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REVIEW

From Gut to Lung: The Role of Bile Acids in Rheumatoid Arthritis-Associated Interstitial Lung Disease (RA-ILD)

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Abstract: Rheumatoid arthritis-associated interstitial lung disease (RA-ILD) is a serious complication of rheumatoid arthritis (RA) that significantly increases both morbidity and mortality. Although advances have been made in elucidating the pathogenesis of RA-ILD, the specific roles of bile acids remain underexplored. Bile acids are known to modulate immune responses, potentially influencing the inflammatory processes central to RA-ILD; however, their exact mechanisms and therapeutic utility remain unclear. This review aims to elucidate the diverse functions of bile acids, highlighting their potential as both biomarkers of disease activity and as novel therapeutic agents to mitigate pulmonary inflammation and fibrosis. By exploring the gut–lung axis and the interactions between bile acid metabolism and immune responses, the review seeks to identify new avenues for RA-ILD treatment. It also discusses the emerging role of bile acid-derived exosomes in RA and RA-ILD, emphasizing their promise as vehicles for modulating inflammation. This review highlights the significance of current findings and the need for further studies to validate bile acids and their derivatives as reliable markers and effective therapies. By reviewing available research and identifying critical gaps for future research, this review aims to enhance our understanding of RA-ILD and to support the development of targeted interventions that could markedly improve patient outcomes.

Keywords: rheumatoid arthritis, interstitial lung disease, bile acids, pulmonary fibrosis, RA-ILD

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disorder that primarily affects the joints, yet it also manifests significant pulmonary complications, most notably interstitial lung disease (ILD). The reported prevalence of RA-ILD varies substantially, with estimates ranging from 4% to 50% depending on the population studied and the diagnostic criteria used.[1,2] Some investigations indicate pulmonary involvement in approximately 60% of RA patients.[3,4] Notably, inter-country variations exist in both the prevalence and incidence of RA-ILD.[5] The median survival after diagnosis of RA-ILD ranges from 3 to 7 years,[6] highlighting its serious impact on patient prognosis. The pathogenesis and determinants of disease progression of RA-ILD is complex and multifactorial, involving genetic predispositions, environmental triggers, and dysregulated immune responses,[7,8] with pulmonary fibrosis being a common pathological progression.[9,10]

Emerging research has begun to elucidate the role of bile acids—traditionally known for their function in lipid digestion—in modulating immune responses and inflammation in autoimmune diseases, including RA.[11–13] Bile acids can influence the production of inflammatory mediators and modulate inflammatory cascades through interactions with various receptors, thereby contributing to the maintenance of pro-inflammatory and anti-inflammatory homeostasis. They also stimulate immune responses by communicating with macrophages and T cells to produce antibodies or affect the balance between Th17 and Treg cells, thus

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altering systemic immunity.[14] Furthermore, exosomes exhibit the capacity to modulate recipient cell behavior[15] and activate macrophages and other immune cells[16] highlighting their potential role in the disease's pathogenesis.

Current therapeutic approaches for RA-ILD demonstrate significant pharmacodynamic heterogeneity. Glucocorticoids, while clinically effective for acute-phase management, are associated with dose-dependent iatrogenic complications. Their pleiotropic adverse effect profiles (eg, osteoporosis, metabolic dysregulation) contraindicate chronic administration.[17] The therapeutic utility of methotrexate (MTX), a cornerstone conventional synthetic disease-modifying antirheumatic drug (csDMARD), remains contentious within rheumatology circles; however, a large-scale retrospective cohort analysis revealed potential pulmonary protective properties.[18] Cyclophosphamide (CYC), as an alkylating agent with immunomodulatory properties, is reserved for refractory disease properties. This evolving therapeutic landscape underscores the critical need for pharmacoepidemiologic investigations incorporating multidimensional outcome assessments to establish evidence-based treatment protocols, given the current paucity of randomized controlled trial data guiding RA-ILD management.[19,20] A comparative analysis was conducted on the initiation of non-tumor necrosis factor inhibitors biologic and targeted synthetic disease-modifying antirheumatic drugs (non-TNFi b/tsDMARDs) in patients with RA-ILD. The results revealed no statistically significant differences in all-cause mortality or pulmonary-related hospitalization rates within the studied population.[21] This review examines the role of bile acids and related factors in RA-ILD, with the aim of identifying novel therapeutic strategies to alleviate patients' symptoms and improve long-term outcomes.

Bile Acids: Structure, Metabolism, and Function

Bile acids (BAs) are essential small molecules with diverse functions in the human body. Structurally, they are steroid molecules with a 24-carbon core featuring both hydrophilic (eg, hydroxyl, carboxyl) and hydrophobic (eg, alkyl) groups.[22] In humans, the two primary bile acids—cholic acid (CA) and chenodeoxycholic acid (CDCA)—are mainly produced via the classical (neutral) pathway, which is regulated by the rate-limiting enzyme cholesterol 7α-hydroxylase (CYP7A1), and, to a lesser extent, the alternative (acidic) pathway mediated by sterol-27-hydroxylase (CYP27α1).[22–24] Conjugation with taurine or glycine in the liver enhances their water solubility without altering receptor affinity.[22] As a principal route of cholesterol catabolism, bile acid synthesis is tightly regulated to maintain metabolic balance. Once synthesized, bile acids are secreted into bile, stored in the gallbladder, and subsequently released into the intestine, where they facilitate nutrient absorption. Approximately 95% are then reabsorbed into the portal circulation and returned to the liver, while only about 5% are excreted in feces.[25] This enterohepatic circulation can occur between four and twelve times daily.[26]

Beyond their established roles in lipid metabolism and vitamin D absorption, bile acids function as signaling mediators that rapidly activate nuclear receptors and modulate immune responses, including those of T-helper (Th) and regulatory T (Treg) cells. Through their integration in metabolic and immunological pathways, bile acids represent promising therapeutic targets for diseases marked by chronic inflammation, including RA-ILD.[27,28] Their ability to modulate receptor activity and immune cell behavior makes them a focus for ongoing research aimed at novel and more effective treatment strategies.

The Role of Bile Acids in Inflammation

Bile acids modulate inflammation and immune responses in RA-ILD through multiple mechanisms. Recent studies have demonstrated that lithocholic acid (LCA) derivatives regulate T cell differentiation: 3-oxoLCA binds to the RORγ-T receptor, suppressing Th17 cell differentiation, while isoalloLCA promotes regulatory T cell (Tregs) development via the conserved noncoding sequence (CNS1).[14,27,28] In addition, certain conjugated bile acids, such as taurochenodeoxycholic acid (TCDCA) and glycochenodeoxycholic acid (GCDCA), reduce T cell viability in a dose-dependent manner, whereas secondary bile acids like LCA and deoxycholic acid (DCA) suppress cytokine production by activated T cells, although ursodeoxycholic acid (UDCA) may enhance T cell functionality.[29]

Bile acids primarily exert their effects primarily through receptors such as farnesoid X receptor (FXR), Takeda G protein-coupled receptor 5 (TGR5), and vitamin D receptor (VDR), abundantly expressed in immune cells including macrophages, dendritic cells, and NK cells. Activation of FXR in macrophages, suppresses pro-inflammatory cytokine production by inhibiting inducible nitric oxide synthase (iNOS) and IL-1β promoter activity.[30] Obeticholic acid-mediated FXR activation has been shown to reduce intestinal dendritic cell differentiation and activation, and lower TNF-α

production in colitis models.[31] Bile acids also modulate inflammation indirectly by affecting inflammasome activity. Moreover, FXR, when activated by chenodeoxycholic acid, suppresses CYP7A1 mRNA transcription through the mediator small heterodimer partner (SHP), thereby inhibiting inflammatory gene expression;[32] SHP deficiency, in contrast, leads to increased production of IL-1β and IL-18 and accumulation of damaged mitochondria.[33]

TGR5 activation by taurocholic acid (TLCA), a selective TGR5 ligand, reduces TNF-α-induced monocyte adhesion, increases nitric oxide (NO) production by raising intracellular calcium ions, and inhibits NF-κB, thereby reducing inflammatory response.[34,35] DCA and LCA, acting through the TGR5-cAMP-PKA axis, inhibit NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome activation.[33,36] TGR5 activation further enhances IL-10 transcription in lamina propria macrophages,[37] dampening inflammatory responses. In vitro studies have demonstrated that exposure of human and mouse macrophages to TGR5 agonists significantly suppresses the expression of pro-inflammatory cytokines (IFN-γ, IL-1β, IL-6, and TNF-α), while upregulating anti-inflammatory cytokines, especially IL10, with a minor effect on the expression of TGF-β.[38,39] Furthermore, activation of the TGR5 receptor by bile acids converts pro-inflammatory M1 macrophages into anti-inflammatory M2 macrophages, boosting IL-10 and TGF-β production.[37] The Vitamin D receptor also contributes by shifting the T cell responses from Th1 to Th2,[40] enhancing Treg induction[41] and reducing Th17 formation.[42] Taken together, these findings suggest the multifaceted role of bile acids in modulating inflammation and highlight their potential as therapeutic targets in RA-ILD.

Bile Acids and Rheumatoid Arthritis

Recent research has revealed that bile acids exert anti-inflammatory effects in rheumatoid arthritis. For example, cholic acid can activate the TGR5 receptor, resulting in reduced inflammation in animal models of collagen-induced arthritis.[43] In these models, Bifidobacterium pseudocentinatus protects joint integrity by protecting the intestinal barrier and remodeling the gut microbial composition, which in turn enhances the activity of bile saline hydrolase, increases levels of un-conjugated secondary bile acids, and inhibits specific antibodies and proinflammatory CD4+ T cells responses.[44] Moreover, bile acids are thought to contribute to shaping the gut microbiota—a factor in RA pathogenesis and progression.[45] UDCA can reduce the disease activity score of arthritis mice to a certain extent.[46]

Exosomes, nanoscale extracellular vesicles, have garnered significant research interest for their ability to carry a variety of bioactive molecules, including microRNAs (miRNAs), proteins, and lipids that modulate recipient cell behavior.[15] In RA, exosomes derived from fibroblast-like synoviocytes (FLSs) facilitate the transfer of non-coding RNAs, which can modulate the inflammatory response and promote joint destruction.[47] Emerging evidence demonstrates that exosomal miRNAs can regulate both inflammatory and apoptotic signaling pathways, exacerbating disease progression.[48] Moreover, exosomes modulate immune responses by activating TH1 and other immune cells, potentially contributing to the chronic inflammation characteristic of RA.[16] Although these findings highlight the potential of exosomes as novel biomarkers for RA progression and as vehicles for delivering anti-inflammatory agents, the precise mechanisms by which they interact with immune and joint cells in RA remain to be fully elucidated. A better understanding of these interactions could lead to innovative therapeutic strategies for managing RA and its associated complications.

Bile Acids and Rheumatoid Arthritis-Associated Interstitial Lung Disease (RA-ILD)

RA-ILD Overview

RA-ILD represents a severe extra-articular manifestation of rheumatoid arthritis, characterized by chronic inflammation that can progress to irreversible pulmonary fibrosis. Its multifactorial aetiology involves genetic predisposition, (with the HLA-DRB1*1502 locus recognized as the most significant susceptibility factor)[49] environmental exposures such as smoking, and immune dysregulation, all contributing to accelerated disease progression and increased mortality. Gender is a potential risk factor with RA-ILD being more common in men according to imaging findings (including X-ray and high-resolution computed tomography [HRCT]).[50] Immunologically, the pathogenesis of RA-ILD is strongly associated with the presence of rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA).[51] Without appropriate intervention, ILD can further progress to pulmonary fibrosis,[52] significantly increasing morbidity and mortality.

Conventional Treatment Options for RA-ILD

Current management strategies for RA-ILD include both pharmacological and non-pharmacological interventions. Pharmacological treatments primarily involve anti-inflammatory, immunomodulatory, and anti-fibrotic agents. Glucocorticoids are commonly used, particularly in acute disease, prompting caution limited RA-ILD-specific data.[17,53] Conventional DMARDs, including cyclophosphamide[54] and mycophenolate mofetil[54,55] have been used in progressive cases. Cyclophosphamide is not used as first-line therapy for RA-ILD due to its cumulative toxicity profile, including hemorrhagic cystitis, gonadal suppression, and elevated bladder malignancy risk.[20] The role of methotrexate in RA-ILD management remains debated; recent evidence suggests it may not elevate ILD risk, careful clinical monitoring remains warranted.[18] The safety and efficacy of newer biological DMARDs are still under evaluation. A population-based cohort study demonstrated a significantly elevated risk of mortality and increased healthcare resource utilization among patients with RA-ILD patients treated with Janus kinase inhibitors (JAKi) compared to those receiving tumor necrosis factor inhibitors (TNFi), with the association being particularly pronounced in individuals aged over 65 years.[56] The 2023 American College of Rheumatology and American College of Chest Physicians guideline conditionally recommended against use of TNF inhibitors as initial therapy in patients with autoimmune disease-associated ILD, including rheumatoid arthritis-associated ILD.[57] Biological agents (eg, TNFi) may have both pro-fibrotic and anti-fibrotic effects, and this delicate balance can be easily disturbed, requiring cautious use.[58,59] Anti-fibrotic agents like pirfenidone have shown promise in reducing cytokine production and fibroblast transformation.[60] Non-pharmacological approaches include pulmonary rehabilitation, oxygen therapy, and lung transplantation in advanced cases.[59]

The Role of Bile Acids in RA-ILD

Clinical observations indicate that RA patients often exhibit a characteristic bile acid profile, marked by an imbalance between primary and secondary bile acids.[28] These alterations likely contribute to gut dysbiosis and hepatic dysfunction, conditions frequently associated with RA. These metabolic disturbances correlate with increased disease severity and may serve as early biomarkers for diagnosis and monitoring of RA-ILD. In fact, the gut–lung axis has emerged as a critical pathway:[61] disruptions in intestinal microbial communities can impair bile acid conversion, thereby influencing systemic inflammatory responses and modulating lung pathology. Furthermore, alterations in bile acid metabolism may reciprocally influence the composition of the gut microbiota. This bidirectional crosstalk between the gut microbiota and bile acids could modulate pulmonary inflammatory responses, highlighting the importance of a balanced gut microbiome in the management of RA-ILD.

Mechanisms of Action

Bile acids exert multifaceted effects on RA-ILD through several receptor-mediated pathways that modulate both innate and adaptive immune responses as well as fibrotic processes (Figure 1). A key mechanism involves the farnesoid X receptor (FXR), a nuclear receptor, expressed in pulmonary epithelial cells and other tissues. FXR contributes to surfactant production and promotes alveolar repair following lung injury, underscoring its importance in pulmonary homeostasis and recovery.[62] FXR expression in alveolar epithelial II cells (ATECII) is considered a protective mechanism against interstitial expansion in pulmonary fibrosis.[63] This receptor critically regulates gene expression related to bile acid metabolism and inflammatory pathways. Emerging evidence suggests that bile acids may exert modulatory effects on pulmonary fibrogenesis through FXR-mediated signaling pathways. This mechanistic link positions the bile acid-FXR axis as a potential molecular bridge connecting hepatointestinal metabolic homeostasis with pulmonary stromal dysregulation in RA-ILD. Upon binding endogenous ligands such as chenodeoxycholic acid, FXR translocates to the nucleus and upregulates SHP. SHP acts as a transcriptional co-repressor, dampening the expression of pro-inflammatory genes,[32] including those encoding IL-6 and TNF-α.[11] This regulatory cascade not only controls bile acid synthesis via feedback inhibition of CYP7A1 but also mitigates systemic inflammation and may contribute to alveolar repair and maintenance of pulmonary homeostasis.

In parallel, the G-protein-coupled receptor TGR5 plays a crucial role in mediating the anti-inflammatory actions of bile acids. Activation of TGR5 by ligands like taurocholic acid (TLCA) leads to increased intracellular cAMP levels, leading to inhibition of the NF-κB pathway, a key driver of inflammatory cytokine production.[33,36,64] TLCA, a specific agonist for TGR5 expressed across various immune cells and tissues, including the lungs.[65] TGR5 activation enhances the secretion of anti-inflammatory mediators[66] and augments the functional capacity of regulatory T cells (Tregs).[67,68] TGR5 activation also

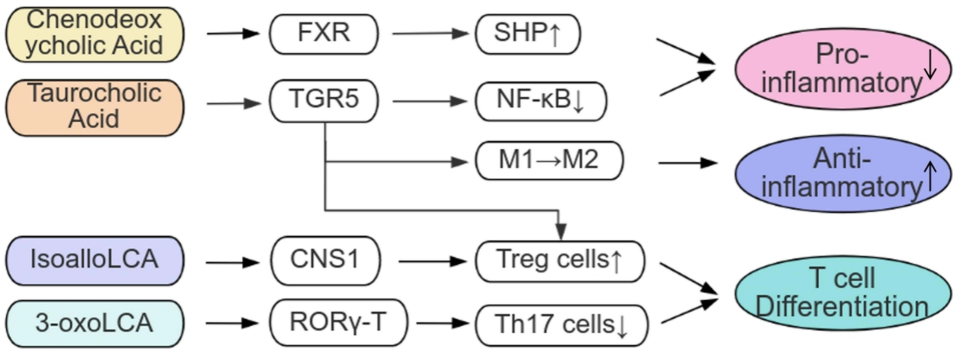

Figure 1 Mechanisms of action of bile acids in RA-ILD. Bile acids exhibit various therapeutic potentials in RA-ILD. For instance, Chenodeoxycholic acid, an FXR receptor ligand, upregulates small heterodimer partner (SHP) to dampen the expression of pro-inflammatory genes. Taurocholic acid (TLCA), a selective TGR5 ligand, suppresses the NF-κB pathway to attenuate inflammatory responses and augment the functional capacity of regulatory T cells (Tregs). The activation of TGR5 also promotes a phenotypic switch in macrophages from the pro-inflammatory M1 state to the anti-inflammatory M2 state. 3-oxoLCA binds to the RORγ-T receptor, inhibiting TH17 cell differentiation and reducing inflammation, while whereas isoalloLCA promotes the expansion of regulatory T cells (Tregs) via conserved noncoding sequences. Together, these findings highlight the multifaceted role of bile acids in managing RA-ILD and related complications.

promotes a phenotypic switch in macrophages from the pro-inflammatory M1 state to the anti-inflammatory M2 state, further enhancing the secretion of IL-10 and TGF-β.[37] These cytokines further promote the resolution of inflammation and inhibit fibrotic remodelling. Collectively, these findings suggest that bile acids may not only suppress pro-inflammatory cascades but also potentiate anti-inflammatory mechanisms through TGR5 activation, further underscoring their therapeutic potential in the management of RA-ILD.

Beyond these receptors, bile acid derivatives such as 3-oxoLCA and isoalloLCA directly influence adaptive immunity by modulating T cell differentiation. Specifically, 3-oxoLCA binds to the RORγ-T receptor to effectively suppress Th17 cell differentiation, a process critical in the propagation of inflammatory responses,[64] whereas isoalloLCA promotes the expansion of regulatory T cells (Tregs) via conserved noncoding sequences.[27,28] This dual modulation of T cell subsets contributes to the re-establishment of immune tolerance and counteract the chronic inflammatory milieu observed in RA-ILD.[13] IL-17A, the principal cytokine secreted by TH17 cells, plays a direct role in inducing human lung fibroblast responses associated with fibrosis and remodeling. Elevated IL-17 expression in RA-ILD is consequently a feature of the underlying inflammatory process. UDCA demonstrates immunomodulatory capabilities, including suppression of pro-inflammatory cytokine production and induction of regulatory T cell differentiation.[69] Collectively, these mechanisms illustrate how bile acids can orchestrate a multi-faceted regulatory network that controls both innate and adaptive immune responses, offering promising targets for therapeutic intervention in RA-ILD.

Therapeutic Applications of Bile Acids

Bile acids represent promising therapeutic avenues for RA-ILD by targeting multiple aspects of the disease process. UDCA, for instance, has an established history in managing cholestatic liver diseases and demonstrates notable hepatoprotective and anti-inflammatory properties[70] (Table 1). In the context of RA-ILD, UDCA may mitigate pulmonary inflammation by suppressing

Table 1 Therapeutic Applications of Bile Acids

Substance	Application	Mechanism of Action
UDCA	Mitigates pulmonary inflammation	Suppresses pro-inflammatory cytokine production and modulates immune cell function
	Improves symptoms	
TUDCA	Inhibits the activation of fibroblast and reduces extracellular matrix deposition (cell)	Alleviates endoplasmic reticulum stress
	Modulates immune responses	Inhibits the proliferation of pathogenic T cells
OCA	Mitigates pulmonary vascular remodeling, and inhibits fibrosis	Counteracts the reduction of FXR

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pro-inflammatory cytokine production and modulating immune cell function. Its ability to improve bile flow and reduce hepatotoxicity could also indirectly benefit pulmonary health, particularly in RA patients with concomitant hepatic impairment.

Tauroursodeoxycholic acid (TUDCA), the taurine-conjugated form of UDCA, has demonstrated additional promise due to its potent anti-apoptotic and anti-fibrotic effects. Preclinical studies indicate that TUDCA alleviates endoplasmic reticulum stress,[71] a key contributor to cellular dysfunction and fibrogenesis, thereby inhibiting the activation of fibroblast and reducing extracellular matrix deposition. This mechanism is particularly relevant in preventing the progression from interstitial inflammation to irreversible pulmonary fibrosis. Moreover, TUDCA has been observed to modulate immune responses by inhibiting the proliferation of pathogenic T cells,[72] which further supports its potential role in attenuating the chronic inflammatory milieu characteristic of RA-ILD. The immunomodulatory properties of TUDCA observed in other pulmonary fibrosis pathogenesis provide a potential mechanistic rationale for its therapeutic exploration in RA-ILD.

Obeticholic acid (OCA), a selective FXR agonist, represents another promising candidate. By activating FXR, OCA not only regulates bile acid synthesis but also exerts direct anti-inflammatory effects. Clinical and experimental studies have demonstrated that OCA can reduce pulmonary inflammation, inhibit tissue remodeling, and improve lung function, while it simultaneously improves physical endurance.[73] Its capacity to enhance alveolar repair and mitigate vascular remodeling highlights its potential in preserving lung architecture and function in RA-ILD patients. Furthermore, the administration of OCA can counteract the reduction of FXR, thereby ameliorating pulmonary inflammation, mitigating pulmonary vascular remodeling, and inhibiting fibrosis.[73] Collectively, these bile acid-based therapies—UDCA, TUDCA, and OCA—target key pathogenic mechanisms in RA-ILD, including inflammation, immune dysregulation, and fibrosis. Their multi-faceted modes of action, coupled with favorable safety profiles observed in other indications, highlight the potential of bile acids as novel therapeutic agents. However, further clinical investigations are warranted to fully establish their efficacy and optimize treatment regimens for RA-ILD.

The Role of Bile Acid-Derived Exosomes in RA-ILD

Emerging evidence suggests that bile-derived exosomes may play a role in RA-ILD pathogenesis by modulating immune responses and modulating key inflammatory mechanisms involved in both RA and its pulmonary complications.

These exosomes substantially influence target cells involved in inflammation and fibrosis via transporting specific miRNAs and proteins. For example, exosomal miRNAs can modulate the expression of pro-inflammatory cytokines and chemokines, thereby influencing the activity of fibroblast-like synoviocytes (FLSs) and macrophages, the two key contributors to RA-ILD development. While insights from other fibrotic diseases such as lung cancer, suggest a potential regulatory role for bile acid-derived exosomal miRNAs,[74] their precise impact on RA-ILD remains unclear and requires further investigation. Nevertheless, these studies highlight their potential dual role as exacerbating or mitigating factors in inflammation and pulmonary fibrosis in RA-ILD.

The immunomodulatory properties of bile-derived exosomes present a promising avenue for treating RA-ILD, particularly in delivering anti-inflammatory signals directly to targeted cells, thereby alleviating lung inflammation and fibrosis in RA-ILD. However, it is worth noting that current evidence is largely derived from studies on exosomes from other sources, such as tumor-associated macrophages, rather than bile-derived exosomes.[75] Given their unique molecular composition, more research is required to elucidate their specific role in RA-ILD pathology. Such studies could help identify novel biomarkers for improved early detection and ongoing assessment of RA-ILD progression.[76]

Challenges and Future Directions

As a chronic injury-induced inflammation, RA seriously impairs joint function, significantly affecting patients' quality of life and placing a considerable emotional and economic burden on both individuals and society. When RA is accompanied by interstitial lung disease, the condition worsens, leading to higher mortality rates as the disease often advances to irreversible pulmonary fibrosis. The absence of standardized treatment guidelines for RA-ILD—combined with the potential pulmonary toxicity of immunosuppressants—presents significant therapeutic challenges. Consequently, there is an urgent need to identify novel, safer therapeutic targets.

Bile acids have emerged as promising candidates due to their potent anti-inflammatory and immunomodulatory properties. They can inhibit the production of inflammatory mediators through their chemical properties and receptor interactions, notably

via FXR and TGR5, and modulate the activity of innate immune cells such as macrophages and dendritic cells. Moreover, bile acids influence T cell differentiation by suppressing Th17 cells while promoting regulatory T cell development, thus restoring immune balance. Despite these promising insights, the precise mechanisms by which bile acids affect RA-ILD remain unclear, and direct evidence is limited. Large-scale clinical trials are necessary to confirm the therapeutic efficacy and safety profiles of bile acids and their derivatives in RA-ILD patients, as well as to assess potential adverse interactions. As the field progresses, further studies are needed to elucidate the precise roles of bile acid-derived exosomes in the pathophysiology of RA-ILD and to evaluate their potential as diagnostic and therapeutic tools. Continued research in this area is essential for unveiling new approaches to the pathogenesis and treatment of both RA and RA-ILD.

A major knowledge gap is the lack of robust clinical data connecting bile acids metabolism with RA-ILD in patients. Addressing this gap will require close collaboration between rheumatologists and pulmonologists. For example, studies should measure bile acids levels in RA-ILD patients and assess correlations between bile acids profiles and lung function (eg, in case-control or cohort analyses). In addition, clinical trials exploring bile acid-based therapies in RA-ILD are warranted. Such investigations will help validate the role of bile acids as diagnostic or prognostic markers in RA-ILD and support the development of bile acid-based personalized therapies for pulmonary fibrosis in RA and beyond.

Conclusion

This review highlights the potential of bile acids as a novel therapeutic target for managing RA-ILD. Although current treatment options for RA-ILD are limited, bile acids offer promising new avenues due to their ability to modulate immune responses and inflammation. Evidence suggests that bile acids can improve T cell balance and attenuate inflammatory signaling, potentially improving patient outcomes. Furthermore, bile acid-derived exosomes represent an additional promising strategy for managing RA-ILD. Future research should focus on elucidating the detailed mechanisms underlying bile acid actions and evaluating their clinical efficacy, ultimately paving the way for safer and more effective therapies for RA-ILD.

Author Contributions

Yan-Chuan Shi and Jianmin Xie are equal senior authors. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All authors declare no competing interests.

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