200 µM)               | DCA induces MUC2 expression and inhibits tumor invasion and migration | [340] |
| Hepatocellular carcinoma (HCC)   | HEPG2, L02                                 | CDCA (10–50 µM)            | CDCA reduces the expression of inflammation mediators, inhibits STAT3 phosphorylation and increases expression of SOCS3 via FXR | [193] |
|                                  | HepG2, Huh7, mouse hepatoma Hepa 1–6       | CDCA (50–100 µM)           | CDCA induces tumor suppressor N-Myc downstream regulated gene 2 (NDRG2) expression through FXR receptor | [194] |
| Neuroblastoma (NB)               | SK-n-MCIXC, BE(2)-m17, SK-n-SH, Lan-1      | LCA (100 µM)               | LCA selectively kills the NB cell lines while sparing normal neuronal cells. LCA triggers intrinsic and extrinsic pathways of apoptosis | [8]   |
phenotype in hepatic stellate cells (HSCs), which in turn secretes various tumor-promoting factors in the liver, thus facilitating HCC development in mice exposed to chemical carcinogen [6]. SHP has a pleiotropic role in HCC, regulates cell proliferation [215], apoptosis [216], epigenetic changes [217] and inflammation [200, 218], which are associated with the antitumor role of SHP in the development of liver cancer.

**Pancreatic adenocarcinoma**

BAs are involved in the induction and development of pancreatic adenocarcinoma at multiple stages. Gallstone formation can block bile flow and, therefore, can induce and sustain pancreatitis [219], a risk factor for pancreatic adenocarcinoma [220–222]. In fact, several BA species showed a drastic increase in pancreatic adenocarcinoma patients [223]. Treatment of pre-malignant pancreatic ductal cells with bile induced carcinogenic transformation [224, 225]. In pancreatic adenocarcinoma cells BAs decrease susceptibility to apoptosis, boost cell cycle progression, the expression of inflammatory mediators and cellular movement, and, in high concentrations, may perturb biomembranes (Table 7) [220, 226]. UDCA, similar to its previously discussed beneficial properties, prevents EMT in pancreatic adenocarcinoma cell lines and, therefore, has antineoplastic properties (Table 5) [227].

**Colorectal carcinoma (CRC)**

The western diet has tumor promoting activity associated with elevated concentrations of colonic BA (mainly LCA and DCA) and increased fecal BA levels, as detected in samples from CRC patients [228]. In animals, a high-fat diet stimulates bile discharge and results in elevated BA levels in the colon [229]. Moreover, cholecystectomy, through prolonging BA exposure of the intestinal mucosa, has been suggested as a risk factor for the development of CRC [230].

BAs induce genetic instability marked by genomic instability and DNA damage via oxidative stress, defects in mitotic checkpoints, cell cycle arrest, improper chromosome alignment and multipolar division [231, 232]. Genomic instability caused by BAs is coupled with apoptosis resistance due to the degradation of p53 and the inhibition of caspase-3 activity [233]. Furthermore, secondary BAs perturb cell membranes and modulate signaling cascades [234, 235].
| Cancer types                  | Cell lines                  | Concentration of bile acids | Effects of bile acids                                                                                                                                                                                                 | Refs. |
|------------------------------|-----------------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| Breast cancer                | 4T1                         | DC (100 µM)                 | DC promotes survival of breast cancer cells by elevating FLK-1 (KDR) and decreasing ceramide-mediated apoptosis of breast cancer progenitor cells                                                                          | [341] |
| Cholangiocarcinoma           | THLE-3                      | CDCA (100 µM) LCA (100 µM)  | CDCA and LCA induce Snai1 and reduce E-cadherin expression and facilitate invasion and migration                                                                                                                          | [188] |
| KMBC                         | TCDC, DC, GCDC (200 µM)     |                             | BAs participate in progression of cholangiosarcoma by activating EGFR and inducing COX-2 expression via MAPK cascade                                                                                            | [342] |
| human: HuCCT1, CCLP1, SG231, | TCA (100 µM)                |                             | TCA promotes cholangiosarcoma cell invasion via activation of S1PR2. TCA induces invasive growth of cells, upregulate COX2 expression and PGE2 production through S1PR2 receptor                                         | [96]  |
| rat: BDE1, BDEspTDEh10       |                             |                             |                                                                                                                                                                                                                       | [95]  |
| RMCCA-1                      | TLCA                        |                             | TLCA induces cell growth through muscarinic acetylcholine receptor (mAChR) and EGFR/ERK1/2 signaling pathways                                                                                                          | [106] |
| Colon cancer / Colorectal carcinoma | HT29, SW620                | LCA (30 µM)                 | LCA induces expression of urokinase-type plasminogen activator receptor (uPAR) and enhances cell invasiveness via ERK1/2 and AP-1 pathway                                                                                   | [343] |
| H508, SNU-C4                 | LCT (300 µM)                |                             | LCT interacts with M3 muscarinic receptor and increases cell growth                                                                                                                                                  | [105] |
| HCT-8/E11, SRC transformed PCmsc cells | LCA, CDCA, DCA (10 µM) |                             | BAs stimulate cellular invasion, which was dependent on several signaling pathways, such as RhoA, Rac1, PI3K, PKC, MAPK, COX2 and FXR receptor                                                                 | [344] |
| Normal human colonic epithelial cells (HCoEpiC) | LCA, DCA (100 µM) |                             | BAs promote colon cancer by inducing cancer stemness in colonic epithelial cells via modulating CHRM3 and Wnt/β-catenin signaling                                                                                         | [238] |
| CaCo-2                       | LCA (26.6 µM)               |                             | LCA increases cell invasion through promoting matrix metalloproteinase 2 (MMP-2) secretion                                                                                                                              | [345] |
| HCT116, HT29                 | LCA (20 µM), DCA (150 µM)   |                             | BAs promote colon carcinogenesis via regulation of Nur77-mediated cell proliferation and apoptosis                                                                                                                     | [190] |
| HCT116                       | LCA (30 µM)                 |                             | LCA induces IL-8 expression by activating Erk1/2 MAPK and suppressing STAT3                                                                                                                                           | [346] |
|                             |                             |                             | Metformin inhibits LCA induced IL-8 upregulation in HCT116 cells by suppressing ROS production and NF-kB activity                                                                                                  | [347] |
### Table 7 (continued)

| Cancer types | Cell lines | Concentration of bile acids | Effects of bile acids | Refs. |
|--------------|------------|------------------------------|-----------------------|-------|
| SNU-C4, H508 | GLCA, GDCA, (50–300 µM), DCA (300–1000 µM) | BAs induce colon cancer cell proliferation which is CHRM3-dependent and is mediated by transactivation of EGFR | [348] |
| HCT116       | DC (0.3–0.5 mM) | DC induces mitochondrial oxidative stress and activates NF-kB in cancer cells through multiple mechanisms involving NAD(P)H oxidase, Na⁺/K⁺-ATPase, CYP, Ca²⁺ and the terminal mitochondrial respiratory complex IV | [349] |
| HT-29        | DCA (2.50 µM) | DCA promotes colorectal tumorigenesis through activation of EGFR-MAPK pathway and induction of calcium signaling | [350] |
| HT-29, Caco-2, HCA7, HCT116 | DCA (300 µM) | DCA activates COX-2 signaling and mediates proliferation and invasiveness of colorectal epithelial cancer cells | [351] |
| HCT-116, HCA-7 | DCA (300 µM) | DCA activates EGFR, MAPK and STAT3 signaling and induces tumorigenicity. DCA-induced activation of cellular signaling is mediated by the TGR5 | [226] |
| SW-480, LoVo | DCA (5–50 µM) | DCA activates β-catenin signaling and promotes colon cancer cell growth and invasiveness | [352] |
| HCT116, DLD-1, SW620 | DCA (100–200 µM) | DCA induces upregulation of *EPHA2* in colon cancer cells, which is due to activation of ERK 1/2 cascade, and is p53-independent | [353] |
| Caco-2       | DCA (20 µM) | DCA stimulates colon cancer cell migration via PKC | [354] |
| Caco-2, HT-29 | DC < 20 µM > 100 µM | Low-dose (< 20 µM) DC stimulates colon cancer cell proliferation, while high dose (> 100 µM) induces apoptosis in colon cancer cells | [355] |
| HCT116       | DCA (250 µM) | DCA stimulates pro-apoptotic and anti-apoptotic signaling pathways; sensitivity to DCA induces apoptosis can be modulated by the ERK/MAP kinase | [356] |
| HCT116       | DCA (200 µM) | DCA suppresses p53 by stimulating proteasome-mediated degradation of p53. DCA suppression of p53 is mediated by stimulating the ERK signaling pathway | [357] |
| Cancer types       | Cell lines                                                                 | Concentration of bile acids | Effects of bile acids                                                                                                                                                                                                                                                                                                                                 | Refs. |
|-------------------|----------------------------------------------------------------------------|------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
|                   |                                                                            | DCA (200 µM)                | DCA upregulates MUC2 transcription via multiple pathways involving activation of EGFR/PKC/Ras/RAf-1/MEK1/ERK/CREB, PI3/Akt/IKKB/NF-κB and p38/MSK1/CREB while DCA induced MUC2 transcription is inhibited by JNK/C-Jun/AP-1 pathway | [358] |
|                   |                                                                            | DCA (50–500 µM)             | DCA induces oxidative stress and upregulates Thioredoxin reductase (TR) mRNA                                                                                                                                                                                                                                                                                  | [359] |
|                   |                                                                            | DCA (50–200 µM)             | DCA activates anti-apoptotic effect of NF-κB and induces IL-8 expression                                                                                                                                                                                                                                                                                     | [360] |
|                   |                                                                            | /                           | DCA and tauro-β-muricholic acid have major role in promoting cancer stem cell proliferation                                                                                                                                                                                                                                                                  | [361] |
| Endometrial cancer| Ishikawa                                                                   | CDCA (5 µM)                 | CDCA enhances cyclin D1 expression and promotes cancer cell proliferation through TGR5-dependent CREB signaling activation                                                                                                                                                                                                                                 | [362] |
| Gastric cancer    | Normal human gastric epithelial cell: GES-1                               | CDCA, DCA (200 µM)          | BAs upregulate CDX2 and MUC2 expression via activation of FXR/NF-κB signaling pathway                                                                                                                                                                                                                                                                      | [176] |
|                   | Normal human gastric epithelial cell: GES-1 tumorigenic gastric cell lines (AGS, MKN45, BGC823, AZ521, N87, KATO III, SGC7901) | DCA (200 µM)                | DCA activates TGR5-ERK1/2 pathway following induction of HNF4α expression, which further promotes metaplasia markers expression through direct regulation of KLF4 and CDX2                                                                                                                                                                                                 | [181] |
|                   | AGS                                                                        | DCA (50 µM)                 | DCA activates ERK1/2, MAPK and causes a TGR5-dependent trans-phosphorylation of the EGFR                                                                                                                                                                                                                                                                     | [182] |
|                   | MKN74, MKN45                                                               | TLCA, TDCA (100 µM)         | Activation of TGR5 by BAs promotes EMT process                                                                                                                                                                                                                                                                                                              | [183] |
|                   | MKN45, AGS                                                                  | DCA (100 µM)                | DCA enhances COX-2 expression via CDX1 and SHP                                                                                                                                                                                                                                                                                                               | [178] |
|                   | MKN28, MGC803, SGC7901                                                     | DCA, CDCA (100 µM)          | BAs under acidic conditions increase TERT expression by activation of c-MYC transcription                                                                                                                                                                                                                                                                     | [179] |
Table 7 (continued)

| Cancer types                              | Cell lines                              | Concentration of bile acids                  | Effects of bile acids                                                                                                                            | Refs. |
|-------------------------------------------|-----------------------------------------|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| Hepatocellular carcinoma (HCC)            | HuH-7, Hep3B                            | CDCA (100 µM)                                | CDCA induces EMT phenotypes in HCC cells via FXR                                                                                                  |       |
|                                           | Huh7, Hep3B and mouse primary hepatocytes (MPH) | LCA (20 µM), DCA (150 µM)                    | BA s promote liver carcinogenesis via regulation of Nur77-mediated cell proliferation and apoptosis                                                                 |       |
|                                           | Huh-BAT, SNU-761, SNU-475               | DCA (100 µM)                                | DCA induces ER stress accelerated apoptosis in NTCP-positive HCC cells under hypoxic conditions, while DCA induces COX-2-dependent IL-8 overexpression in NTCP-negative human HCC cells mediated by NFκB |       |
|                                           | SMMC7721, Huh7                          | GCDC (200 µM)                                | GCDC promotes HCC invasion and migration by AMPK/mTOR dependent autophagy activation                                                                 | [363] |
|                                           | HepG2, Bel-7402, Huh7                  | GCDA (100 µM)                                | GCDA contributes to the development of HCC and chemoresistance by inducing MCL1 phosphorylation at T163 via ERK1/2, which stabilizes MCL1 protein to enhance its antiapoptotic function |       |
|                                           | HepG2, Bel7402, QGY7703, SMMC7721, Huh7 | GCDA (100 µM)                                | GCDA induces survival and chemoresistance of liver cancer cells through activation of BCL-2 by phosphorylation                                                                 | [364] |
|                                           | LX2, Huh7                               | DCA (20–80 µM)                               | DCA causes HSC senescence by modulating malignant behavior of HCC                                                                                   | [365] |
|                                           | HepG2                                  | TCDCA (100 µM)                               | TCDCA promotes liver cancer via down-regulation of the expression of tumor suppressor gene CEBPα                                                                 |       |
|                                           | Hep3B                                  | LCA, CDCA (100 µM)                           | BA s increase cancer invasiveness in human hepatocellular carcinoma and cholangiocarcinoma through repressing E-cadherin and inducing Snail expression | [366] |
| Hypopharyngeal squamous cell carcinoma    | FaDu cells                              | CA (100 µM), CDCA (100 µM), DCA (100 µM), LCA (20 µM) | BA s induce EMT markers TGFβ1 and MMP-9 in vitro                                                                                                  |       |
| Non-small cell lung cancer (NSCLC)        | H1975, H1299, PC-9, A549                | DCA (20–40 µM)                               | DCA increases cell migration and invasion through a TGR5-dependent way. TGR5 promotes NSCLC cell proliferation and migration via JAK2/STAT3 pathway |       |
| Oesophageal adenocarcinoma (EAC) /         | HET-1A                                  | DCA (300 µM), CDCA (300 µM), LCA (25 µM)     | BA s activate the unfolded protein response and induce Golgi fragmentation via a src-kinase dependent mechanism contributing to cancer progression in the esophagus | [367] |
| Barett’s esophagus                        |                                        |                                              |                                                                                                                                                  |       |
| Cancer types | Cell lines | Concentration of bile acids | Effects of bile acids | Refs. |
|--------------|------------|----------------------------|---------------------|-------|
| SEG-1, BE3, CPC-A, CPC-C | CDCA (100–300 µM) | CDCA induces activation of IKKβ/TSC1/ mTOR pathway leading to enhanced EAC cell proliferation | [370] |
| OE-33, SK-GT-4 | CDCA (100 µM) | CDCA stimulates the development of human esophageal cancer by promoting angiogenesis via the COX2 pathway | [371] |
| HET-1A, QH | DCA (100–300 µM) | DCA promotes development of gastroesophageal reflux disease and Barrett’s oesophagus by modulating integrin-αv trafficking | [372] |
| OE19, OE33 | DCA (100, 300 µM) | DCA inhibits Notch signaling pathway with induction of CDX2 gene expression contributing to the formation of Barrett’s oesophagus | [373] |
| OE19 | DCA (300 µM) | DCA shows carcinogenic effects via upregulation of COX2, CDX2 and downregulation of DNA repair enzymes (MUTYH, OGG1) | [374] |
| OE-19, OE-33 | TCA (100 µM) | TCA promotes invasive growth of EAC cells via S1PR2 | [165] |
| OE19 | DCA (50–300 µM) | DCA promotes the progression of EAC by inducing inflammation | [375] |
| HET-1A, CP-A, CP-C, OE33 | DCA (0.2 mM) | DCA increases Beclin-1/BECN1 expression and autophagy but chronic exposure to BAs leads to decreased Beclin-1/BECN1 expression and autophagy resistance | [376] |
| BAR-T | DCA (250 µM) | DCA induces ROS/RNS production, which causes genotoxic injury, and simultaneously induces activation of the NF-κB pathway, which enables cells with DNA damage to resist apoptosis | [377]a |
| OE33, KYSE-30 | DCA (100–200 µM) | DCA is genotoxic to oesophageal cells at neutral and acid pH through the induction of ROS | [378] |
| | DCA ≥ 100 µM | DCA induces DNA damage and NF-κB activation (at doses of 100 µM and higher in oesophageal OE33 cells) | [379] |
| SEG-1, SKGT-4, CP-A | CDCA, DCA (100 µM, 200 µM) | BAs induce CREB and AP-1-dependent COX2 expression in Barrett’s oesophagus and EAC through ROS-mediated activation of PI3K/AKT and ERK1/2 | [380] |
Table 7 (continued)

| Cancer types       | Cell lines          | Concentration of bile acids | Effects of bile acids                                                                                                                                                                                                 | Refs. |
|--------------------|---------------------|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------|
| Het-1A, SEG-1, HKESC-1, HKESC-2 | DCA (100–1000 µM) | DCA upregulates both intestinal differentiation factor *CDX2* and goblet cell-specific gene *MUC2* in normal esophageal and cancer cell lines suggesting the involvement of DCA in the pathogenesis of Barrett esophagus | [381] |
| SEG-1 cells        | DCA (50–300 µM)    | DCA induces *MUC2* overexpression by activation of NF-kB transcription through a process involving PKC-dependent but not PKA, independent of activation of MAP kinase | [382] |
| SKGT-4             | DCA (300 µM)       | DCA induces *COX2* expression via Erk1/2, p38-MAPK and AP-1-dependent mechanisms | [383] |
| OE33 cells         | DCA (250 µM)       | DCA promotes the expression of *KLF4* and *OCT4* via IL-6/STAT3 signaling pathway. DCA has a malignancy-inducing effect on the transformation of EAC stem cells | [384] |
| BAR-T, OA, FLO     | TDCA (10⁻¹¹ M)     | TDCA induces cell proliferation through the upregulation of NOX5-S expression and ROS production mediated by activation of the TGR5 receptor | [164] |
| OE33, FLO-1, Esc2  | DCA (100 µM)       | DCA enhances the aggressive phenotype of EAC cells with concomitant metabolic changes occurring via downregulation of *UCP2* | [385] |
### Table 7 (continued)

| Cancer types       | Cell lines          | Concentration of bile acids | Effects of bile acids                                                                 | Refs. |
|--------------------|---------------------|-----------------------------|--------------------------------------------------------------------------------------|-------|
| Pancreatic cancer  | T3M4, HPAF, Capan-1 | DCA, CDCA (5–100 µM)        | BAs increase the tumorigenic potential of pancreatic cancer cells by inducing FXR/FAK/c-Jun axis to upregulate MUC4 expression | [386] |
|                    | BxPC-3, AsPC-1, Capan-2 | DCA (300 µM)                | DCA activates EGFR, MAPK and STAT3 signaling and induces tumorigenicity. DCA-induced activation of cellular signaling is mediated by the TGR5 | [226] |

**Abbreviations:**
- AKT: Serine/Threonine Kinase 1
- AMPK: AMP-activated protein kinase
- Ap-1: activator protein-1
- BA: bile acid
- Bcl-2: B-cell lymphoma 2
- Beclin-1: Coiled-Coil Myosin-Like BCL2-Interacting Protein
- CDCA: chenodeoxycholic acid
- CDX1: Caudal Type Homeobox 1
- CDX2: Caudal Type Homeobox 2
- CEBPα: CCAAT/enhancer-binding protein alpha
- CHRM3: Muscarinic Acetylcholine Receptor M3
- COX2: cyclooxygenase-2
- CREB: cAMP response element-binding protein
- DC: Deoxycholate
- DCA: Deoxycholic acid
- DCF: Deoxycholic acid
- EAC: Oesophageal adenocarcinoma
- EMT: epithelial-mesenchymal transition
- EPHA2: EPH Receptor A2
- ERK: extracellular signal-regulated kinase
- FAK/PTK2: focal adhesion kinase
- FGFR2: Fetal liver kinase 1
- FXR: farnesoid X receptor
- GCDA: Glycochenodeoxycholic acid
- GLCA: Glycolithocholic acid
- HCC: hepatocellular carcinoma
- HNF4α: hepatocyte nuclear factor-4α
- HSC: hepatic stellate cells
- IKKβ: Inhibitor Of Nuclear Factor Kappa B Kinase Subunit Beta
- IL1: interleukin 1
- IL6: interleukin 6
- IL8/CXCL8: interleukin 8
- JAK2: Janus kinase 2
- JNK: c-Jun N-terminal kinase
- JUN: Jun Proto-oncogene, AP-1 Transcription Factor Subunit
- KLF4: Kruppel Like Factor 4
- LCA: Lithocholic acid
- LCT: Lithocholyltaurine
- mAChR: muscarinic acetylcholine receptor
- MAPK/MEK: mitogen-activated protein kinase
- MCL1: myeloid leukemia cell differentiation protein
- MMP2: matrix metalloproteinase 2
- NR4A1/Nur77/TR3/NGFIB: Nuclear receptor subfamily 4 group A member 1
- NSCLC: non-small cell lung cancer
- NTCP/SLC10A1: sodium/taurocholate cotransporting polypeptide
- OCT4/POU5F1: Octamer-Binding Transcription Factor
- OGG1: 8-Oxoguanine DNA Glycosylase
- PGE2: prostaglandin E2
- PI3K: Phosphatidylinositol 3-kinase
- PKA: protein kinase A
- PKC: protein kinase C
- Rac: Rac family GTPase 1
- Rac1: Ras Homolog Family Member A
- RNS: reactive nitrogen species
- ROS: reactive oxygen species
- SHP: Small heterodimer partner
- STAT: signal transducer and activator of transcription
- TCA: Taurocholic acid
- TCDC: Taurochenodeoxycholic acid
- TCDCA: Taurochenodeoxycholic acid
- TGF-β: Transforming growth factor β-1
- TGR5: G-protein-coupled bile acid receptor
- uPAR/PLAUR: urokinase-type plasminogen activator receptor
- WNT: Wingless-type MMTV integration site family

**Other abbreviations:**
- ABC: ATP-binding cassette
- CGI: cAMP response element-binding protein
- CYP: Cytochrome P450 oxidase
- ER: estrogen receptor
- ETS: ETS Transcription Factor
- FFA: free fatty acids
- FGF: fibroblast growth factor
- HIF-1α: hypoxia-inducible factor 1α
- IL: interleukin
- JAK: Janus kinase
- JUN: Jun Proto-oncogene
- KLF: Kruppel Like Factor
- MAPK: mitogen-activated protein kinase
- MSH: mismatch repair proteins
- NAMPT: nicotinamide phosphoribosyltransferase
- NF-κB: nuclear factor κB
- NOX: NADPH oxidase
- OGD: oxidative gene damage
- PPAR: Peroxisome proliferator-activated receptor
- SIRT1: sirtuin 1
- TLR: Toll-like receptor
- TSC1: TSC Complex Subunit 1
- TXNRD1: Thioredoxin reductase 1
- uPAR: urokinase-type plasminogen activator receptor
- WNT: Wingless-type MMTV integration site family
- XBP: X-box binding protein
- XPG: X-ray repair cross-complementing group 1
- YAP: Yes-associated protein
- ZEB1: Zinc finger E-box binding homeobox 1

**Notes:**
- The table continues with additional entries and details on the effects of bile acids on various cancer types and cell lines.
These all lead to colonic cell hyperproliferation, survival and invasion [236, 237].

The disruptive effect of BAs on colon epithelium evokes a compensatory cell renewal mechanism by inducing colonic epithelial cells to become cancer stem cells (CSCs) through β-catenin signaling (Table 7) [238]. In the CRC rodent model, both LCA and DCA have tumor promoter role on colonic crypt cells in the early stages of colon carcinogenesis [239]; however, it is important to note that BAs are suggested as tumor promoters, but not as mutagenic agents, since they can not induce tumor formation without a carcinogen/mutagen or a genetic alteration [240, 241]. It should be noted that DCA in low concentrations (0.05–0.3 mM) inhibit colonic cell proliferation via cell cycle block and apoptosis pathways (Table 6) [242].

UDCA can reduce the concentration of toxic BA in stool and blood [243] and has shown to protect against CRC by inhibiting CSC and CRC cell formation and proliferation [244, 245], oncogenic signaling pathways [246], as well as, inducing tumor surveillance [247] (Table 5). Moreover, UDCA can reduce CRC recurrence [248], as well as the risk to develop CRC in patients with pre-cancerous conditions, as colitis [249] or primary biliary cirrhosis [250].

Sustained inflammation was implicated in the pathogenesis of colorectal cancer due to barrier breach, and bacterial translocation leading to inflammation and neoplastic transformation of colonic epithelial cells [251–253]. TGR5 activation by UDCA and LCA may also exert anti-inflammatory responses through TLR4 activation or by reducing pro-inflammatory cytokine production in the colon that can decrease the frequency of developing CRC [254]. BAs can change the gut microbial community [255, 256], suggesting that BAs may also interfere with bacterial translocation.

Breast cancer

The BAs in the breast are of gut origin [257, 258]. Hepatic production of BA is reduced in breast cancer patients as marked by decreasing levels of serum and fecal BAs [7, 259]. Furthermore, bacterial conversion of BAs to secondary BAs is also suppressed, which is the most dominant in in situ and stage I patients [7]. The serum bile acid composition of breast cancer and benign breast disease patients is different; specifically, breast cancer patients had higher serum chenodeoxycholic acid levels and lower dihydroxy tauro-conjugated BA (Tdi-I) and sulfated dihydroxy glyco-conjugated bile acids (Gdi-S-I) [260]. Total fecal bile acid levels are lower in breast cancer patients as compared to controls [259]. LCA concentrations in the breast can be higher than the serum levels [261] (Table 6). Reports showed increased DCA levels in the serum [262] and the breast cyst fluid [263] of breast cancer patients.

LCA is an inhibitor of breast cancer cell proliferation (Table 6) [7, 258, 264]. However, the reports on DCA and UDCA are contradictory [7, 258, 262–264] in physiological concentrations, LCA tunes cancer cell metabolism towards a more oxidative state (through AMP-activated protein kinase (AMPK), PGC-1β and NRF1/NFE2L1) and induces mild oxidative stress through reducing NRF2 (nuclear factor erythroid 2-related factor 2, NFE2L2) expression and inducing Inducible nitric oxide synthase (iNOS) that reverts EMT, reduces VEGF expression, induces antitumor immunity and changes to cancer metabolism that culminates in reduced metastasis formation [7, 11]. In supraphysiological concentrations (> 1 µM) LCA inhibits fatty acid biosynthesis [10] and induces cell death [8–10, 265, 266]. LCA does not exert antiproliferative effects in its tissue reference concentrations on non-transformed primary fibroblasts [7]. LCA exerts its antineoplastic effects through the TGR5 [7] (Table 6).

CDCA in supraphysiological concentrations induces MDRs through FXR [265] and modulates estrogen and progesterone receptor-mediated gene transcription [267]. Furthermore, CDCA inhibits tamoxifen-resistant breast cancer cell proliferation through the activation of the FXR receptor [268] (Table 6). In contrast to that, a report by Journe and colleagues [269] showed that FXR activation has a positive correlation with estrogen receptor expression and luminal characteristics, as well as supported cancer cell proliferation.

Prostate cancer

Among the BAs LCA, UDCA and CDCA exerted antiproliferative effects in prostate cancer. Activation of FXR by CDCA inhibits proliferation of prostate cancer cells, reduces lipid anabolism via inhibiting Sterol Regulatory Element Binding Transcription Factor 1 (SREBF1) [270] and induces the expression of the tumor suppressor phosphatase and tensin homolog (PTEN) [271] (Table 6). Interestingly, FXR signaling also controls androgen metabolism in prostate cancer cells, its activation reduces the expression of UDP-glucuronosyltransferase (UGT) 2B15 and UGT2B17 within cells and causes a reduction of androgen glucuronidation [272]. Similar to CDCA, LCA has antiproliferative effects in prostate cancer and induces apoptosis, endoplasmic reticulum stress, autophagy and mitochondrial dysfunction [9, 273] (see Table 6). UDCA induces death receptor-mediated apoptosis in human prostate cancer cells [274] (Table 5).

Ovarian cancer

In the serum of ovarian cancer patients, 3b-hydroxy-5-cholenoic acid, GUDCA, DCA and TCDCA levels decreased [275, 276]; importantly, taurochenodeoxycholic acid levels decreased in early-stage epithelial ovarian cancer [276]. Zhou and colleagues have shown that sulfolithocholyglycine
and TCA showed changes in the serum of ovarian cancer patients [277]. Changes to the BA pool are so characteristic that Guan and colleagues suggested [278] a set of 12 BAs, including glycolithocholic acid, to be used as markers to separate healthy controls from ovarian cancer patients.

The available studies assessed the effects of BAs at supraphysiological concentrations. These concentrations of BAs are cytotoxic and induce apoptosis likely due to changes to membrane damage [279, 280] that is unlikely at physiological concentrations of BAs [7]. DCA can modulate the expression of breast cancer type 1 susceptibility protein (BRCA1) and the estrogen receptor and, through these, can control drug sensitivity of ovarian cancer cells [Table 6] [281]. Furthermore, cholyglycinate interferes with the transport of cisplatin [282] and TCDC sensitizes ovarian carcinoma cells to doxorubicin and Mitomycin [280]. LXR [283–285], PXR [286], VDR [287–296] or CAR [297, 298] activation was shown to exert protective features against ovarian cancer, similar to BA-elicited effects suggesting that BAs may have a more profound role in protecting against ovarian cancer. These protective effects involved the suppression of proliferation [283, 284, 286], invasion [291], EMT [288], de novo fatty acid biosynthesis [295], the proportions of the cancer stem cell population [289], and the improvement of the efficacy of chemotherapy [285, 297, 298] culminating in better patient survival [292, 293]. Conflicting with these observation on report provided evidence that under certain conditions PXR may support proliferation [299]. BAs can influence the expression and the activity of multiple PARP enzymes [300]; therefore, it is likely that BAs could modulate the efficacy of PARP inhibition that is a novel modality in the chemotherapy of ovarian cancer.

Conclusions

Primary and secondary BAs are long-standing players in carcinogenesis. Although these molecules were considered as initiators of neoplasias, recent advances have shown that the pro- or anticarcinogenic activity of BAs varies among neoplasias [301], most probably due to differences in the expression of BA receptors, transporters and cell-specific differences in the outcome of receptor activation. Key pathways activated in neoplasias by BAs are regulated by nuclear receptors, FXR, CAR, SHP, PXR, LXR and VDR and other membrane receptors such as S1PR2, TGR5, CHRM2 and CHRM3. They activate numerous downstream signaling pathways such as EGFR, STAT3, MAPK, HNF4α, NF-kB, TLR4, SOCS3 and β-catenin just to name some. Furthermore, BAs regulate all aspects of tumor development and progression, the EMT, invasion, metabolism, apoptosis, proliferation, senescence, immune environment and response to chemotherapy.

The effect of BAs on neoplasias also depends on the concentrations used in the studies. While in certain models BAs in low concentration have anti-cancer effects, in super physiological concentrations BAs have pro-cancer effects. This phenomenon is related to their amphipathic structure and the activation of additional off-target pathways not triggered at physiological concentration. At high concentrations, BAs may perturb membranes and activate signaling pathways that sense disturbance of membranes, such as PLA2 and PKC. At high concentrations, they are also toxic and activate the detoxifying pathways, which regulate the activity of transporters of steroid hormones and chemotherapeutics.

Therefore, we would urge the community to carry out studies where the concentrations of BAs correspond to the reference concentrations established for the tissue or, as a proxy, to the serum reference concentrations. As a continuation of that, in the case of UDCA the therapeutic serum concentrations can also be used as a guide. These data are summarized in Table 1. Such studies would be invaluable to understand the (patho)physiological roles of BAs and would give a good frame for the therapeutic applicability.

Along the same lines, it is apparent that BAs can be considered as possible treatment options in certain cancers. Foremost, UDCA, that is a therapeutically available drug, has beneficial effects in multiple neoplasias (e.g. [227, 248, 302]. Table 5) pointing towards the possibility for repurposing UDCA. The picture for other BAs is hazier due to frequent contradictions making it hard to outline applicability. However, before the application of BAs in neoplasias we would need to decipher the cross-talk between BAs and drug metabolism, the effect on drug efficacy and drug availability, and discover the possible adverse effects of BAs, that is currently largely missing. Moreover, it is tempting to consider the manipulation of the intestinal microbiome to affect the levels of selected secondary bile acids in humans. Finally, the modulators of BA receptors should be considered as therapeutic options as well. Given the emerging evidence on the potential anti-cancer effects of BAs, further studies are vital in order to develop novel therapeutic strategies using BAs.

Search strategy and selection criteria

References to this review were identified through the prior knowledge of the authors that was complemented by systematic search of PubMed by using the combinations “Prostate cancer AND (bile acid)”, “Gastric cancer AND (bile acid)”, “Hepatocellular carcinoma AND (bile acid)”, “Oesophageal cancer AND (bile acid)”, “(bile acid) receptors AND cancer”, “(bile acid) receptors AND prostate cancer”, “(bile acid) receptors AND gastric cancer”, “(bile acid) receptors AND hepatocellular carcinoma”, “(bile acid) receptors...
AND oesophageal cancer”, “(bile acid) AND ABC AND transporter”, “(bile acid) AND SLC AND transporter”, “(bile acid) AND SLCO AND transporter”, “(bile acid) AND transport AND review”, “Farnesoid X receptor (FXR) AND the cancer types assessed in the study”, “Pregnane X receptor (PXR) AND the cancer types assessed in the study”, “Constitutive androstane receptor (CAR) AND the cancer types assessed in the study”, “Vitamin D receptor (VDR) AND the cancer types assessed in the study” “Liver X receptor (LXR) AND the cancer types assessed in the study”, “Small heterodimer partner (SHP) AND the cancer types assessed in the study”. Articles published in English were included with no restriction on publication date. All references were checked at Pub Peer, two papers were flagged ([215] and [156]), but when reviewing the reports we decided that the issues raised do not impact on the main message and kept the message.

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Declarations

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