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REVIEW ARTICLE

Emerging Roles of Porcine Bile Acids in Disorders Involving the Gut-Liver-Brain Axis: Novel Insights into Therapeutic Targeting

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ABSTRACT

Bile acids (BAs) are not only a key component of nutrient metabolism but also serve as signaling molecules that regulate metabolic processes and immunity. BAs play a significant role in shaping the gut microbiota and maintaining metabolic equilibrium, which encompasses lipid, glucose, and energy metabolism, primarily through enterohepatic circulation. In humans, disturbances in bile acid metabolism, coupled with microbial imbalances, can lead to the onset of metabolic disorders involving the gut-liver-brain axis. This axis represents a complex communication network that links the gut, liver, and brain through neural, hormonal, and immunological pathways, allowing for bidirectional interactions that influence overall metabolic health. Beyond the gut, liver, and brain, BAs also affect other organs or tissues, including the muscle and adipose tissue, by interacting with specific receptors. In addition to their inherent biological effects, BAs can be modulated by various external factors, including probiotics, prebiotics, traditional Chinese medicines, and natural products, thereby offering potential health benefits. Notably, the content of BAs differs between species. Specific BAs across the species play unique functions. Recent studies underscore the crucial role of porcine BAs, particularly hyocholic acid, in regulating various biological processes such as metabolism, immune responses, and gut microbiota in humans. Here we review the diversity and functionality of uncovered BAs across species, the significant contributions of BAs in metabolic regulation, and their health implications, providing a comprehensive overview of their multifaceted roles in human and animal physiology.

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INTRODUCTION

The bile acid (BA) profile varies significantly among mammalian species under healthy conditions (Table 1). Primary BAs include chenodeoxycholic acid (CDCA) and cholic acid (CA) in humans; CA, CDCA, α-muricholic acid (α-MCA), and β-muricholic acid (β-MCA) in rodents; and hyocholic acid (HCA) along with CDCA in pigs. It has been reported that approximately 80% of BAs in porcine plasma consist of HCA and its conjugated forms (GHCA, THCA, GHDCA, and THDCA). In contrast, these BAs account for only 1% of total BA content in human and mouse plasma (Spinelli *et al.*, 2016).

BAs can be detected systemically. The functions of BAs have been documented in the liver, gut, and brain (Yan *et al.*, 2023; Fuchs *et al.*, 2025). These molecules are essential for maintaining metabolic cholesterol homeostasis, facilitating the absorption and digestion of fat-soluble nutrients (Schneider *et al.*, 2018), and acting as signaling molecules that regulate endocrine and metabolic processes, energy and glucose homeostasis, as well as inflammation and immunity. Dysregulated BA synthesis is associated with the development of metabolic dysfunction-associated steatotic liver disease, obesity, inflammatory bowel disease, and diabetes in humans (Perino *et al.*, 2021). In livestock, BAs are applied to improve the gut health and promote the growth performance of piglets (de Diego-Cabero *et al.*, 2015; Zong *et al.*, 2019; Song *et al.*, 2021, 2022; Hu *et al.*, 2023; Liu *et al.*, 2023; Pi *et al.*, 2023; Wang *et al.*, 2023). This review summarizes the roles of uncovered BAs in response to infections or in diseases from the gut to the brain across species, with particular focus on porcine models that are widely used in research related to cardiovascular diseases, diabetes, and obesity,

transplantation studies, pharmaceutical testing, and nutritional studies. Furthermore, strategic modulation of the gut microbiome and BA metabolism through dietary interventions (e.g., BA supplementation, probiotics, prebiotics), traditional Chinese medicine, and natural products is discussed as a potential approach to strengthening enteroprotection, modulating immune responses, and maintaining multiorgan homeostasis in the gastrointestinal tract, liver, brain, and other systems.

Table 1: Bile acid profile across different mammals

Animal Species	Major primary bile acids	Major secondary bile acids
Human (Russell, 2003; Spinelli *et al.*, 2016; Zheng *et al.*, 2024)	CA, CDCA	DCA, UDCA, LCA
Mice (Russell, 2003; Zheng *et al.*, 2024)	CA, CDCA, UDCA, α-MCA, β-MCA	DCA, LCA, MDCA, ω-MCA
Rats (Russell, 2003; Spinelli *et al.*, 2016; Zheng *et al.*, 2024)	CA, CDCA, α-MCA, β-MCA	HDCA, DCA, ω-MCA
Porcine (Spinelli *et al.*, 2016; Fang *et al.*, 2019; Pi *et al.*, 2023) (Pigs)	HCA, CDCA	HDCA, UDCA
Canine (Giaretta *et al.*, 2018; Blake *et al.*, 2019) (Dogs)	TCA, TCDCA	TDCA, TLCA
Bovine (Tsai *et al.*, 2011; Sánchez-Guijo *et al.*, 2016; Blaschka *et al.*, 2020) (Cattle)	CA, CDCA	DCA, LCA

Function of bile acids in humans and animal models: As crucial signaling molecules, BAs regulate glucolipid metabolism, the gut microbiome, and immune responses by binding to BA receptors. The functionality of BAs among species is summarized in Table 2.

Glucolipid metabolism: BAs emulsify lipids into micelles, enhance the absorption of fats and fat-soluble vitamins and counteract abnormal lipid deposition induced by high-fat diets, thereby improving metabolic control in mice (Watanabe *et al.*, 2006; Lefebvre *et al.*, 2009). In addition, BAs also serve as signaling molecules by activation or deactivation of farnesoid X receptor (FXR), Takeda G protein-coupled receptor 5 (TGR5), vitamin D receptor (VDR), pregnane X receptor (PXR), sphingosine-1-phosphate receptor 2 (S1PR2), and constitutive androstane receptor (CAR) to coordinate glucose and lipid metabolism (Staudinger *et al.*, 2001; Makishima *et al.*, 2002; Ma *et al.*, 2006; Thomas *et al.*, 2009; Thibaut and Bindels, 2022; Miao *et al.*, 2025).

The binding affinity of BAs to their receptors varies significantly. The potency of BAs in activating FXR decreases in the order CDCA > DCA > LCA > CA (Wang *et al.*, 1999). FXR activation ameliorates obesity, diabetes, and MASLD, and concurrently improves hyperlipidemia and hyperglycemia (Panzitt *et al.*, 2025; Ren *et al.*, 2025). In contrast, inhibiting FXR in the intestine alleviates obesity and insulin resistance in high-fat diet (HFD)-fed mice (Jiang *et al.*, 2015; Beau *et al.*, 2023). Mechanistically, BAs act as FXR agonists to regulate the expression of fibroblast growth factor 15 (FGF15) and sterol regulatory element binding protein-1 (SREBP-1c), affecting cholesterol absorption and reducing triglycerides, fatty acids, and cholesterol levels in the blood and the liver (Watanabe *et al.*, 2004; Wang *et al.*, 2019). Notably, elevated secondary BAs (e.g., DCA), in MASLD rats, impair lipid metabolism by inhibiting hepatic FXR and fibroblast growth factor receptor 4 (FGFR4) signaling (Jiao *et al.*, 2018). Meanwhile, LCA can induce severe liver injury and regulate the expression of BA metabolism genes through PXR/VDR activation (Fleishman and Kumar, 2024; Cao *et al.*, 2025), highlighting BA receptors as therapeutic targets for BA-related metabolic disorders.

Glucagon-like peptide-1 (GLP-1), an incretin hormone that stimulates insulin secretion and lowers blood glucose, is regulated by both TGR5 (Wang *et al.*, 2023) and FXR (Trabelsi *et al.*, 2015). Intestinal BAs activate TGR5, raising GLP-1 and insulin levels and enhancing energy expenditure (Thomas *et al.*, 2009). Female TGR5 knockout mice fed an HFD develop marked obesity (Lun *et al.*, 2024). Conversely, CA activates TGR5 in brown adipose tissue, induces uncoupling proteins via TGR5-cAMP-PKA, increases lipid oxidation, and prevents HFD-induced obesity (Watanabe *et al.*, 2006). Intriguingly, HCA improves glycemia by activating TGR5 and inhibiting FXR in pigs and diabetic mice (Zheng *et al.*, 2021).

In vitro, DCA, TDCA, and TCA activate epidermal growth factor receptor (ERBB1), ERBB2, and insulin receptors in primary hepatocytes, triggering AKT-GSK3 and enhancing glycogen synthase (Fang *et al.*, 2004; Han *et al.*, 2004). In HepG2 cells, CA and CDCA suppress gluconeogenic genes including glucose-6-phosphatase (G6Pase), phosphoenolpyruvate carboxykinase (PEPCK), and fructose 1,6-bis phosphatase (FBP1) through short heterodimer partner (SHP)-dependent mechanisms (Yamagata *et al.*, 2004). As an FXR agonist, CDCA upregulates BA transporter expression, modulates adipokines and inflammation, protects hepatocytes, and reduces insulin resistance (Heianza *et al.*, 2022). Notably, GUDCA gavage inhibits intestinal FXR and increases GLP-1 in mice (Sun *et al.*, 2018), whereas TCA reduces fecal bile salt hydrolysis (BSH) activity, elevates taurine-conjugated BAs in the liver and feces, and suppresses hepatic proglucagon mRNA expression via FXR activation (Tian *et al.*, 2020).

Collectively, BAs orchestrate glucose and energy homeostasis through systemic modulation of nuclear and membrane receptors, resulting in complex cross-organ regulatory networks. Importantly, species-specific BA profiles dictate differential receptor activation, underscoring the need for species-tailored therapeutic strategies.

Enteroprotection: BAs regulate intestinal barrier integrity and epithelial proliferation. In newly weaned piglets, the immature gastrointestinal tract compromises nutrient digestion/absorption (e.g., lipids), predisposing the animals to post-weaning stress and immune dysfunction. CDCA improves the growth performance via dual roles as an enteral nutrient and stimulator of glucagon-like peptide 2 (GLP-2) secretion (Jain *et al.*, 2012; de Diego-Cabero *et al.*, 2015; Song *et al.*, 2021). GLP-2, secreted by the enteroendocrine L cells in response to luminal nutrients, promotes mucosal regeneration, transcellular transport, and tight-junction protein expression; exogenous GLP-2 restores these functions (Jain *et al.*, 2012; Brubaker, 2018). Notably, CDCA alleviates LPS-induced intestinal epithelial barrier damage in both IPEC-J2 cells and murine models (Song *et al.*, 2019). Similarly, TCA, TDCA, GDCA, and GCDCA stimulate IEC-6 cell proliferation (Ishizuka *et al.*, 2012), with TDCA exhibiting proliferative in IEC-6 and Caco-2 cells in a dose-dependent

Table 2: Function of bile acids in pigs, humans, rodents, and bacteria

Species	Bile acid	Functionality
Pig	CA	• Enhancing SADS-CoV entry via caveolae-mediated endocytosis (Yang *et al.*, 2022). • Altering the trafficking dynamics of SADS-CoV along the endo-lysosomal system (Yang *et al.*, 2022). • Increasing FGF19 and GLP-1/2 secretion in the gut (Jain *et al.*, 2012). • Increasing the villus height-to-crypt depth (V:C) ratio (Song *et al.*, 2021).
Pig	CDCA	• Increasing goblet cell numbers and the expression of tight junction proteins (Song *et al.*, 2021). • Increasing jejunal lipase activity and the mRNA expression of pancreatic lipases (Song *et al.*, 2021). • Increasing the relative abundance of *Prevotella 9* and Prevotellaceae *TCG-001* (Song *et al.*, 2021).
Pig	HCA	• Promoting GLP-1 secretion via simultaneously activating TGR5 and inhibiting FXR (Zheng *et al.*, 2021).
Pig	HDCA	• Increasing abundance of the gut bacteria associated with BAs metabolism (Song *et al.*, 2020). • Inhibiting the PI3K/AKT pathway (Song *et al.*, 2020).
Pig	HDCA/DCA	• Activating FXR in hepatocytes (Lin *et al.*, 2019). • Decreasing cell proliferation (Lin *et al.*, 2020).
Pig	LCA	• Decreasing expression of antioxidant enzymes (Lin *et al.*, 2020). • Stimulating inflammatory responses (Lin *et al.*, 2020). • Inducing M2 macrophage polarization (Pi *et al.*, 2023).
Pig	UDCA	• Reducing inflammatory cytokine production by engaging BA receptor FXR (Pi *et al.*, 2023). • Suppressing NF-κB activation in macrophages (Pi *et al.*, 2023).
Pig	17% CDCA, 68% HDCA, and 9% HCA (MIX)	• Promoting the ileum development (Liu *et al.*, 2022). • Increasing the plasma albumin, triglyceride, and total protein concentrations (Liu *et al.*, 2022). • Decreasing plasma AST, ALT, CHE, LDH, and NH3 levels (Liu *et al.*, 2022).
Human	CDCA	• Reducing the mRNA expression of G6Pase, PEPCK, and FBP1 (Yamagata *et al.*, 2004). • Repressing gluconeogenic gene promoter activities via HNF-4 or Foxo1 (Yamagata *et al.*, 2004).
Human	TCA	• Inducing CXCL16 mRNA expression (Ma *et al.*, 2018).
Human	GLCA	• Inverse correlation with CXCL16 expression (Ma *et al.*, 2018).
Human and mouse	CDCA	• Rescuing cells from ferroptotic cell death by competing lipid peroxidation through activating FXR (Tschuck *et al.*, 2023). • Enhancing hepatic NKT cell accumulation (Ma *et al.*, 2018). • Enhancing the inhibition of liver tumor growth caused by antibiotic treatment (Ma *et al.*, 2018). • Levels correlated with CXCL16 expression (Ma *et al.*, 2018). • Suppressing of hepatic FXR-mediated and FGFR4-mediated signaling (Jiao *et al.*, 2018).
Human and mouse	DCA	• Enhancing ROS production (Fang *et al.*, 2004). • Inhibiting protein tyrosine phosphatases activity (Fang *et al.*, 2004). • Activating the ERBB1, ERK1/2 and AKT pathways (Fang *et al.*, 2004).
Human and mouse	DCA/LCA	• Promoting innate antiviral response via the TGR5-GRK-β-arrestin-SRC axis (Hu *et al.*, 2019).
Human and mouse	LCA	• Blocking LPS-primed caspase-1 maturation and TNF-α, IL-1β or IL-18 secretion in a dose-dependent manner (Guo *et al.*, 2016). • Inhibiting NLRP3 inflammasome activation via TGR5-cAMP-PKA axis (Guo *et al.*, 2016). • Upregulating the PXR expression (Staudinger *et al.*, 2001). • Resulting in a robust induction of hepatic CYP3A11 and Oatp2 expression (Staudinger *et al.*, 2001).
Mouse	CA	• Reducing IL-1β, IL-18, and TNF-α production in white adipose tissue (Guo *et al.*, 2016). • Preventing HFD-induced insulin resistance via TGR5 signaling (Guo *et al.*, 2016). • Reducing the mRNA levels of gluconeogenic genes, including G6Pase, PEPCK, and FBP1 (Yamagata *et al.*, 2004). • Decreasing the triglycerides in serum and liver (Watanabe *et al.*, 2004). • Decreasing the expression of SREBP-1c (Watanabe *et al.*, 2004). • Inducing the expression of SHP (Watanabe *et al.*, 2004). • Attenuating LXR agonist-induced lipogenesis in vivo (Watanabe *et al.*, 2004). • Increasing fat oxidation (Watanabe *et al.*, 2006). • Increasing the number of lamellar cristae in the mitochondria of brown adipose tissue (Watanabe *et al.*, 2006). • Decreasing the expression of endogenous SREBP-1c (Watanabe *et al.*, 2004).
Mouse	CDCA	• Decreasing proglucagon mRNA levels (Trabelsi *et al.*, 2015). • Potentiating SeV- or HSV-1-induced phosphorylation of IRF3 (Hu *et al.*, 2019). • Inhibiting VSV replication (Hu *et al.*, 2019).
Mouse	CDCA/DCA/GDCA	• Inducing the PM localization of NPC1L1 and cholesterol dispersal (Xiao *et al.*, 2023). • Transporting ERC cholesterol to the ER and PM (Xiao *et al.*, 2023).
Mouse	CDCA/DCA/GDCA/ TDCA	• Inhibiting SREBP2 processing (Xiao *et al.*, 2023). • Entering cells independent of NTCP (Xiao *et al.*, 2023).
Mouse	GUDCA	• Suppressing intestinal FXR signaling (Sun *et al.*, 2018). • Elevating active GLP-1 production substantially (Sun *et al.*, 2018).
Mouse	HDCA	• Ameliorating diet-induced NAFLD by activating hepatic PPARα-dependent fatty acid oxidation (Zhong *et al.*, 2023).
Mouse	T-β-MCA	• Inducing CXCL16 mRNA expression (Ma *et al.*, 2018).
Mouse	3-Keto-LCA	• Activating the PXR (Staudinger *et al.*, 2001).
Mouse	3-OxoLCA	• Inhibiting TH17 cell differentiation (Hang *et al.*, 2019).
Mouse	Isoallo LCA	• Promoting Treg cell differentiation (Hang *et al.*, 2019).
Mouse	DCA	• Suppressing the differentiation of secretory lineages by inhibiting the WNT signaling pathway, leading to the down-regulation of Paneth cell-AMPs (Wang *et al.*, 2023). • Increasing PI-stained cells and decreased CFDA-stained bacteria (Tian *et al.*, 2020). • Activating ERBB1, ERBB2, and the insulin receptor (Han *et al.*, 2004). • Enhancing tyrosine phosphorylation of IRS-1 (Han *et al.*, 2004). • Activating the AKT/GSK3 pathway via the insulin receptor (Han *et al.*, 2004).
Mouse	DCA/TCA	• Decreasing fecal BSH activity (Tian *et al.*, 2020).
Mouse	DCA/TCA/TDCA	• Enhancing glycogen synthase activity (Han *et al.*, 2004).
Mouse	LCA	• Increasing the mRNA expression of intestinal PXR target genes (Tian *et al.*, 2020). • Inducing CYP3A expression through activating VDR (Makishima *et al.*, 2002).
Mouse	LCA/ω-MCA	• Reversing the inhibition of liver tumor growth caused by antibiotic treatment (Ma *et al.*, 2018).
Mouse	TCA	• Increasing PI-stained cells and decreased CFDA-stained bacteria (Tian *et al.*, 2020).

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Mouse		• Decreasing level of proglucagon mRNA expression in the liver (Tian *et al.*, 2020).
Mouse	TCA/TDCA	• Stimulating AKT phosphorylation (Han *et al.*, 2004).
Mouse	TDCA	• Inducing the PM localization of NPC1L1 and cholesterol dispersal (Xiao *et al.*, 2023).
Mouse	TLCA	• Blocking LPS-primed caspase-1 maturation and IL-1β or IL-18 secretion in a dose-dependent manner (Guo *et al.*, 2016). • Mitigating LPS-induced systemic inflammation and alum-induced peritoneal inflammation via TGR5 signaling (Guo *et al.*, 2016). • Promoting NLRP3 phosphorylation and ubiquitination via TGR5 in vivo (Guo *et al.*, 2016).
Mouse	UDCA	• Suppressing the proliferation of CRC cells by inhibiting YAP and activating TGR5 (Zhang *et al.*, 2021).
Mouse	ω-MCA	• Decreasing CXCL16 mRNA expression (Ma *et al.*, 2018). • Reversing hepatic NKT accumulation (Ma *et al.*, 2018).
Mouse	TCA, β-MCA and T-β-MCA (MIX)	• Inducing the expression of pro-inflammatory genes MIP-2, KC and ICAM-1 (Zhang *et al.*, 2012).
Rodent	TDCA	• Activating the expression of ERBB1, ERK1/2 and AKT pathways (Fang *et al.*, 2004).
Bacteria	CDCA	• Resulting in a slower growth rate (Marion *et al.*, 2019). • A reduced peak cell density and a lower end point cell density in a dose-dependent manner (Marion *et al.*, 2019).
Bacteria	DCA/LCA	• Enhancing the inhibitory activity of 1-acetyl-b-carboline and turbomycin A secreted by *Clostridium scindens* and *Clostridium sordellii*, respectively (Kang *et al.*, 2019). • Inhibiting the growth of *Clostridium difficile* (Kang *et al.*, 2019).

Abbreviation: BSH, bile salt hydrolysis; cAMP, Cyclic adenosine 3′,5′-monophosphate; CFDA, carboxyfluorescein diacetate; CRC, colorectal cancer; CXCL16, CXC-chemokine ligand 16; CYP3A, cytochrome P450 3A; CYP3A11, cytochrome P450, family 3, subfamily a, polypeptide 11; ER, endoplasmic reticulum; ERC, endocytotic circulating chamber; FBP1, fructose 1,6-bis phosphatase; FGFR4, fibroblast growth factor receptor 4; FXR, farnesoid X receptor; G6Pase, glucose-6-phosphatase; GLP-1, glucagon-like peptide-1; GRK, G-protein coupled receptor-related kinases; HNF-4, hepatocyte nuclear factor 4; HSV-1, Herpes simplex virus-1; ICAM-1, intercellular adhesionmolecule 1; IRF3, interferon regulatory factor 3; IRS-1, insulin receptor substrate 1; KC, keratinocyte-derived chemokine; LXR, liver X receptor; MIP-2, macrophage-inflammatoryprotein-2; NKT, natural killer T; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; NPC1L1, Niemann-Peak C1-like 1; NTCP, sodium taurocholate cotransporting polypeptide; PEPCK, phosphoenolpyruvate carboxykinase; PKA, protein kinase A; PM, plasma membrane; PXR, pregnane X receptor; ROS, reactive oxygen species; SeV, Sendai virus; SHP, short heterodimer partner; SREBP-1c, sterol regulatory element binding protein-1; SREBP2, sterol regulatory element binding protein-2; TGR5, Takeda G protein-coupled receptor 5; VDR, vitamin D receptor; VSV, vesicular stomatitis virus; YAP, yes associated protein.

manner (Toledo *et al.*, 2004; Yamaguchi *et al.*, 2004). Furthermore, TUDCA enhances the developmental capacity of *in vitro* matured porcine oocyte embryos (Li *et al.*, 2017), collectively supporting that BAs are protective nutraceuticals for intestinal homeostasis and epithelial repair.

BA-microbiota crosstalk critically shapes the intestinal milieu. While secondary BAs (e.g., DCA, LCA) are generally more cytotoxic, their dysregulated accumulation disrupts epithelial proliferation and barrier function, contributing to inflammatory bowel disease (Feng *et al.*, 2022; Yang *et al.*, 2024). LCA induces apoptosis in HT-29 and HCT-116 colon cancer cells (Katona *et al.*, 2009). Paradoxically, co-administration of LCA and UDCA by gavage ameliorates hyperlipidemia by activating FXR and restoring intestinal barrier integrity in HFD-fed mice (Wang *et al.*, 2019), while FXR agonists upregulate tight junction proteins and reduce inflammation in bile duct ligated rats (Yan *et al.*, 2022). These data suggest UDCA offsets LCA toxicity by remodeling microbial BA metabolism and the BA pool.

Diet shapes BA dynamics. Compared with high fiber diets, high protein intake elevates fecal DCA and LCA levels in humans (Windey *et al.*, 2012; Ou *et al.*, 2013). Conversely, high fiber or resistant starch halves fecal DCA levels, indicating that colonic carbohydrate fermentation limits secondary BA accumulation.

Immunity and inflammation: BAs regulate immune responses by interacting with immune cells and regulating cytokine production. Innate immune cells expressing BA receptors are activated by BAs to produce cytokines, affecting the differentiation of adaptive immune cells. BA receptors have been identified in monocytes, macrophages, dendritic cells, and natural killer T (NKT) cells (Fiorucci *et al.*, 2024).

Primary BAs promote the expression of CXC-chemokine ligand 16 (CXCL16) in liver sinusoidal endothelial cells (LSECs), thereby recruiting NKT cells to the liver and displaying anti-tumor effects. Conversely, secondary BAs inhibit the expression of CXCL16 (Schramm, 2018). In SK-HEP1 cells (a human hepatic cell line), TCA upregulates the mRNA expression of CXCL16, while GLCA negatively correlates with CXCL16 expression. Similarly, in mouse LSECs, T-β-MCA likewise increases CXCL16, whereas ω-MCA reduces its expression and reverses the accumulation of NKT cells and the inhibitory effect of antibiotics on liver tumor growth. Feeding mice CDCA enhances the accumulation of hepatic NKT cells and reinforces the tumor-suppressive effects of antibiotics (Ma *et al.*, 2018). Collectively, CXCL16 expression is positively associated with primary BAs but negatively correlated with secondary BAs.

DCA and LCA are endogenous ligands for the G protein-coupled receptor TGR5 (Han *et al.*, 2021), playing crucial roles in regulating immune responses (Antonini Cencicchio *et al.*, 2025; Chang *et al.*, 2025). The rank order of BA potency in activating TGR5 is: LCA > DCA > UDCA > CDCA > CA. By activating TGR5, BAs trigger the cAMP-PKA-CREB signaling pathway, thereby inhibiting the NF-κB signaling pathway and reducing the levels of pro-inflammatory cytokines such as IL-6, IL-8, and TNF-α in immune cells (Meng *et al.*, 2021; Perino *et al.*, 2021; Wang *et al.*, 2022; Hoff *et al.*, 2023). Studies have shown that LCA can inhibit the differentiation of Th17 cells and promote the differentiation of Tregs, thus regulating the host immune response (Hang *et al.*, 2019). Intraperitoneal injection of LCA or TLCA in mice attenuates LPS-induced inflammatory responses (Guo *et al.*, 2016). TGR5 also plays a role in regulating the differentiation of M1 and M2 macrophages, reducing the secretion of TNF-α, IFN-γ, IL-6, and IL-1β in M1 macrophages, while promoting the differentiation of IL-10-producing M2 macrophages (Hang *et al.*, 2019).

FXR inhibits the NF-κB and MAPK signaling pathways, reducing the production of inflammatory factors (He *et al.*, 2024), and regulates the maturation of intestinal dendritic cells (Fiorucci *et al.*, 2022; Fu *et al.*, 2022). UDCA (drug name: Actigall, Urso) is primarily used as an

anti-cholestatic agent, serving as the main treatment option for patients with autoimmune biliary diseases, such as primary biliary cholangitis. It may also inhibit the progression of gastrointestinal cancers, such as colorectal cancer (CRC) and HCC (Shen *et al.*, 2022). By binding to FXR, UDCA inhibits NF-κB activation in macrophages, thereby reducing the production of inflammatory cytokines and alleviating gut inflammation in low birth weight (LBW) piglets (Pi *et al.*, 2023).

Microbial regulation: The composition and abundance of gut microbiota are closely associated with the gut environment. BAs exert direct antibacterial effects on intestinal microbiota through their cleaning properties. BAs have the following characteristics in regulating the gut microbiota quota: 1) Unconjugated BAs have stronger antibacterial activity than conjugated BAs, 2) Gram-positive bacteria are more sensitive to BAs than Gram-negative bacteria, 3) BAs directly affect the overall metabolism of bacteria, including causing membrane damage, amino acid, nucleotide, and carbohydrate metabolism disorders (Tian *et al.*, 2020), and indirectly regulate intestinal homeostasis and immunity through interactions with nuclear membrane receptors (Levy *et al.*, 2017; Bustos *et al.*, 2018).

The size and composition of BA pools remodel the microbiota. In rodent models of biliary obstruction and liver injury, BAs reverse small-intestinal bacterial overgrowth (Zhou *et al.*, 2023). TCA or T-β-MCA given to newborn mice shifts the microbiota toward an adult-like profile (van Best *et al.*, 2020). CA supplementation expands Firmicutes (from 54% to 93%-98%) and *Clostridium* (from 39% to 70%) (Islam *et al.*, 2011). Combining secondary BAs and bacteria-secreted antibacterial reveals synergistic effects. DCA and LCA can enhance the production of antibacterial compounds (1-acetyl-β-carboline and turbomycin A) by bacteria to inhibit the growth of *Clostridium difficile in vivo* (Kang *et al.*, 2019). DCA and TCA lower cecal total bacteria load, reduce fecal Firmicutes to Bacteroidetes ratio, decrease microbial metabolite levels, and diminish BSH activity in mice (Tian *et al.*, 2020). *In vitro*, LCA broadly inhibits growth, with DCA being more potent (Tian *et al.*, 2020). Through FXR and TGR5, BAs protect the intestinal epithelium from barrier dysfunction and bacterial invasion, mitigating inflammation (Fogelson *et al.*, 2023; Fleishman and Kumar, 2024). In healthy individuals, the synthesized FXR agonist obeticholic acid (drug name: Ocaliva) inhibits endogenous BAs and induces the proliferation of Gram-positive bacteria (e.g., *Streptococcus thermophilus*, *Lactobacillus casei*, *Lactobacillus paracasei*, *Bifidobacterium brevis*, and *Lactobacillus lactis*), suggesting that FXR activation affects the composition of gut microbiota through a negative feedback loop in regulating BA synthesis.

Beyond bacteria, BAs influence viral replication. CA enhances SADS-CoV replication in porcine intestinal enteroid in the early stages of infection (Yang *et al.*, 2022). BAs facilitate enteroviruses including porcine sapovirus, porcine enteric calicivirus (PEC), and Noroviruses. PEC replication in LLC-PK1 cells requires GCDCA and CDCA, and BAs drive nuclear to cytoplasmic escape to initiate replication (Shivanna *et al.*, 2014; Alwin and Karst, 2021). In PEC-infected LLC-PK9 cells, GCDCA and TCDCA are the most effective BAs in inhibiting innate immunity by downregulating the phosphorylation of signal transduction and signal transducer and activator of transcription factor 1 (Chang *et al.*, 2004).

Human NoV subtype Gll.3 replication in human intestinal enteroid depends on GCDCA-induced endosomal/lysosomal acidification and ASM activation (Ettayebi *et al.*, 2016; Murakami *et al.*, 2020). The mouse norovirus capsid protein VP1 binds BAs (GCDCA>TCA), triggering structural changes that enhance receptor binding, infectivity, and antibody evasion (Nelson *et al.*, 2018; Williams *et al.*, 2021). UDCA reduces the susceptibility to SARS-CoV-2 both *in vitro* and *in vivo* by reducing FXR signaling and downregulating ACE2 in human lung and bile duct cells, as well as intestinal organoids, and in the corresponding tissues of mice and hamsters (Brevini *et al.*, 2023).

BAs participate in the antiviral immunity. CDCA, LCA, and DCA promote the innate antiviral immune response by activating the TGR5-β-arrestin-SRC axis. Specifically, viral infections lead to the rapid expression of BA transport proteins and rate-limiting synthetic enzymes, causing endogenous accumulation of BAs (CDCA, DCA) in hepatic and extrahepatic cells. These accumulated BAs activate the TGR5-β-arrestin-SRC axis, resulting in the tyrosine phosphorylation of key components in the RIG-I/MDA5 and cGAS-mediated pathways. This phosphorylation is essential for the activation of the innate antiviral immune response. BAs further induce antiviral genes and display robust antiviral activity in cells and mice, underscoring TGR5 as a key host factor (Hu *et al.*, 2019).

DCA restores the reduction in plasmacytoid dendritic cell numbers and IFN responses compromised by intestinal microbiota depletion, limiting the Chikungunya virus dissemination. In piglets infected with Porcine epidemic diarrhea virus, LCA reshapes the intestinal T-cell compartment. LCA increased the expression of swine leukocyte antigen (SLA) class I in pig intestinal epithelial cells through the FXR receptor, which recruited $CD8^+$ cytotoxic T lymphocytes (CTLs) to exert an antiviral effect (Xing *et al.*, 2024).

Bile acids in the brain: BAs are soluble products of cholesterol catabolism. The brain, which contains approximately 25% of the body's total cholesterol, is one of the most cholesterol-rich organs. Cholesterol and related lipids are key components of the plasma membranes of neurons and glial cells, as well as the main components of myelin (Björkhem and Meaney, 2004; Montesinos *et al.*, 2020). BAs in the brain originate through two pathways: 1) diffusion or active transport of BAs to the brain via BAs transporters during systemic circulation, and 2) local synthesis in astrocytes and neurons (Wu *et al.*, 2023). Secondary BAs in the brain can only be obtained from the gut, as their biosynthesis depends on the enzymatic activity of gut bacteria (de Aguiar Vallim *et al.*, 2013) (Fig. 1). Despite this dual origin, systemic circulation predominantly regulates BA levels in the brain (Mano *et al.*, 2004; Reddy *et al.*, 2018).

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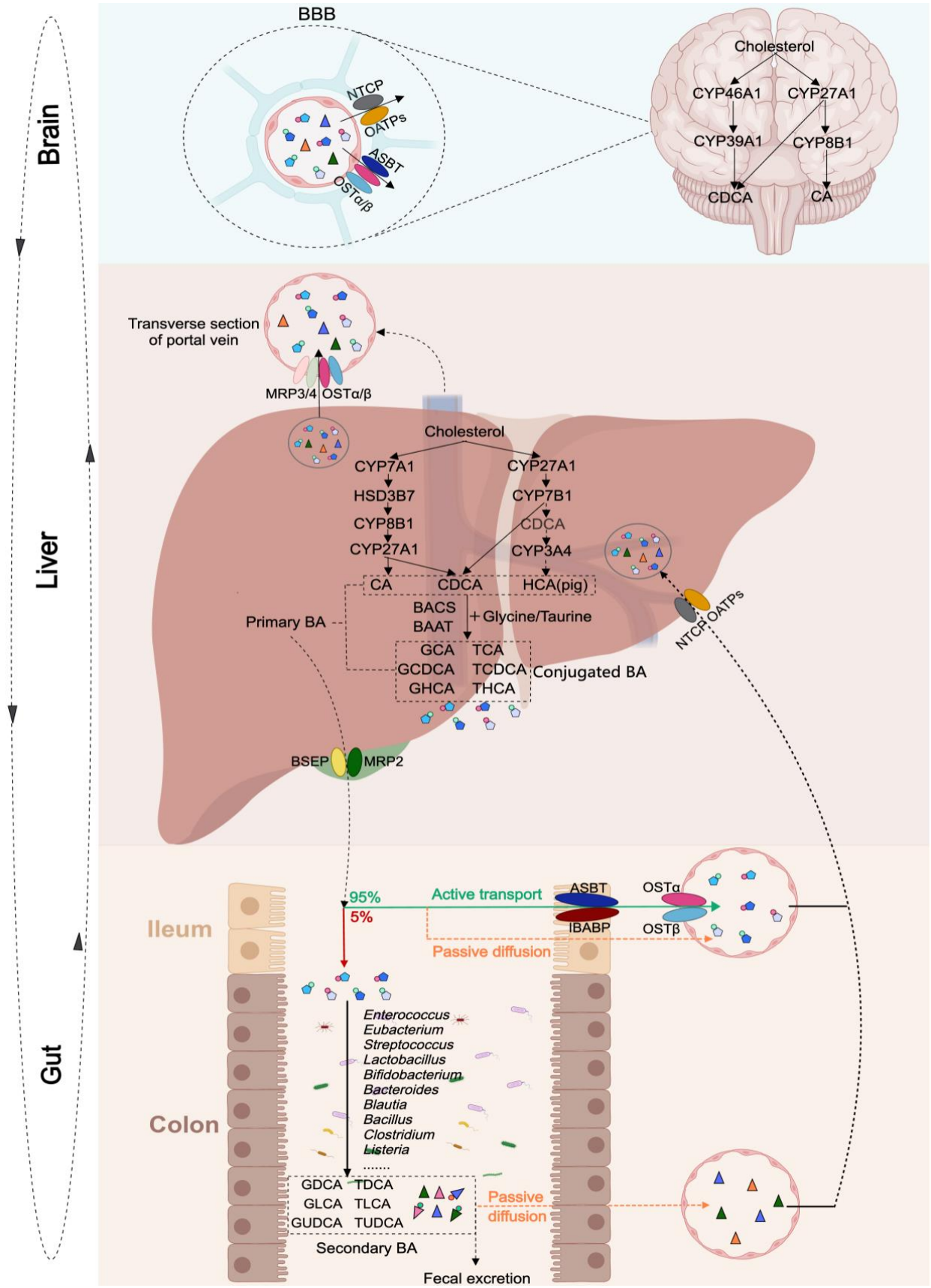

Fig. 1: Bile acids in the gut-liver-brain axis. Cholesterol is metabolized into primary bile acids (BAs) such as cholic acid, chenodeoxycholic acid (Ferdinandusse and Houten, 2006), and hyocholic acid (Zheng *et al*., 2021), which is unique to pigs. In the liver, primary BAs are conjugated with taurine and glycine by BA CoA synthase (BACS) and BA-CoA: amino acid N-acyltransferase (BAAT) to form conjugated BAs (GCA, TCA, GCDCA, TCDCA, GHCA, THCA), which are stored in the gallbladder (Fuchs *et al*., 2025). Upon eating, the gallbladder contracts and releases BAs into the duodenum via the BA transporters. When passing through the terminal ileum, 95% of BAs are reabsorbed into the liver for recycling via the enterohepatic circulation. The remaining 5% are metabolized into secondary BAs by microorganisms in the colon (Chiang, 2013). Some secondary BAs combine with glycine or taurine to form conjugated secondary BAs. BAs in the bloodstream can cross the blood-brain barrier (BBB) and enter the brain, including both primary and secondary BAs (Lund *et al*., 2003).

Hydrophobic unconjugated BAs exhibit potential neurotoxic effects (Quinn *et al.*, 2014). They can compromise blood-brain barrier integrity and impair its ability to regulate neuroinflammation and brain cholesterol metabolism (McMillin *et al.*, 2017, 2018). Thus, enterohepatic circulation and systemic circulation of BAs may affect brain health (Quinn *et al.*, 2014).

Emerging evidence highlights BA signaling as a key modulator of the gut-liver-brain axis, which can transmit metabolic signals and display neuroprotective effects (Perino *et al.*, 2021; Khalaf *et al.*, 2022; You *et al.*, 2024). Metabolic dysfunction is a major risk factor for neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease. Disturbances in BA signaling have been linked to a variety of neurodegenerative diseases, suggesting BAs as an important therapeutic target for neurodegenerative diseases (Weiss *et al.*, 2016; Xie *et al.*, 2018; Hadjihambi *et al.*, 2019; Hertel *et al.*, 2019; MahmoudianDehkordi *et al.*, 2019; Nho *et al.*, 2019; Baloni *et al.*, 2020; Clifford *et al.*, 2021). Currently, UDCA and TUDCA have shown promise in the treatment of neurodegenerative diseases. UDCA and TUDCA, as agonists of TGR5, are also FXR antagonists. They play a neuroprotective role by regulating protein folding and clearance (Khalaf *et al.*, 2022), suppressing inflammation (Wu *et al.*, 2018), regulating mitochondrial function (Elia *et al.*, 2016; Bell *et al.*, 2018), and mitigating oxidative stress (Lu *et al.*, 2018). These studies suggest that activating the BA-TGR5 signaling pathway may be a promising strategy for the treatment of neurological disorders. While current studies on BAs in the brain have focused on humans and mice, the role of the gut-liver-brain axis in porcine BA metabolism remains to be studied.

Porcine bile acid profile: Porcine BAs in different tissues of healthy pigs across various breeds, ages, or weights, as reported in the literature, are summarized in Table 3. In the liver, BAs were mainly glycine-conjugated, primarily GHCA, GHDCA, GCDCA, and GDHCA. With age, the major BAs in the liver changed from GHCA to GHDCA, probably because of the richness of intestinal flora, which promoted BA metabolism. In bile, HCA, HDCA, and CDCA are the main BAs. Similarly, the main BAs in bile change from primary BAs to secondary BAs with aging. BAs in the blood and ileum were mainly composed of HCA and HDCA. Compared with the ileum, BAs in the cecum and colon were mainly composed of secondary HDCA and LCA, which were related to regional microbial abundance. The microbial transformation of BAs involves four pathways: deconjugation, dehydroxylation, oxidation, and epimerization. In addition, BAs can be sulfated, esterified, and even reconjugated by microbiota, thereby increasing the diversity of BA pools (Larabi *et al.*, 2023). The composition of the BA pool is also regulated by dietary factors. For example, high-fat and high-cholesterol diets increase BA levels (Cai *et al.*, 2020). The functions of porcine BAs are summarized in Fig. 2 and Table 4.

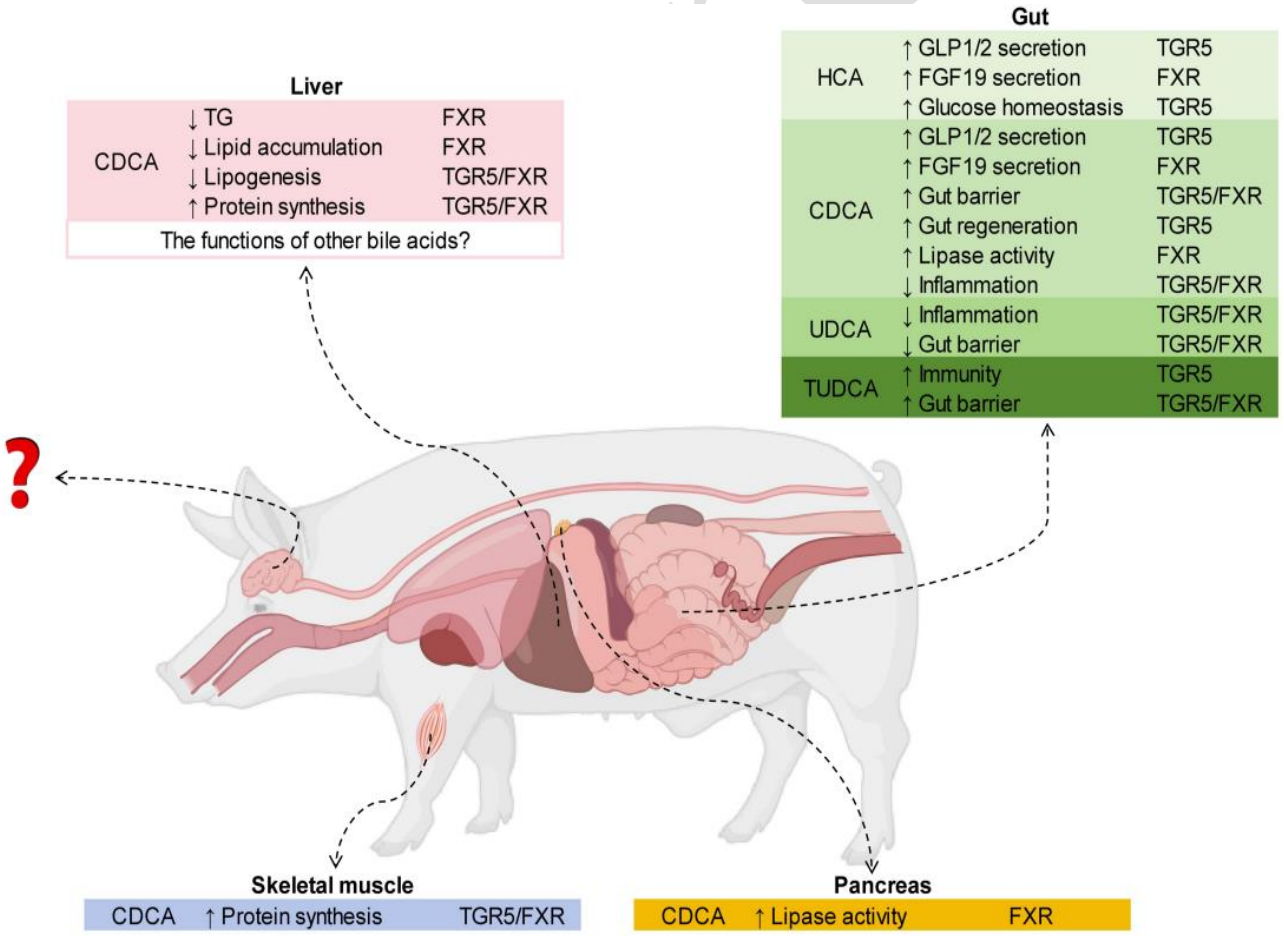

Fig. 2: Roles of bile acids in pigs. Through bile acid (BA) receptors, BAs (e.g., CDCA, HCA, UDCA, TUDCA) have functions in various organs (e.g., gut, liver, skeletal muscle, and pancreas). The role of porcine BAs in the brain remains to be studied.

Table 3: Porcine bile acid profile

Breeds	Days of body weight/age at trial initiation	Test days/day	Age at sampling/day	Tissue	Bile acid content ranking (descending from left to right)	Reference
Yorkshire × Duroc	0 day	0	0	Liver	GHCA; GDHCA; GCDCA; TCDCA; THCA; THDCA; GCA; TCA; GUDCA; GLCA	(Vonderohe *et al.*, 2022)
Yorkshire × Duroc	0 day	3	3		GHCA; GDHCA; GCDCA; TCDCA; THCA; THDCA; GCA; TCA; HDCA; UDCA	(Vonderohe *et al.*, 2022)
Duroc × Landrace × Large White	15 kg	28	76		GHDCA; GCDCA; GHCA; THDCA; TCDCA; THCA; HDCA; GLCA; GUDCA; HCA	(Li *et al.*, 2022)
Landrace × Yorkshire	40 kg	28	118		GHDCA; GCDCA; THDCA; TCDCA; GLCA; GUDCA; HCA; HDCA; GCA; CDCA	(Hou *et al.*, 2020)
Large White × Landrace, male	5 days	14	19		HCA; HDCA; CDCA; CA; LCA	(Lavallee *et al.*, 2019)
Duroc × Landrace × Yorkshire	33 days	21	54	Bile	GHDCA; GCDCA; THDCA; GUDCA; GDCA; GCA; THCA; GLCA; TCA; HDCA	(Hu *et al.*, 2023)
Large White, male	64 days	28	92		HDCA; CDCA; HCA; DCA; UDCA	(Gunness *et al.*, 2016)
3-day-old conventional piglets	3 days	21	24	Small intestine	GCDCA; CDCA; TCDCA; DCA; CA; TDCA	(Yang *et al.*, 2022)
Duroc × Landrace × Yorkshire, half	28 days	17	45	Ileum	HCA; HDCA; GHDCA; CDCA; GHCA; THCA; GCDCA	(Lin *et al.*, 2020)
Duroc × Landrace × Large White	15 kg	28	76		HCA; HDCA; CDCA; GHCA; GHDCA; THCA; GCDCA; LCA;	(Li *et al.*, 2022)
Landrace × Yorkshire	40 kg	28	118		GHDCA; HDCA; THCA; GCDCA; CDCA; HCA; THDCA; TCDCA	(Hou *et al.*, 2020)
Duroc × Large White, Male	11.05 kg	72	119		CDCA; GUDCA; GCDCA; UDCA+HDCA; HCA; TCDCA; THDCA; THCA; LCA; TLCA	(Fang *et al.*, 2018)
Duroc × Landrace × Yorkshire	28 days	28	56	Cecum	CDCA; HDCA; CA; LCA; UDCA	(Tang *et al.*, 2022)
Duroc × Large White, Male	11.05 kg	72	119		UDCA+HDCA; LCA; HCA; CDCA; GUDCA; GCDCA; TCDCA; THCA; THDCA; TLCA	(Fang *et al.*, 2018)
Duroc × Landrace × Large White	28 days	0	28	Colon	HDCA; LCA; HCA; DCA; UDCA; CDCA	(Lin *et al.*, 2019)
Duroc × Landrace × Large White	21 days	28	49		HDCA; HCA; CDCA; LCA; GUDCA; GCDCA	(Wen *et al.*, 2023)
Duroc × Large White, Male	11.05 kg	72	119		UDCA+HDCA; LCA; HCA; CDCA; GUDCA; GCDCA; THDCA; TCDCA; THCA; TLCA	(Fang *et al.*, 2018)
Duroc × Landrace × Yorkshire	28 days	0	28	Portal Blood	HCA; HDCA; CDCA; GHCA; GHDCA	(Lin *et al.*, 2019)
Duroc × Landrace × Large White	15 kg	28	76	Plasma	HDCA; HCA; GHDCA; CDCA; GHCA; GCDCA; THDCA; TCDCA; LCA; THCA	(Li *et al.*, 2022)
Adult Göttingen non-obese non-diabetic minipigs (male:female=4:2)	"Adult"	-	-		HCA; UDCA; GUDCA; GHCA; CDCA; GCDCA; TUDCA; THCA; CA; TCDCA	(Spinelli *et al.*, 2016)
Landrace × Yorkshire	40 kg	28	118	Serum	GHDCA; HCA; HDCA; CDCA; GCDCA; THDCA; TCDCA; LCA; THCA; GLCA	(Hou *et al.*, 2020)
Duroc × (Landrace × Large White)	2 days	0	2		HCA; HDCA; UDCA; 3-DHCA; CDCA; LCA; UCA; CA	(Pi *et al.*, 2023)
Duroc × Landrace × Yorkshire (male:female=4:5)	28 days	30	58	Feces	HDCA; LCA; DCA; CDCA	(Song *et al.*, 2021)
Duroc × Large White, Male	11.05 kg	72	119		LCA; UDCA+HDCA; CDCA; GUDCA; HCA; GCDCA; THDCA; TCDCA; THCA; TLCA	(Fang *et al.*, 2018)

Therapeutic applications of bile acids in porcine models: Newly weaned piglets have immature gastrointestinal tracts and insufficient bile salts and lipases, impairing dietary fat digestion and absorption. This deficiency results in early weaning syndrome, which is typically manifested as diarrhea, poor growth, and hypoimmunity (Campbell *et al.*, 2013; Gresse *et al.*, 2017). A beneficial strategy to alleviate intestinal stress in weaned piglets is to use BAs to enhance lipid digestion. Oral CDCA protects intestinal mucosa, improves intestinal morphology and barrier function, enhances lipid digestion, and increases growth in weaned piglets (de Diego-Cabero *et al.*, 2015; Song *et al.*, 2021). A combination of antibiotics and zinc oxide, commonly employed to stimulate pig growth or prevent post-weaning enteritis, can promote the microbial production of BAs (Ipharraguerre *et al.*, 2018). This results in an altered BA ratio (increased CDCA and decreased HCA), which leads to tissue-specific changes in BA, thereby amplifying BA signals in the intestine, liver, and white adipose tissue (Ipharraguerre *et al.*, 2018). The consequences include enhanced antibacterial protection, reduced colonic and adipose inflammation, altered hepatic protein and lipid metabolism, and increased circulating fibroblast growth factor-19 (FGF-19), mediating antibiotic-driven growth (Ipharraguerre *et al.*, 2018). Moreover, a mixture of BAs (17% CDCA, 68% HDCA, and 9% HCA) has been shown to promote ileal development and increase the proportion of potentially beneficial bacteria in the small intestine of piglets (Liu *et al.*, 2022).

Total parenteral nutrition (TPN) disrupts enterohepatic BA circulation and reduces the expression of FGF-19, GLP-1, and GLP-2 in the intestine, predisposing to TPN-associated liver disease (PNALD). In neonatal piglet models of PNALD, treatment with CDCA induced a nearly 4-fold increase in direct bilirubin levels while normalizing serum BAs and hepatic triglycerides. CDCA promotes plasma FGF-19, GLP-1, and GLP-2 secretion and improves intestinal mucosal properties (Jiang *et al.*, 2024).

The postnatal growth performance is associated with intestinal inflammation and dysbiosis. Notably, UDCA is differentially abundant between LBW piglets and normal birth weight piglets (Pi *et al.*, 2023). Transplantation of the microbiota of LBW piglets into antibiotic-treated mice causes intestinal inflammation, whereas oral UDCA

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Table 4: Function of bile acids in pigs.

Type of bile acid	Bile acid	Biological functions and effects on pigs	Age (days)			Breeds / Gender
			Days of age at trial initiation/day	Test days /day	Age at sampling /day	
Primary	CA	Enhance SADS-CoV replication by acting on PIEs at the early phase of infection (Yang *et al.*, 2022).	3	21	24	"Conventional", randomly
Primary	CDCA	Improve the protection of the intestinal mucosa (de Diego-Cabero *et al.*, 2015).	20	14	34	Large White × Landrace × Pietrain, half
Primary	CDCA	Treating PNALD (Jain *et al.*, 2012). Improve gut atrophy (Jain *et al.*, 2012).	2	14	16	Crossbred pigs, randomly
Primary	CDCA	Improve intestinal morphology and barrier function (Song *et al.*, 2021). Enhance lipid digestion (Song *et al.*, 2021). Improve the growth performance of weaned piglets (Song *et al.*, 2021).	21	30	51	Duroc×Landrace×Yorkshire, male:female=4:5
Primary	HCA	Mediate the growth promoting effect of AMA (Ipharraguerre *et al.*, 2018).	22-23	35	57-58	Largewhite × Landrace × Pietrain, half
Primary		Mediate the growth promoting effect of AMA (Ipharraguerre *et al.*, 2018).	22-23	35	57-58	Largewhite × Landrace × Pietrain, half
Primary		Regulate glucose homeostasis (Zheng *et al.*, 2021).	94-108	-	-	Bama miniature pigs (Sus scrofa), male
Secondary	DCA	Detrimental to porcine intestinal cell proliferation (Lin *et al.*, 2019). Detrimental to porcine intestinal barrier function (Lin *et al.*, 2019).	21	7	28	Duroc × Landrace × Yorkshire, randomly
Secondary	HDCA	Alter the BAs metabolism profiles (Song *et al.*, 2020). Suppress intestinal epithelial cell proliferation (Song *et al.*, 2020).	28	28	56	Duroc × Landrace × Yorkshire, male: female=4:5
Secondary	LCA	Detrimental to porcine intestinal cell proliferation (Lin *et al.*, 2019). Detrimental to porcine intestinal barrier function (Lin *et al.*, 2019).	21	7	28	Duroc × Landrace × Yorkshire, randomly
Secondary	LCA	Impair enterocyte proliferation and permeability (Lin *et al.*, 2020).	28	17	45	Duroc × Landrace × Yorkshire, half
Secondary	UDCA	Alleviate intestinal inflammation in LBW piglets (Pi *et al.*, 2023).	0	8	8	Duroc × (Landrace × Large White), randomly
BA mixture	CDCA (17%), HDCA (68%), HCA (9%)	Protect the liver (Liu *et al.*, 2022). Increase the proportion of potentially beneficial bacteria in the small intestine (Liu *et al.*, 2022). Contributing to intestinal development and health of weaned piglets (Liu *et al.*, 2022).	28	28	56	Large White × Landrace, male

Abbreviation: ALT, alanine aminotransferase; AMA, antimicrobials; AST, aspartate transaminase; BAs, bile acids; CHE, choline esterase; FGF19, fibroblast growth factor-19; FXR, farnesoid X receptor; GLP-1, Glucagon-like peptide-1; GLP-2, glucagon-like peptide-2; LBW, low birth weight; LDH, lactate dehydrogenase; PNALD, parenteral nutrition-associated liver disease; SADS-CoV, swine acute diarrhoea syndrome coronavirus; TGR5, Takeda G protein-coupled receptor 5.

administration reduces intestinal inflammation in LBW piglets. The anti-inflammatory effects of UDCA are mediated by activating FXR and simultaneously inhibiting activation of NF-κB in macrophages (Pi *et al.*, 2023). It suggests that targeting gut microbiota and BA metabolism may restore intestinal health and ameliorate postnatal growth retardation in LBW infants.

However, certain secondary BAs may exert detrimental effects on porcine gut health. The accumulation of DCA, LCA, and their conjugated BAs seriously impaired the proliferation and barrier function of porcine intestinal epithelial cells (Lin *et al.*, 2019). Further studies are required to optimize BA dosing strategies for disease prevention or treatment in swine models.

Microbial modulation in bile acid metabolism: Gut microbiota modulates BA pool dynamics through biotransformation, shaping hydrophobicity and enterohepatic circulation. These microbes help maintain low circulating BA levels, thereby protecting liver and intestinal cells. Elevated BAs can drive cholesterol accumulation, gallstones, colon cancer, and liver disease (Fleishman and Kumar, 2024). Antibiotic-induced dysbiosis profoundly disrupts BA metabolism via multiple pathways, characterized by reduced BSH activity, impaired deconjugation of primary BAs, and diminished secondary BA production (Foley *et al.*, 2023).

Probiotics restore BA transformations and excretion. Probiotic mixture VSL#3 enhances BAs deconjugation and fecal excretion in mice by modulation of gut flora (Degirolamo *et al.*, 2014). BSH-harboring probiotics in humans expand the unconjugated BA pool (Song *et al.*, 2023; Wu *et al.*, 2024). *Lactobacillus reuteri* NCIMB 30242 dissolves intestinal BAs, reduces cholesterol absorption, and lowers cholesterol level (Jones *et al.*, 2012). Intestinal bacterial infections disrupt the absorption of ileal BAs and the endocrine regulation of BA production (Uribe *et al.*, 2016). Microbiota loss upregulates colonic BA transporters, increasing BA absorption (Selwyn *et al.*, 2015). Fecal microbiota transplantation restores secondary BAs and mitigates *Clostridium difficile* infection (Yau *et al.*, 2024). *Parabacteroides distasonis* reduces body weight gain, hyperglycemia, and hepatic steatosis in HFD-fed mice (Wang *et al.*, 2019). *Cyberlindnera jadinii* yeast upregulates the biosynthesis of secondary BAs and iron carriers in the cecum of weaned pigs (Cruz *et al.*, 2019).

Firmicutes are the primary BSH-expressing bacteria, followed by Bacteroides and Actinobacteria (Guzior and Quinn, 2021). Loss of BSH-expressing taxa limits deconjugation, reduces secondary BA formation, and raises conjugated primary BAs in the terminal ileum (Guzior *et al.*, 2024). Activation of BA receptors largely depends on unconjugated BAs (Table 5). FXR and TGR5 in epithelial, endothelial, and immune cells preserve barrier function and restrain inflammation (Larabi *et al.*, 2023). Reduced LCA weakens VDR activation in macrophages, undermining their anti-inflammatory activity (Thompson *et al.*, 2023). Interestingly, probiotics can restore dysbiosis and the FXR-FGF15 axis in colitis models (Degirolamo *et al.*, 2014). Thus, probiotic-driven biotransformation of primary to secondary BA is central to host health.

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Table 5: Expression and agonists of bile acid receptors

Receptor	Classification	Tissue Distribution	Main agonist Rank of potency	Reference
FXR	Nuclear receptor	Hepatocytes, small intestine, macrophages NKT cells, adipocytes	CDCA > LCA = DCA > CA	(Wang *et al.*, 1999; Wu *et al.*, 2015; Hanafi *et al.*, 2018)
PXR	Nuclear receptor	Hepatocytes, intestine	3-keto-LCA, LCA ≈ CDCA ≈ DCA	(Staudinger *et al.*, 2001; Xie *et al.*, 2001)
VDR	Nuclear receptor	Small intestine, colon, skin, heart, kidney	LCA and its major metabolites	(Makishima *et al.*, 2002; Bookout *et al.*, 2006)
TGR5	G-protein-coupled	Heart, skeletal muscle, lung, spleen, kidney, adrenal glands, liver, gallbladder, central nervous system, enteric nervous system, gastrointestinal tract, placenta, female reproductive organs, adipocytes	LCA > DCA > UDCA > CDCA > CA	(Maruyama *et al.*, 2002; Kawamata *et al.*, 2003; Vassileva *et al.*, 2006; Keitel *et al.*, 2010; Ibrahim *et al.*, 2018; Zhong *et al.*, 2022; Li *et al.*, 2024)
S1PR2	G-protein-coupled	Placenta, liver, gallbladder, lung, intestine, heart, adipose tissue, central nervous system, female reproductive organs, brain, lymph nodes	TCA	(Meng and Lee, 2009; Studer *et al.*, 2012; Blaho and Hla, 2014; Kwong *et al.*, 2015; Chen *et al.*, 2017; McMillin *et al.*, 2017; Chen *et al.*, 2018; Keitel *et al.*, 2019)

Abbreviation: FXR, farnesoid X receptor; NKT, natural killer T; PXR, pregnane X receptor; S1PR2, sphingosine-1-phosphate receptor 2; TGR5, Takeda G protein-coupled receptor 5; VDR, vitamin D receptor.

Prebiotics exhibit dose-dependent effects in altering the gut microbiota, promoting the growth of beneficial bacteria, regulating BA metabolism, alleviating inflammation, and enhancing gut barrier function (Gunness *et al.*, 2016; Nohara *et al.*, 2019; Rao *et al.*, 2020; Tang *et al.*, 2022; Hu *et al.*, 2023; Tian *et al.*, 2023; Yin *et al.*, 2023). Prebiotics such as pectin (Yin *et al.*, 2023), xylooligosaccharides (Tang *et al.*, 2022), and galacto-oligosaccharides (Tian *et al.*, 2023) have been shown to alter the composition of gut microbiota and increase the abundance of BSH-expressing bacteria and bacterial metabolites in pigs. These changes enhanced intestinal barrier function and immunity. The increase of CDCA level in the ileum induced by galacto-oligosaccharide decreases the production of LPS-induced proinflammatory factors and enhances the expression of TGR5 and its downstream cAMP production (Tian *et al.*, 2023). Fructooligosaccharides (Hu *et al.*, 2023) and arabinoxylan (Gunness *et al.*, 2016) regulate lipid metabolism and BA metabolism in pigs. Arabinoxylan reduces circulating BAs, resulting in reduced lipid digestion and absorption (Gunness *et al.*, 2016). Arabinoxylan compounded glucans (β-glucan or xyloglucan) (Chen *et al.*, 2021), flammulina velutipes polysaccharides (Zhao *et al.*, 2023), radix puerariae lobataepolysaccharide (PL-S2) (Rao *et al.*, 2020), and hyperoside (Wang *et al.*, 2021) improve lipid metabolism by regulating BA metabolism in obese mice or MASLD rats. These prebiotics activate the FXR signaling pathway, inhibit the expression of CYP7A1, reduce the level of liver unconjugated BAs, promote BAs excretion, and ultimately reduce body weight, cholesterol, and triglyceride levels in mice.

Phytochemical modulation in bile acid metabolism: The regulatory effects of Chinese traditional medicines and natural products on BA metabolism primarily manifest through indirect mechanisms. They regulate BA metabolism by affecting bacterial metabolism, particularly by targeting BSH-associated microorganisms. Several studies have demonstrated that succinate (Li *et al.*, 2022), nuciferine (Sun *et al.*, 2022), L-Theanine (Xu *et al.*, 2023), theabrownin (Huang *et al.*, 2019), nobiletin (Nohara *et al.*, 2019), resveratrol (Pang *et al.*, 2023), and berberine (Tian *et al.*, 2019) reduce the abundance of BSH-associated bacteria.

In HFD-fed mouse or rat models, nuciferine (Sun *et al.*, 2022), theabrownin (Huang *et al.*, 2019), nobiletin (Nohara *et al.*, 2019), and resveratrol (Pang *et al.*, 2023) modulate the gut microbiota and decrease BSH activity, resulting in increased conjugated BAs and reduced secondary BAs. This further inhibits the FXR-FGF15 signaling pathway and upregulates enzyme genes involved in BA synthesis. These changes reduce hepatic cholesterol while increasing lipolysis. Berberine decreases specific *Clostridium clusters* and BSH activity and activates the FXR pathway (Tian *et al.*, 2019; Wang *et al.*, 2025). Notably, this compound simultaneously promotes *Bacteroides* abundance in the terminal ileum and large intestine (Guo *et al.*, 2016). Berberine modulates the JAK2-STAT5 pathway to enhance BA uptake and maintain BA homeostasis (Bu *et al.*, 2017). Similarly, Pien Tze Huang (PZH) suppresses colorectal tumorigenesis in mouse models by modulating the gut microbiota, increasing beneficial metabolites, and restoring gut barrier function, while also inhibiting pro-inflammatory and pro-tumorigenic signaling pathways (Gou *et al.*, 2023).

In swine models, natural products have anti-inflammatory properties and metabolic regulatory functions. Caffeic acid, a plant-derived phenolic compound, enhances the expression of Claudin-1 and ZO-1 in weaned piglets, improving intestinal barrier function compromised by LPS. It also alleviates metabolic disorders by increasing primary BAs and isovaleric acid production (Wen *et al.*, 2023). Additionally, dietary interventions using flaxseed meal and oat husks in growing pigs effectively reduce fat digestibility and serum cholesterol, while promoting poor absorption of primary BAs and enhanced excretion of secondary BAs and neutral cholesterol (Ndou *et al.*, 2017). Betaine supplementation in the diets of pregnant and lactating sows elevates liver cholesterol levels and increases the expression of low-density lipoprotein receptors and scavenger receptor class

B type I genes (Cai *et al.*, 2016). This is accompanied by reduced BA content and suppressed CYP7A1 expression, with these effects being mediated through the AMPK/LXR pathway and histone modifications (Cai *et al.*, 2016).

Conclusions: In summary, the changes of BA signaling and interactions between BAs and the host in response to probiotics, prebiotics, Chinese traditional medicine, and natural products treatment are complex and dependent on species, diet, and other factors. The beneficial effects of these interventions may depend on their regulation of the gut-liver axis by restoring gut microbiota, metabolic, and immune homeostasis. This suggests that the bidirectional regulation of the gut-liver axis is a critical factor affecting enterohepatic health.

Given the physiological importance of BAs in both human and animal systems, and particularly due to porcine similar BA synthesis pathways and unique HCA class of BAs that regulate glucose homeostasis, this species serves as an invaluable model for studying human metabolic diseases. The distinct BA profile observed in pigs provides crucial insights into pathophysiological mechanisms, suggesting that targeted modulation of BA signaling represents a promising therapeutic strategy for improving metabolic disorders across species.

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Declaration of competing interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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