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The Emerging Potential of Bile Acids as a Modulator of Psoriatic Inflammation

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Abstract

Background: Bile acids (BAs) are cholesterol-based amphipathic surfactants that are most widely known for their contributions to lipid metabolism, but more recently have been increasingly recognized as a key signaling molecule in inflammatory diseases as well as, potentially, psoriatic disease. **Objective:** This brief review reviews relevant literature in order to briefly describe the synthesis of bile acids and their subsequent metabolism and to analyze recent animal and human data that supports anti-inflammatory activity of some BAs in psoriasiform dermatitis. **Methods:** Pubmed and other public sources were used to survey the literature relevant to the topic of bile acids and their potential use in psoriasis. **Conclusion:** There is clinical and preclinical evidence to support a potential role for BA Supplementation (or modulation BA metabolism and signaling) in the treatment of psoriasis.

Keywords

bile acids, psoriasis, inflammation, dermatitis

Structure and Function of Bile Acids

Bile acids (BAs) are cholesterol-derived steroidal acids that function as amphipathic surfactants. The primary BAs, cholic acid (CA) and chenodeoxycholic acid (CDCA), are initially synthesized in liver hepatocytes via a cascade of hydroxylation, oxidation, and conjugation.[1,2] Following hepatic conjugation to amino acids glycine or taurine to increase aqueous solubility, BAs are then secreted into bile and stored in the gallbladder.[1,2] Release of the hormone cholecystokinin in response to food intake results in gallbladder contraction and BA release into the duodenum where they act as natural detergents in lipid digestion and emulsification. The vast majority of primary BAs are reabsorbed in the terminal ileum and return to the liver via enterohepatic recycling (Figure 1).

However, a subset enters the large intestine and are further converted into secondary BAs by colonic bacteria, including deoxycholic acid (DCA), lithocholic acid (LCA), ursodeoxycholic acid (UDCA), hyodeoxycholic acid (HDCA), and isolithocholic acid (ILCA).[2] Here, the gut microbiome is responsible for biotransforming primary BAs to secondary BA derivatives, including deconjugation by the bacterial phylae *Firmicutes* and *Bacteroidetes*.[3] As such, changes in the diversity of the gut microbiome can influence levels of secondary BAs produced. Dietary shifts to a high-fat diet can increase the population of resident *Clostridium* bacteria from the *Firmicutes* phylae and levels of secondary BAs produced.[4] Conversely, vancomycin antibiotic and lactulose supplement use have been shown to decrease levels of *Clostridium* and consequently, secondary BAs as well.[4]

While BAs are most well-known for their roles in lipid metabolism and cholesterol homeostasis, recent years have seen a surge of evidence supporting multiple biologic functions for these acidic sterols. They are now recognized to have a much broader impact on amino acid, glucose, and overall nutrient homeostasis, and have been linked to obesity and insulin resistance, hepatobiliary disease, cardiovascular disease, and the gut microbiota.[2,5,6] Remarkably, BAs have even been linked to neurodegenerative disease, effects on aging, and immune regulation and inflammation.[5,6] On a cellular level, BAs are also associated with changes in tissue plasticity, including hepatocyte regeneration, stromal osteoblast and adipocyte differentiation, and epithelial proliferation.[5]

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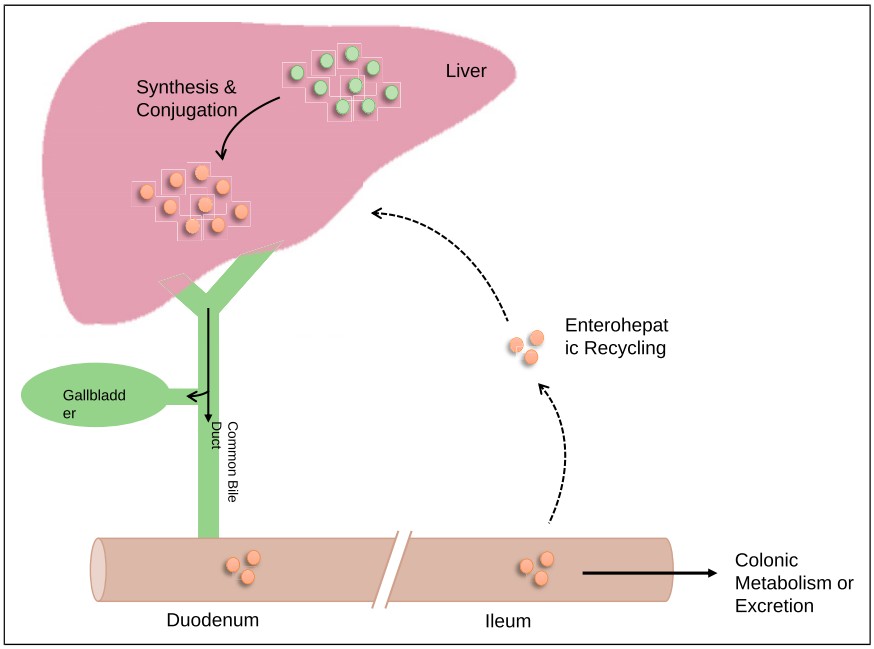

Figure 1. Bile Acid Synthesis and Enterohepatic Recycling. Primary bile acids are synthesized in the liver and stored in the gallbladder. In response to food intake, they are released into the duodenum to assist with lipid digestion and emulsification. Most bile acids are reabsorbed in the terminal ileum and return to the liver via enterohepatic recycling. A subset enters the colon and are further metabolized by the gut microbiota.

Role of Bile Acids in Inflammation

The discovery of specific BA receptors has resulted in increasing recognition of BAs as key signaling molecules in the aforementioned pathophysiological processes, particularly in innate and adaptive immunity. The most well-studied BA receptors are the farnesoid X receptor (FXR), a nuclear receptor, and the G-protein-coupled bile acid receptor-1 (GPBAR-1/TGR5), a membrane receptor.[2,5] Both receptors possess immunomodulatory properties and are found on a number of immune cells, including macrophages, dendritic cells, and natural killer T-cells.[5] BA interaction with the FXR or GPBAR-1/TGR5 results in activation of multiple anti-inflammatory cascades, including decreased NF-κB signaling, increased regulatory T-cell recruitment, and downregulation of the NLRP3 inflammasome.[7] Uniquely, BA-induced activation of the GPBAR-1/TGR5 also promotes macrophage conversion from the proinflammatory M1 to anti-inflammatory M2 phenotype and monocytic differentiation of tolerogenic dendritic cells with reduced production of pro-inflammatory cytokines.[8] Interestingly, receptor-ligand interactions differ between the 2 receptors, since primary BAs possess a higher affinity for the FXR whereas secondary BAs demonstrate a higher affinity for the GPBAR-1/TGR5.[8] Though less well known, additional receptors known to interact with BAs include nuclear receptors: vitamin D3 receptor (VDR), pregnane X receptor (PXR), and constitutive androstane receptor (CAR), along with membrane receptors: sphingosine 1-phosphate receptor 2 (S1PR2), formyl peptide receptor (FPR), and muscarinic acetylcholine receptor (mAChR).[5] Many of these are considered low-affinity BA receptors with diverse functions in BA detoxification, cellular membrane integrity, and mucosal homeostasis and immunity.[1,6] The VDR and 1,25-dihydroxyvitamin D3 (1,25(OH)D3) ligand pair, in particular, is a known anti-inflammatory regulator of inflammation and autoimmunity, downregulating monocytic differentiation, dendritic cell maturation, and proinflammatory T-lymphocyte activation.[7] While the effects of VDR activation following BA-specific binding have yet to be fully elucidated, early studies demonstrating LCA inhibition of ERK phosphorylation and downstream Th1 signaling suggest that VDR-BA receptor-ligand dynamics possess similar anti-inflammatory qualities to the VDR-1,25(OH)D3 pair.[9] It is tempting to speculate that some of the therapeutic effects of vitamin D analogues used in psoriasis such as calcipotriol may work through pathways activated by some BAs.

Thus, it may come as no surprise that the signaling pathways of BAs and their receptors are linked to a wide variety of inflammatory diseases. For example, dysregulation in FXR and GPBAR-1/TGR5 signaling are associated with the development of hepatobiliary diseases, including primary biliary cholangitis, autoimmune hepatitis, and nonalcoholic fatty liver disease. FXR knockout mice display greater hepatic inflammation, steatotic and fibrotic infiltration, and progression to hepatic fibrosis and hepatocellular carcinoma.[5] Similarly, murine models with deficient FXR receptors have increased mucosal inflammation in inflammatory bowel disease, whereas FXR agonism has been shown to be protective.[8] It is also well-established that chronic inflammation is a major player in malignant transformation. However, the role of FXR

Table 1. Studies Evaluating the Link Between Bile Acids and Psoriasis.

Citation	Title	Major Findings
Shi et al, 2022	Bile acids improve psoriasiform dermatitis through inhibition of IL-17A expression and CCL20-CCR6-Mediated trafficking of T cells	BAs improve symptoms of psoriasiform dermatitis by inhibiting IL-17a production and CCL20-mediated Th17 cell recruitment
Paine et al, 2022	Dysregulation of bile acids, lipids, and nucleotides in psoriatic arthritis revealed by unbiased profiling of serum metabolites	BAs are significantly dysregulated and decreased in psoriasis patients, particularly those at risk for developing psoriatic arthritis
Chen et al, 2021	Microbiome and Metabolome analyses Reveal novel Interplay between the skin microbiota and plasma metabolites in psoriasis	BAs are among the cutaneous microbiome metabolites noted to be significantly altered in psoriasis
Lajevardi et al, 2020	Evaluating the efficacy of ursodeoxycholic acid plus methotrexate vs methotrexate alone in the treatment of moderate to severe plaque-type psoriasis: A randomized clinical trial	Supplementation of BAs in methotrexate systemic therapy for psoriasis resulted in significantly improved psoriasis area and severity index (PASI) scores
Gyurcsovics & Bertók, 2003	Pathophysiology of psoriasis: Coping endotoxins with bile acid therapy	434 of 551 psoriasis patients (78.8%) treated with oral BA supplementation experienced symptom resolution compared to 24.9% on standard therapy

Abbreviations: Bile acids, BAs; Helper T-cell, Th.

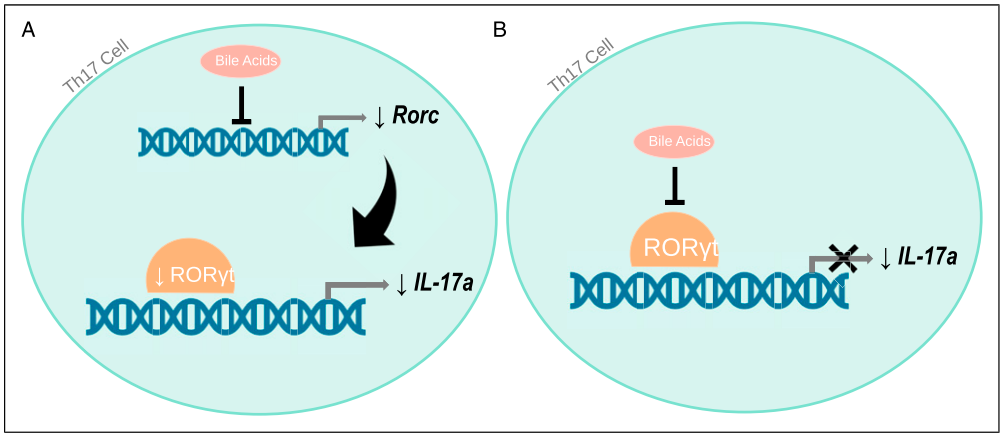

Figure 2. Proposed Mechanisms for Bile Acid Inhibition of IL-17a Production. Secondary bile acids inhibit the production of IL-17a. Potential mechanisms of action underlying this blockade include (A) downregulation of *Rorc* gene expression or (B) physical binding and obstruction of the activity of the RORγt transcription factor.

and GPBAR-1/TGR5 receptors in carcinogenesis remains controversial, as both pro-inflammatory tumor promoting and anti-inflammatory tumor suppressing effects have been observed.[10] Potential hypotheses to explain this observed divergency include variable action of BAs between hydrophilic vs hydrophobic states and across organ and tissue type.[11]

Link Between Bile Acids and Psoriasis

More recently, novel advances in the understanding of BA signaling have linked BAs to psoriasis, a chronic inflammatory skin disorder commonly seen in dermatology (Table 1). The interleukin (IL)-17/IL-23 immune axis is central to the development of chronic inflammation and psoriasis pathogenesis. In particular, the primary psoriatic effector cytokine, IL-17A, stimulates epidermal keratinocyte proliferation and CCL20 chemokine-induced trafficking of pro-inflammatory CCR6 + T helper (Th)17 cells and gamma-delta (γδ) T cells to the epidermis.[12] Here, BAs are primed to influence this system given their role in T-lymphocyte homeostasis, including production of regulatory T cells (Tregs) and downregulation of Th17 differentiation.[13,14] Secondary BAs decrease psoriatic inflammation by blocking T-lymphocyte production of IL-17A.[15] Growing evidence suggests that BAs may decrease Th17 differentiation and production of the IL-17A cytokine through either downregulation of *Rorc* gene expression or via physical binding and blocking the activity of RORγt, a transcription factor highly expressed in Th17 cells (Figure 2).[14,15] Further, secondary BAs also inhibit trafficking of inflammatory Th17 lymphocytes to the skin via downregulation of the CCL20 chemokine in keratinocytes.[15] In a murine model of psoriasiform dermatitis, mice treated with

secondary BAs, DCA and LCA, displayed significantly reduced skin thickness, erythema, and scale.[15]

Clinically, BAs have promising potential in the management of psoriasis. In a trial of BA supplementation, 80% of patients treated with a synthetic BA, dehydrocholic acid, experienced resolution of symptoms compared to 25% of patients receiving conventional therapy.[16] Intervention patients were provided a Suprachol® bile acid supplement dosed at 2 to 3 pills daily or dehydrocholic acid powder dosed at .25 g 2 to 3 times daily for 1 to 6 weeks in acute cases and 3 to 8 weeks in chronic cases.[16] The primary endpoint measured to show improvement in psoriasis were Psoriasis Area and Severity Index (PASI) scores combined with clinical evaluation.[16] Among intervention patients with a baseline PASI score of 19.1, 78.8% of participants experienced complete resolution of symptoms with PASI scores of 0 and 21.2% experienced improvement in PASI scores reduced to 12.8.[16] Comparatively, among patients receiving conventional therapy with a baseline PASI score of 18.9, 24.9% of participants experienced complete resolution of symptoms with PASI scores of 0 and 75.1% experienced improvement in PASI scores reduced to 14.4.[16] In another trial, addition of UDCA as a supplement to systemic methotrexate regimens has also been shown to improve skin lesion severity in plaque-type psoriasis.[17] The intervention group received 300 mg daily of UDCA, whereas the comparator group received a placebo, in addition to their methotrexate regimens for 24 weeks of treatment.[17] Primary endpoints included PASI scores and dermatology life quality index (DLQI) scores.[17] Among intervention patients with a baseline PASI score of 15.7 and DLQI 18.4, supplementation with UDCA to their methotrexate regimen improved a PASI of 3.24 and a DLQI of 6.89, respectively.[17] Conversely, among the control group with a baseline PASI score of 16.35 and DLQI score of 17.15, methotrexate alone resulted in an improvement in PASI to 6.52 and DLQI to 8.6, respectively.[17]

Metabolomic analyses of the serum further suggest that a dysregulated BA metabolomic profile exists in both psoriasis and psoriatic arthritis patients.[18,19] Chen et al[18] performed a series of 16S genomic sequencing on skin microbiome samples and chromatography-mass spectrometry on plasma samples from a 32-patient cohort with severe plaque-type psoriasis. The resulting metabolomic profiles demonstrated significant alterations in microbiome metabolites, including bile acids, among psoriasis patients. Of interest, a longitudinal study also showed psoriasis patients with decreased serum levels of secondary BAs were more prone to progression to PsA.[19] Here, a pre-progression metabolic analyses of serum from psoriasis patients who would eventually develop psoriatic arthritis demonstrated significant metabolic shifts, including a greater than 50% reduction in secondary bile acids deoxycholate, glycoursodeoxycholic acid sulfate, and deoxycholic acid 12-sulfate, compared to non-progressors.[19] Conversely, increases in BA serum levels correlated with decreased odds of psoriatic arthritis progression with a 1-unit increase in glycoursodeoxycholic acid sulfate correlating to a decreased odds of progression by 95%.[19]

Prospective Role of Bile Acids in Inflammatory Skin Disease

Despite growing in vitro and clinical evidence suggesting that certain BAs can downregulate skin inflammation, the role of BAs in inflammatory skin disease remains puzzling. Psoriasis, as a systemic and inflammatory disease, has been linked to multiple extracutaneous comorbidities such as liver disease, where it is thought that the association between psoriasis and liver disease is caused by alterations in the hepatodermal axis and aberrant cytokine signaling.[20] Given that endogenous BAs are often elevated in liver disease, one would suspect that these patients would display improvement in psoriasis or other inflammatory skin diseases, yet to our knowledge this has not been observed. Notably, however, a few cases of patients with psoriasis vulgaris and comorbid nonalcoholic fatty liver disease have been reported demonstrating significant improvement in psoriatic skin lesions following treatment of liver disease with ursodeoxycholic acid (UCDA).[21] It is hypothesized that this occurs via UDCA-induced inhibition of phospholipase A2 and consequent reduction in production of inflammatory mediators, such as prostaglandins and leukotrienes.[21] Thus, the paradoxical lack of expected improvement in psoriasis among patients with liver disease may be explained by a wide variation in BA subtypes, with those endogenously produced in liver disease less involved in psoriatic inflammatory signaling cascades.

The hypothesis that unique BA populations are involved in distinct signaling cascades is further supported by the observation that certain BAs activate itch pathways. Taurolithocholic acid (TLCA), for example, is the most potent endogenous ligand for the GPBAR-1/TGR5 receptor and is elevated in those with liver disease.[22] GPBAR-1/TGR5 has been recognized as a potent mediator of pruritus and recent advances suggest that the FXR receptor may be implicated in itch signaling as well.[23,24] The GPBAR-1/TGR5 receptor is expressed on sensory afferents in the dorsal root ganglia and dorsal horns. The growing hypothesis posits that BA-induced agonism of GPBAR-1/TGR5 receptor on free nerve endings of sensory afferents releases pruritogenic neurotransmitters, such as gastrin-releasing peptide (GRP) and opioids, from the that then go on to activate itch signaling via the GRPR and MOR1D/GRPR heterodimer, respectively.[23] This signaling cascade has been most commonly linked to pruritus in cholestatic disease given the predominance of BA dysregulation, however, BA alterations localized to the cutaneous milieu suggest these cascades may be associated with pruritus in inflammatory skin diseases as well.[25] Additional studies are clearly needed to determine if and how these itch-related pathways differ from inflammatory pathways with respect to BA signaling.

Conclusion

BAs are cholesterol-based amphipathic surfactants that are most widely known for their contributions to lipid metabolism, but more recently have been increasingly recognized as a key signaling molecule in psoriatic disease. There is both clinical and preclinical evidence to support a potential role for BA supplementation or modulating BA metabolism and signaling in the treatment of psoriasis, although much more research is needed to help understand the complex roles of BAs in the regulation of itch and inflammatory disease, which often coincide. Future research is needed to further elucidate the molecular mechanisms underlying the action of BAs in the psoriatic immune response and the link between BAs and other forms of inflammatory skin disease.

Appendix

Abbreviations

BAs	bile acids
CA	cholic acid
CDCA	chenodeoxycholic acid
DCA	deoxycholic acid
FXR	farnesoid X receptor
GPBAR-1/TGR5	G-protein-coupled bile acid receptor-1
γδ	gamma-delta
LCA	lithocholic acid
NF-κB	nuclear factor kappa B
NLRP3	NLR family pyrin domain containing 3
Th	T helper
UDCA	ursodeoxycholic acid

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Consent

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Ethics

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