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Original article

Bile acids as candidate therapies for multiple sclerosis: inverse signal analysis using the FDA adverse event reporting system and preclinical validation

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ABSTRACT

Background: Alterations in bile acid metabolism have been observed in individuals with multiple sclerosis (MS), yet the therapeutic implications of bile acid supplementation remain uncertain.
Methods: We conducted a two-stage study integrating pharmacovigilance analysis with preclinical validation to evaluate bile acid derivatives as candidate therapies for MS. A disproportionality analysis of the FDA Adverse Event Reporting System (FAERS; Q4/2003–Q2/2025) was performed to identify inverse associations between MS and bile acid preparations. The effects of ursodeoxycholic acid (UDCA) and obeticholic acid (6-ECDCA) were evaluated in a therapeutic experimental autoimmune encephalomyelitis (EAE) model, with treatment initiated after disease onset.
Results: Among 13,734,539 FAERS reports, 75,659 involved MS. Inverse associations were identified for UDCA (odds ratio [OR]: 0.197, 95% confidence interval [CI]: 0.117–0.333) and 6-ECDCA (OR: 0.128, 95% CI: 0.041–0.396). In the EAE model, UDCA was associated with lower clinical scores at the peak (day 18) and late phases (days 26–28), whereas 6-ECDCA showed only a non-significant trend toward improvement at day 28.
Conclusion: This two-stage investigation highlights the potential utility of pharmacovigilance-guided approaches for identifying therapeutic candidates. Bile acid derivatives, particularly UDCA, are biologically plausible candidates meriting further investigation in the context of MS.

1. Introduction

Bile acids (BAs) are increasingly being recognized as regulators of neuroinflammation and neurodegeneration, processes central to the pathophysiology of multiple sclerosis (MS) (Antonini Cencicchio et al., 2025; Erngren et al., 2025). Beyond their established role in lipid

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absorption, BAs interact with receptors such as the farnesoid X receptor (FXR) and the G-protein-coupled bile acid receptor 1 (GPBAR1/TGR5) and modulate immune responses and gut–brain axis signaling (Tyagi and Kumar, 2025). In experimental autoimmune encephalomyelitis (EAE), supplementation with ursodeoxycholic acid (UDCA) and other bile acids attenuates disease severity and reduces neuroinflammation through GPBAR1/TGR5-dependent mechanisms (Bhargava et al., 2020; Sonoda et al., 2025).

Clinical investigations have underscored the relevance of BA metabolism in the pathophysiology of MS. A cohort study reported significant reductions in circulating BA metabolites in patients with adult- or pediatric-onset MS compared with healthy controls (Bhargava et al., 2020). More recently, a randomized controlled trial in progressive MS demonstrated the safety of tauro-ursodeoxycholic acid (TUDCA) supplementation and its association with immunological changes, including reductions in central memory CD4+ T cells and Th1/17 cells, as well as increases in naïve CD4+ T cells (Ladakis et al., 2025). The same study also reported alterations in gut microbiota composition. However, despite these findings, the therapeutic implications of BA supplementation in MS remain unclear.

Pharmacovigilance-based drug repositioning represents a complementary strategy for identifying novel therapeutic applications. Spontaneous reporting systems have traditionally been used to detect adverse drug reactions by identifying drug–event pairs reported more frequently than expected. Conversely, a reduced reporting frequency of specific drug–disease combinations, referred to as inverse signals, may suggest protective effects and thereby generate hypotheses for drug repurposing (Böhm et al., 2021). The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS)—one of the largest publicly accessible pharmacovigilance databases—has been widely used for hypothesis generation in drug repositioning research (Ko et al., 2023; Morris et al., 2024). In this study, we performed a disproportionality analysis using FAERS to evaluate the potential association between BA preparations and MS, followed by preclinical validation in an experimental autoimmune encephalomyelitis model.Fig. 1

2. Methods

2.1. FAERS data

FAERS— maintained by the US FDA—is one of the largest spontaneous reporting databases for adverse events associated with drugs and biological products. We conducted a disproportionality analysis of individual case safety reports from FAERS as part of a retrospective pharmacovigilance study. Adverse event reports submitted worldwide between the fourth quarter of 2003 and the second quarter of 2025 were included, and all quarterly FAERS releases up to the second quarter of 2025 were accessed on August 5, 2025. Reports relevant to the adverse events of interest were identified using 12 Standardized MedDRA Queries (SMQs) (Table 1) (MedDRA, 2025). In addition to BA derivatives, such as UDCA and obeticholic acid (6-ECDCA), calcitriol, the active form of vitamin D, was included as a reference drug. Calcitriol was selected based on prior clinical trials and meta-analyses indicating the potential benefits of vitamin D supplementation for MS-related outcomes (Serag et al., 2025; Thouvenot et al., 2025). Its inclusion enabled contextual comparison between BA derivatives and a compound with reported clinical relevance in MS.

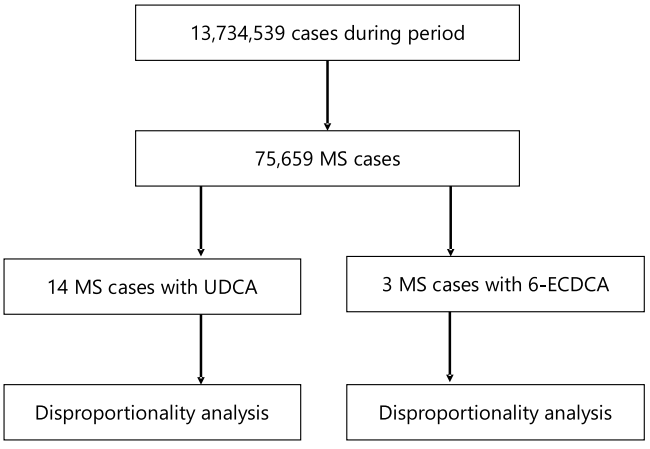

Fig. 1. Flow diagram of the study. MS, multiple sclerosis; UDCA, ursodeoxycholic acid; 6-ECDCA, obeticholic acid.

2.2. Data analysis and identification of inverse signals

FAERS data were accessed and processed using the OpenVigil 2.1 platform, which provides standardized preprocessing and query functionalities. Duplicate reports were removed using the OpenVigil platform, which applies FDA-recommended case-based deduplication procedures. Formal adjustment for concomitant medications was not performed, given the heterogeneous and incomplete reporting of concomitant drug use in FAERS. Disproportionality analyses were conducted to assess whether BA preparations, including UDCA, 6-ECDCA, cholic acid, and dehydrocholic acid, were disproportionately reported in association with MS using nine SMQs (Table 1). Disproportionality was quantified using the odds ratio (OR) and the information component (IC), both derived from 2×2 contingency tables. An inverse signal was defined as statistically significant underreporting of MS among users of a given drug to identify potential protective associations. Operationally, this was defined as an OR < 1, with the upper limit of the 95% confidence interval (CI) < 1.0, and at least three reported cases, in accordance with previous pharmacovigilance studies (Bate et al., 1998; Sakaeda et al., 2013; Van Puijenbroek et al., 2002). Cases of MS were defined using MedDRA terminology based on the High Level Term (HLT) "Multiple sclerosis acute and progressive" and its corresponding Preferred Terms (PTs). A report was classified as an MS case if at least one of these PTs was present. For sensitivity analysis, the PT composition contributing to the MS signal was examined. Specifically, we assessed whether inverse reporting signals were consistently observed across general MS-related PTs (e.g., "Multiple sclerosis") and relapse-related PTs (e.g., "Multiple sclerosis relapse") to determine whether the observed signals were driven by a specific disease state. This approach assumed underrepresentation of a specific disease in spontaneous reports as indicative of a potential therapeutic or protective association rather than a harmful effect. Accordingly, such inverse associations were considered hypothesis-generating findings for drug repurposing and were therefore selected for preclinical validation in the present study. IC was calculated on the log2 scale, and its 95% CI was estimated using the Wald approximation. An upper 95% CI limit of ≤ 1.0 was considered statistically significant.

2.3. Mice

Seven-week-old, female C57BL/6J mice (weighing 18–20 g) were purchased from CLEA Japan Inc. (Tokyo, Japan) and maintained with ad libitum access to water and food (type NMF; Oriental Yeast Co., Ltd, Tokyo, Japan). Mice were housed in groups of 4–6 per cage under controlled conditions (relative humidity: 50% $\pm$ 10%; temperature: 26°C $\pm$ 1°C; 12-h light/dark cycle, lights on at 08:00 and off at 20:00).

2.4. EAE induction and evaluation

In addition to pharmacovigilance analysis, EAE was used to evaluate the therapeutic efficacy of UDCA and 6-ECDCA. Although calcitriol was not included in the preclinical evaluation, its potential was inferred from the FAERS analysis. Fifty mice were used throughout the experiment. The mice were divided into at least three cohorts to verify efficacy. Each

cohort included ms-vehicle, ms-UDCA (5,500 mg/kg), and ms-6ECDCA (5 mg/kg). In accordance with previously established protocols (Ho and Steinman, 2016; Ishizaki et al., 2005), EAE was induced in 8-week-old female mice after being habituated to the experimental environment for a week. On day 0, mice were immunized subcutaneously with 100 μg of myelin oligodendrocyte glycoprotein (MOG)35–55 (MEVGWYRSPFSRVVHLYRNGK; Genemed Synthesis Inc., South San Francisco, CA, USA) emulsified in complete Freund's adjuvant, consisting of incomplete Freund's adjuvant and 0.4 mg of heat-inactivated *Mycobacterium tuberculosis* strain H37Ra (Difco Laboratories, Detroit, MI, USA). Two hundred microliters of this emulsion were injected subcutaneously into the flank of each mouse. On days 0 and 2, mice were also injected intraperitoneally with 400 ng pertussis toxin (List Biological Labs, Inc., Campbell, CA, USA) in 0.2 mL 1 × phosphate-buffered saline. The EAE disease grade was measured on days 0, 3, and 10 after MOG administration, and mice were randomly grouped on day 14 after MOG administration based on the EAE disease grade. Mice with a score of 0 on day 14 were excluded from subsequent efficacy evaluations because they could not be properly assessed for treatment effect. Mice were given UDCA (5, 500 mg/kg) or 6-ECDCA (5 mg/kg) orally each day, diluted with 0.5% carboxymethyl cellulose. Treatment was initiated on day 14 after MOG immunization, when mice had already developed clinical symptoms. This therapeutic design was chosen to better approximate clinical conditions, in which interventions are introduced after disease onset rather than prophylactically. The vehicle control contained equivalent amounts of 0.5% carboxymethyl cellulose. Based on previous studies demonstrating that 6-ECDCA is more effective when administered orally compared with intraperitoneal injection (Ho and Steinman, 2016), oral administration was chosen for this study. Additionally, as UDCA was administered orally, we maintained consistency across experimental conditions by administering 6-ECDCA via the same route. From Day 0 onwards, the EAE disease grade was monitored daily by using the following scoring system: 0, no clinical deficit; 1, partial tail paralysis; 2, full tail paralysis; 3, partial hindlimb paralysis; 4, full hindlimb paralysis; 5, forelimb paresis; and 6, death (Miyamura et al., 2019).

2.5. Statistical analysis

All analyses were performed using R software (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria). Two-sided tests were conducted, and statistical significance was defined as $P < 0.05$. Associations in FAERS data were assessed using Fisher's exact test. EAE clinical scores over time were analyzed using two-way repeated-measures analysis of variance, with time after MOG administration and treatment group as factors. Comparisons were made among the vehicle-, UDCA-, and 6-ECDCA-treated groups. Post hoc analyses were conducted using Bonferroni's post hoc test. The cumulative EAE disease grade was calculated using the Kruskal-Wallis test.

2.6. Ethics

For this observational pharmacovigilance study, we used a publicly accessible database (FAERS) that contains anonymized information. No therapeutic interventions or collection of human samples were involved; therefore, informed consent was not required. All animal experiments were conducted in accordance with the Guidelines for Proper Conduct of Animal Experiments issued by the Ministry of Education, Culture, Sports, Science and Technology of Japan and the relevant institutional guidelines. The Animal Research Committee of Tokushima University Graduate School approved all procedures, and the protocol was authorized by the Institutional Animal Care and Use Committee of Tokushima University Graduate School (permit number: T2021-62).

3. Results

3.1. FAERS analysis findings

A total of 13,734,539 cases were identified based on case IDs, including 75,659 cases of MS. The proportion of MS cases for each drug and their corresponding ORs are summarized in Table 2. UDCA and obeticholic acid 6-ECDCA were associated with lower reporting odds of MS, with ORs of 0.197 (95% CI: 0.117–0.333) and 0.128 (95% CI: 0.041–0.396), respectively. Calcitriol also demonstrated an inverse reporting signal (OR: 0.177, 95% CI: 0.092–0.340). Cholic acid and dehydrocholic acid were excluded from further analyses because no relevant MS-related reports were identified. For sensitivity analysis, we examined the distribution of PTs contributing to the MS signal. For UDCA, MS-related reports were evenly distributed between the PT "Multiple sclerosis" (n=8) and the PT "Multiple sclerosis relapse" (n=8), indicating that a single disease state did not drive the inverse signal. Similarly, calcitriol showed an even distribution across these two PTs (n=4 and n=4). In contrast, all MS-related reports associated with obeticholic acid were classified under the PT "Multiple sclerosis relapse," suggesting that the inverse reporting signal for obeticholic acid was confined to relapse-related events.

3.2. Oral administration of UDCA or 6-ECDCA is an effective EAE treatment

We selected UDCA and 6-ECDCA as potential therapeutic agents based on the results of the FAERS data analysis. We monitored the clinical course of EAE over 28 days to evaluate the therapeutic potential of BAs (Fig. 2 A). Vehicle-treated mice showed a typical disease progression, reaching a peak score of approximately 3.5 around day 18. In contrast, administration of UDCA (500 mg/kg) and 6-ECDCA (5 mg/kg) significantly attenuated the clinical severity. Notably, the high-dose UDCA group demonstrated a marked reduction in disease grade compared to the vehicle group starting from day 17, with significant differences observed at the end of the study (day 28, $P < 0.05$). The cumulative disease grade, representing the overall disease burden, was calculated for each group (Fig. 2 B). Consistent with the clinical course, UDCA at 500 mg/kg significantly reduced the cumulative score compared to the vehicle-treated mice ($P < 0.05$). Although 6-ECDCA and low-dose UDCA (50 mg/kg) showed a trend toward decreased cumulative scores, the effects did not reach statistical significance in this model. The mice in both groups did not differ in terms of weight throughout the experimental period (Supplemental Fig. 1).

4. Discussion

In this study, we employed a two-stage approach combining pharmacovigilance data analysis with preclinical validation to explore the potential of BA derivatives as candidate therapies for MS. Analysis of the FAERS database identified inverse associations between MS reporting and the use of UDCA (OR, 0.197) and 6-ECDCA (OR, 0.128). Consistent with these observations, evaluation in a therapeutic EAE model demonstrated that UDCA significantly reduced disease severity, whereas 6-ECDCA administration showed a non-significant trend toward improvement. These findings align with previous studies demonstrating the efficacy of 6-ECDCA in EAE models (Ho and Steinman, 2016), and together reinforce the hypothesis that altered BA metabolism contributes to MS pathophysiology. To ensure the robustness of these findings, we performed independent replication experiments including a lower dose of UDCA (50 mg/kg). Notably, the 50 mg/kg dose failed to significantly ameliorate disease severity, suggesting a dose-dependent threshold for UDCA's therapeutic efficacy. The lack of effect at 50 mg/kg further confirms that the significant improvement observed with 500 mg/kg was due to pharmacological intervention rather than an artifact of initial group allocation. Together, these complementary

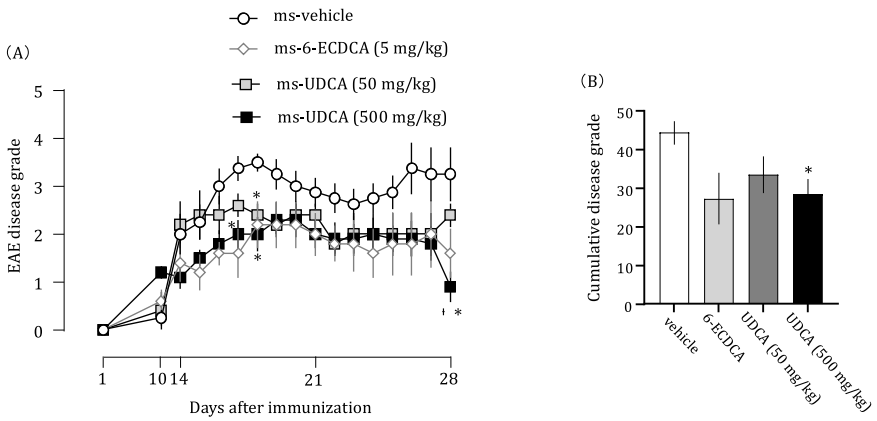

Fig. 2. EAE disease grades of mice administered UDCA, 6-ECDCA, or vehicle. (A) Clinical course of EAE. Data are presented as mean ± SEM (ms-vehicle; n=8, ms-UDCA [50 mg/kg]; n=5, ms-UDCA [500 mg/kg]; n=10, ms-6ECADA; n=5). *P < 0.05 vs. vehicle group at indicated time points. ǂP < 0.05 vs. ms-UDCA (50 mg/kg) by two-way ANOVA with Bonferroni's multiple-comparisons test. (B) Cumulative disease grade. The total disease burden was calculated as the sum of daily clinical scores for each mouse throughout the study period. Data are shown as mean ± SEM. Statistical significance was determined by the Kruskal–Wallis test. *$P < 0.05$ vs. vehicle. UDCA, ursodeoxycholic acid; 6-ECDCA, obeticholic acid; EAE, experimental autoimmune encephalomyelitis; *$P < 0.05$.

findings reinforce the hypothesis that BA metabolism contributes to MS pathophysiology and support further investigation of BA-based interventions. Importantly, our results extend prior observations of BA signaling in neurodegenerative diseases by highlighting a potential protective association specifically in MS, a clinical context in which direct human data remain limited.

Our findings are consistent with accumulating evidence that altered BA metabolism plays an important role in MS. Several metabolomic studies have revealed reduced levels of circulating BAs, particularly in progressive forms of MS (Bhargava et al., 2020; Ladakis et al., 2025). UDCA is water-soluble and has low blood–brain barrier permeability (Ueda et al., 2022). It exhibits higher affinity for the membrane-bound receptor TGR than for the nuclear receptor FXR. A recent randomized controlled trial demonstrated the safety of TUDCA supplementation and its association with favorable immunological changes, including decreases in pro-inflammatory Th1 and Th17 cells and modulation of the gut microbiota composition (Ladakis et al., 2025). These observations, together with our data, support the notion that restoration of BA homeostasis may have therapeutic potential in MS. Sensitivity considerations based on the distribution of MS-related Preferred Terms indicated that a single disease state did not drive the inverse reporting signal for ursodeoxycholic acid, whereas the signal for obeticholic acid appeared to be confined to relapse-related events. These findings support the internal consistency of the pharmacovigilance analysis, but are hypothesis-generating in nature.

Mechanistically, BA derivatives may act through distinct receptor-mediated pathways, consistent with our findings. 6-ECDCA is a potent agonist of FXR implicated in remyelination as it reduces pro-inflammatory cytokines and promotes oligodendrocyte differentiation (Jia et al., 2021; Ladakis et al., 2025). In contrast, UDCA shows low affinity for FXR but activates TGR5, which is expressed on astrocytes and microglia. Activation of TGR5 suppresses nuclear factor kappa-B (NF-κB) signaling, inhibits nucleotide-binding oligomerization domain-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation, and reduces pro-inflammatory cytokine release (Ito et al., 2024; Miyazaki et al., 2011; Xu et al., 2023). Our separate investigations have identified TGR5 as a pivotal mediator of UDCA's neuroprotective effects (Sonoda et al., 2025), consistent with our observation that UDCA, but not 6-ECDCA, significantly ameliorated EAE severity. UDCA-treated microglia regulated the expression of several proteins involved in the transcriptional regulation of inflammatory cytokines and their own activation via TGR5. These findings suggest TGR5-mediated signaling as a key mechanism contributing to the observed neuroprotective effects. These receptor-mediated pathways may collectively influence demyelination and remyelination dynamics in the central nervous system, providing a biologically plausible mechanistic framework for the phenotype observed in UDCA-treated EAE mice.

Beyond these mechanistic implications, this study also underscores the methodological utility of pharmacovigilance-guided discovery as a complementary approach to traditional, target-driven drug development. Inverse signals from large-scale adverse event databases can highlight unexpected protective associations, providing valuable leads to repurpose existing drugs (Böhm et al., 2021; Ko et al., 2023). By combining FAERS-based hypothesis generation with EAE-based preclinical validation, we demonstrated a reproducible workflow for the identification and prioritization of candidate compounds for the treatment of neuroimmunological diseases. This approach integrates real-world data with experimental evidence, bridging the translational gap between population-level safety databases and mechanistic animal models (Morris et al., 2024). Overall, this pharmacovigilance-guided workflow illustrates a scalable and data-driven strategy for informing preclinical prioritization in neuroinflammatory disease research.

Despite the promising signals identified in this study, some limitations should be acknowledged. First, the FAERS database is primarily intended for pharmacovigilance and hypothesis generation and relies on voluntary reporting. Consequently, it is susceptible to reporting bias and confounding by indication. The lack of detailed patient-level information, including medical history, comorbidities, and concomitant treatments, precludes comprehensive adjustment for potential confounders. Another limitation of this study is the lack of adjustment for concomitant medications, which are incompletely and heterogeneously reported in FAERS. Accordingly, disproportionality analysis based on FAERS cannot establish causality and should be interpreted as hypothesis-generating rather than indicative of protective clinical effects. Second, the EAE model is widely used in preclinical studies of MS. However, it does not fully recapitulate the complexity of the human disease, particularly with respect to chronic progression, demyelination, and interindividual heterogeneity. Thus, the present findings should be interpreted with appropriate caution and primarily as a basis for further investigation. Future studies incorporating prospective clinical data, as well as longitudinal designs integrating pharmacovigilance data with genetic and metabolomic profiling, may help clarify causal pathways and identify patient subgroups that are most likely to benefit from bile acid–based therapeutic strategies. Finally, in this study, UDCA was administered orally, directly mirroring its clinical use as an FDA-approved drug. This ensures that the findings are translatable to a non-invasive, long-term treatment regimen for patients with MS. However, a high dose of UDCA

(500 mg/kg) was required to achieve a significant reduction in EAE severity. This dose-dependency likely stems from the physicochemical properties of UDCA; as a hydrophilic BA, its passive diffusion across the blood–brain barrier is relatively low. Consequently, higher systemic concentrations are necessary to ensure sufficient receptor engagement (e.g., TGR5) on CNS resident cells such as microglia. This is a critical consideration for clinical translation, as neuroprotective strategies using UDCA in humans often require doses higher than those standardly used for primary biliary cholangitis to ensure adequate CNS exposure. Development of more effective, fat-soluble BAs and investigation of drug delivery to the brain are necessary.

In conclusion, this two-stage investigation integrating pharmacovigilance analysis with preclinical experimentation identified UDCA as a biologically plausible candidate warranting further investigation in the context of MS. The convergence of inverse safety signals observed in real-world data and supportive findings in the EAE model supports the hypothesis that BA signaling may modulate neuroinflammatory processes relevant to MS pathology. However, these findings should be interpreted as hypothesis-generating rather than confirmatory. Additional mechanistic and clinical studies will be required to clarify causal pathways, define optimal dosing strategies, and determine the translational relevance of UDCA and related BA derivatives in MS. Ultimately, such work may facilitate the rational repositioning of well-characterized bile acid compounds toward future clinical evaluation in patients with MS.

Glossary

6-ECDCA (obeticholic acid): A semisynthetic bile acid analog used for cholestatic liver diseases.

EAE: Experimental autoimmune encephalomyelitis, an animal model commonly used to study multiple sclerosis.

FAERS: Food and Drug Administration Adverse Event Reporting System, a large pharmacovigilance database in the United States.

UDCA: Ursodeoxycholic acid, a bile acid used clinically for liver diseases.

Consent for publication

Not applicable.

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The funding bodies had no role in the study design, data collection, analysis and interpretation of data, writing of the report, or the decision to submit the article for publication.

Data availability

The FAERS data used in this study are publicly available on the OpenVigil website (https://openvigil.sourceforge.net). The datasets generated and analyzed during the animal experiments are available from the corresponding author upon reasonable request.

Supplemental Fig. 1. Body weight of mice administered UDCA, 6-ECDCA or vehicle

UDCA, ursodeoxycholic acid; 6-ECDCA, obeticholic acid; EAE, experimental autoimmune.

CRediT authorship contribution statement

Mizuho Asada: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Fuka Aizawa:** Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Takahisa Mikami:** Writing – review & editing, Methodology, Conceptualization. **Mitsuhiro Goda:** Writing – review & editing, Writing – original draft, Formal analysis. **Yuhei Sonoda:** Writing – review & editing, Investigation, Data curation. **Takahiro Niimura:** Writing – review & editing, Methodology, Investigation, Formal analysis, Data curation. **Yoshito Zamami:** Writing – review & editing, Methodology, Funding acquisition. **Masayuki Chuma:** Writing – review & editing, Methodology. **Yoshihiro Uesawa:** Writing – review & editing, Supervision. **Keisuke Ishizawa:** Writing – review & editing, Supervision, Funding acquisition.

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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Supplementary materials

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References

Antonini Cencicchio, M., Montini, F., Palmieri, V., et al., 2025. Microbiota-produced immune regulatory bile acid metabolites control central nervous system autoimmunity. Cell Rep. Med. 6, 102028. https://doi.org/10.1016/j.xcrm.2025.102028.

Bate, A., Lindquist, M., Edwards, I.R., et al., 1998. A Bayesian neural network method for adverse drug reaction signal generation. Eur. J. Clin. Pharmacol. 54, 315–321. https://doi.org/10.1007/s002280050466.

Bhargava, P., Smith, M.D., Mische, L., et al., 2020. Bile acid metabolism is altered in multiple sclerosis and supplementation ameliorates neuroinflammation. J. Clin. Invest. 130, 3467–3482. https://doi.org/10.1172/jci129401.

Böhm, R., Bulin, C., Waetzig, V., Cascorbi, I., Klein, H.J., Herdegen, T., 2021. Pharmacovigilance-based drug repurposing: the search for inverse signals via OpenVigil identifies putative drugs against viral respiratory infections. Br. J. Clin. Pharmacol. 87, 4421–4431. https://doi.org/10.1111/bcp.14868.

Erngren, I., Vaivade, A., Carlsson, H., et al., 2025. Bile acid metabolism in multiple sclerosis is perturbed and associated with the risk of confirmed disability worsening. BMC Med 23, 212. https://doi.org/10.1186/s12916-025-04041-x.

Ho, P.P., Steinman, L., 2016. Obeticholic acid, a synthetic bile acid agonist of the farnesoid X receptor, attenuates experimental autoimmune encephalomyelitis. Proc. Natl Acad. Sci. U. S. A. 113, 1600–1605. https://doi.org/10.1073/pnas.1524890113.

Ishizaki, K., Imada, T., Tsurufuji, M., 2005. Hepatoprotective bile acid "ursodeoxycholic acid (UDCA)" Property and difference as bile acids. Hepatol. Res. 33, 174–177. https://doi.org/10.1016/j.hepres.2005.09.029.

Ito, E., Inuki, S., Izumi, Y., et al., 2024. Sulfated bile acid is a host-derived ligand for MAIT cells. Sci. Immunol. 9, eade6924. https://doi.org/10.1126/sciimmunol.ade6924.

Jia, Y., Zhang, D., Li, H., et al., 2021. Activation of FXR by ganoderic acid A promotes remyelination in multiple sclerosis via anti-inflammation and regeneration mechanism. Biochem. Pharmacol. 185, 114422. https://doi.org/10.1016/j.bcp.2021.114422.

Ko, M., Oh, J.M., Kim, I.W., 2023. Drug repositioning prediction for psoriasis using the adverse event reporting database. Front. Med. (Lausanne). 10, 1159453. https://doi.org/10.3389/fmed.2023.1159453.

Ladakis, D.C., Harrison, K.L., Smith, M.D., et al., 2025. Bile acid metabolites predict multiple sclerosis progression and supplementation is safe in progressive disease. Med 6, 100522. https://doi.org/10.1016/j.medj.2024.09.011.

Med, D.R.A., 2025. Medical dictionary for regulatory activities. https://www.meddra.org/how-to-use/support-documentation/english. Accessed 14 Aug 2025.

Miyamura, S., Matsuo, N., Nagayasu, K., Shirakawa, H., Kaneko, S., 2019. Myelin oligodendrocyte glycoprotein 35–55 (MOG 35–55)-induced experimental autoimmune encephalomyelitis: a model of chronic multiple sclerosis. Bio Protoc 9, e3453. https://doi.org/10.21769/BioProtoc.3453.

Miyazaki, Y., Miyake, S., Chiba, A., Lantz, O., Yamamura, T., 2011. Mucosal-associated invariant T cells regulate Th1 response in multiple sclerosis. Int. Immunol. 23, 529–535. https://doi.org/10.1093/intimm/dxr047.

Morris, R., Ali, R., Cheng, F., 2024. Drug repurposing using FDA Adverse Event Reporting System (FAERS) database. Curr. Drug Targets. 25, 454–464. https://doi.org/10.2174/0113894501290296240327081624.

Sakaeda, T., Tamon, A., Kadoyama, K., Okuno, Y., 2013. Data mining of the public version of the FDA Adverse Event Reporting System. Int. J. Med. Sci. 10, 796–803. https://doi.org/10.7150/ijms.6048.

Serag, I., Abouzid, M., Alsaadany, K.R., et al., 2025. Role of vitamin D as adjuvant therapy on multiple sclerosis: an updated systematic review and meta-analysis of randomized controlled trials. Eur. J. Med. Res. 30, 736. https://doi.org/10.1186/s40001-025-02981-x.

Sonoda, Y., Aizawa, F., Tomochika, N., et al., 2025. Ursodeoxycholic acid alleviates multiple sclerosis via TGR5-dependent microglial regulation in mice. Eur. J. Pharmacol. 1003, 177941. https://doi.org/10.1016/j.ejphar.2025.177941.

Thouvenot, E., Laplaud, D., Lebrun-Frenay, C., et al., 2025. High-dose vitamin D in clinically isolated syndrome typical of multiple sclerosis: the D-Lay MS randomized clinical trial. JAMA 333, 1413–1422. https://doi.org/10.1001/jama.2025.1604.

Tyagi, A., Kumar, V., 2025. The gut microbiota-bile acid axis: a crucial regulator of immune function and metabolic health. World J. Microbiol. Biotechnol. 41, 215. https://doi.org/10.1007/s11274-025-04395-7.

Ueda, H., Honda, A., Miyazaki, T., et al., 2022. Sex-, age-, and organ-dependent improvement of bile acid hydrophobicity by ursodeoxycholic acid treatment: a study using a mouse model with human-like bile acid composition. PLOS One 17, e0271308. https://doi.org/10.1371/journal.pone.0271308.

Van Puijenbroek, E.P., Bate, A., Leufkens, H.G.M., Lindquist, M., Orre, R., Egberts, A.C. G., 2002. A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. Pharmacoepidemiol. Drug Saf. 11, 3–10. https://doi.org/10.1002/pds.668.

Xu, N., Bai, Y., Han, X., et al., 2023. Taurochenodeoxycholic acid reduces astrocytic neuroinflammation and alleviates experimental autoimmune encephalomyelitis in mice. Immunobiology 228, 152388. https://doi.org/10.1016/j.imbio.2023.152388.