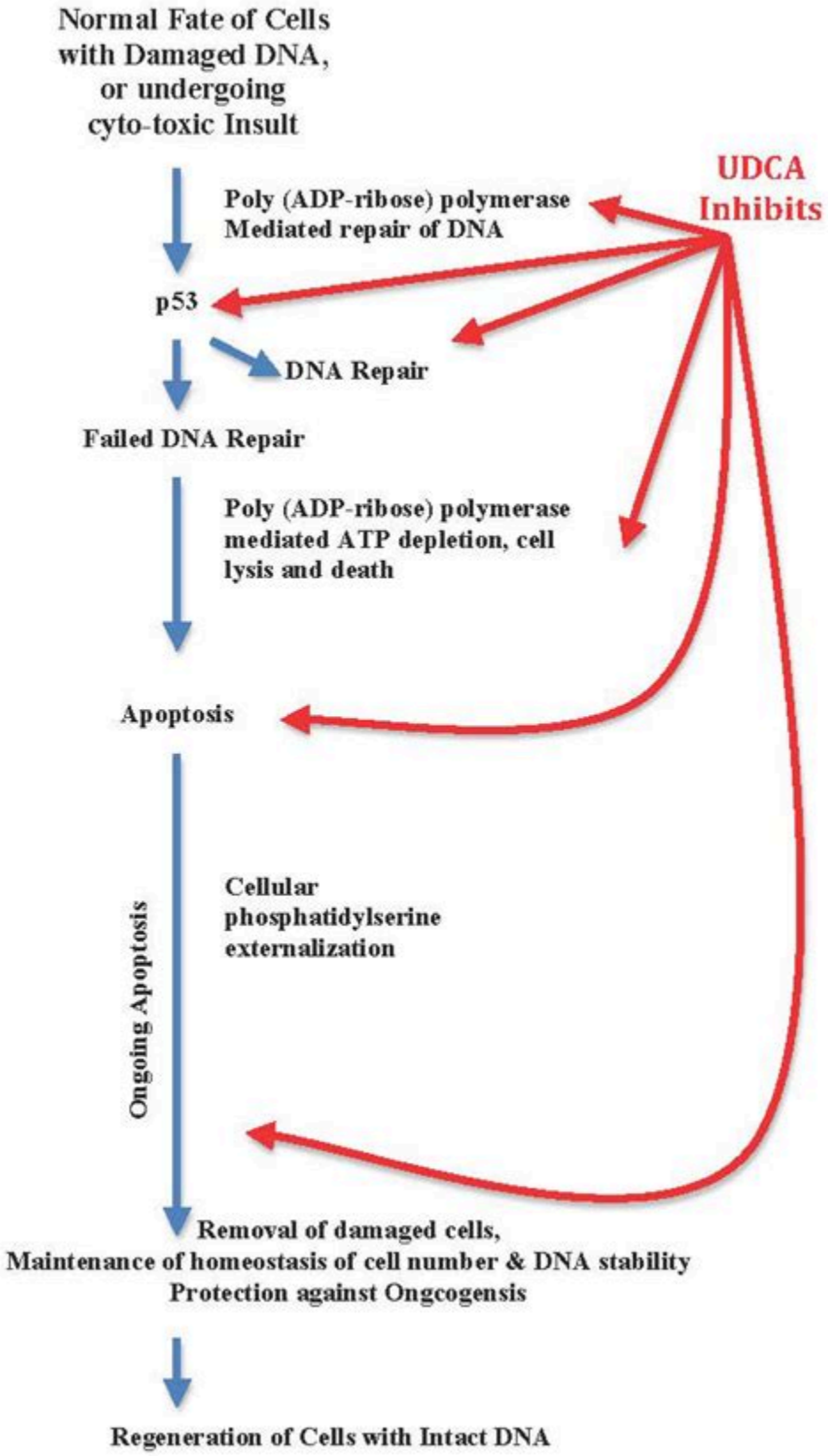
1. Introduction Tauroursodeoxycholic acid (TUDCA) composed of taurine conjugated with the ursodeoxycholic acid (UDCA), together with its precursor UDCA, belong to the most hydrophilic bile acids [ 1, 2] ( Figure 1 ). Figure 1 Chemical structure of tauroursodeoxycholic acid, TUDCA.

**Molecular Mechanisms of Ursodeoxycholic Acid Toxicity & Side Effects .**



Purpose: To determine local ocular tissue levels of the bile acid, tauroursodeoxycholic acid (TUDCA), in the pig model using oral, intravenous (IV), intravitreal injection (IVitI) and low- and high-dose suprachoroidal, sustained-release implants (SCI-L or SCI-H). . Methods: Forty-six pigs (92 globes) were included in the study. TUDCA was delivered orally in 5 pigs, IV in 4, IVitI in 6, SCI-L in .

## PDF Tauroursodeoxycholic Acid (TUDCA) - alzdiscovery

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*Article*

# Tauroursodeoxycholic Acid (TUDCA)—Lipid Interactions and Antioxidant Properties of TUDCA Studied in Model of Photoreceptor Membranes

**Michal J. Sabat [1], Anna M. Wiśniewska-Becker [1], Michal Markiewicz [2], Katarzyna M. Marzec [3], Jakub Dybas [3], Justyna Furso [1], Pawel Pabisz [1], Mariusz Duda [1] and Anna M. Pawlak [1,*]**

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[2] Department of Computational Biophysics and Bioinformatics, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, 30-387 Krakow, Poland; m.markiewicz@uj.edu.pl
[3] Jagiellonian Centre for Experimental Therapeutics, Jagiellonian University, 30-348 Krakow, Poland; katarzyna.marzec@uj.edu.pl (K.M.M.); jakub.dybas@uj.edu.pl (J.D.)
* Correspondence: anna.pawlak@uj.edu.pl

**Abstract:** Tauroursodeoxycholic acid (TUDCA), a hydrophilic bile acid containing taurine conjugated with the ursodeoxycholic acid (UDCA), has been known and used from ancient times as a therapeutic compound in traditional Chinese medicine. TUDCA has recently been gaining significant interest as a neuroprotective agent, also exploited in the visual disorders. Among several mechanisms of TUDCA's protective action, its antioxidant activity and stabilizing effect on mitochondrial and plasma membranes are considered. In this work we investigated antioxidant activity of TUDCA and its impact on structural properties of model membranes of different composition using electron paramagnetic resonance spectroscopy and the spin labeling technique. Localization of TUDCA molecules in a pure POPC bilayer has been studied using a molecular dynamics simulation (MD). The obtained results indicate that TUDCA is not an efficient singlet oxygen ($^1O_2$ ($^1\Delta_g$)) quencher, and the determined rate constant of its interaction with $^1O_2$ ($^1\Delta_g$) is only $1.9 \times 10^5$ $M^{-1}s^{-1}$. However, in lipid oxidation process induced by a Fenton reaction, TUDCA reveals substantial antioxidant activity significantly decreasing the rate of oxygen consumption in the system studied. In addition, TUDCA induces slight, but noticeable changes in the polarity and fluidity of the investigated model membranes. The results of performed MD simulation correspond very well with the experimental results.

**Keywords:** bile acids; liposome; photoreceptor membrane; lipid peroxidation; antioxidant; electron paramagnetic resonance

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**Citation:** Sabat, M.J.; Wiśniewska-Becker, A.M.; Markiewicz, M.; Marzec, K.M.; Dybas, J.; Furso, J.; Pabisz, P.; Duda, M.; Pawlak, A.M. Tauroursodeoxycholic Acid (TUDCA)—Lipid Interactions and Antioxidant Properties of TUDCA Studied in Model of Photoreceptor Membranes. *Membranes* **2021**, *11*, 327. https://doi.org/10.3390/membranes11050327

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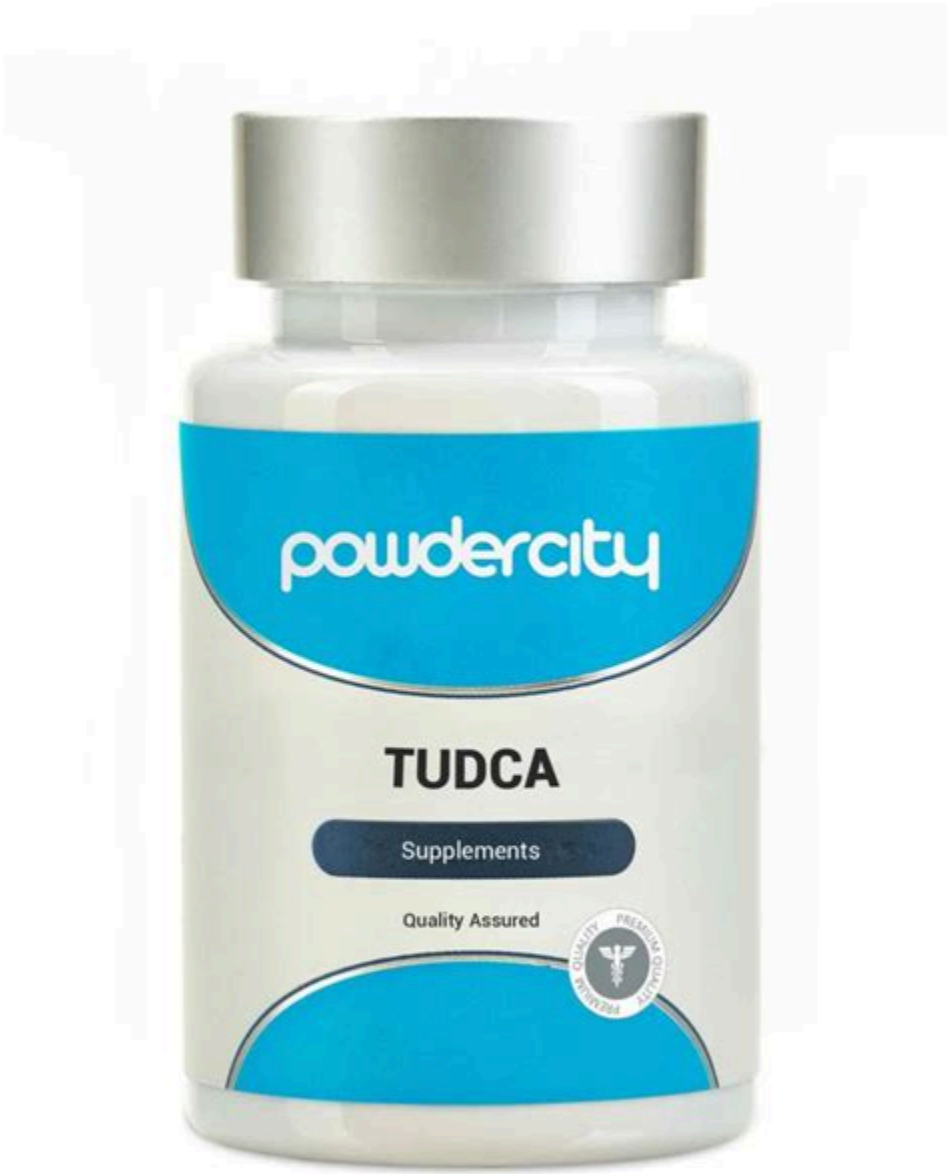
**Figure 1.** Chemical structure of tauroursodeoxycholic acid, TUDCA.



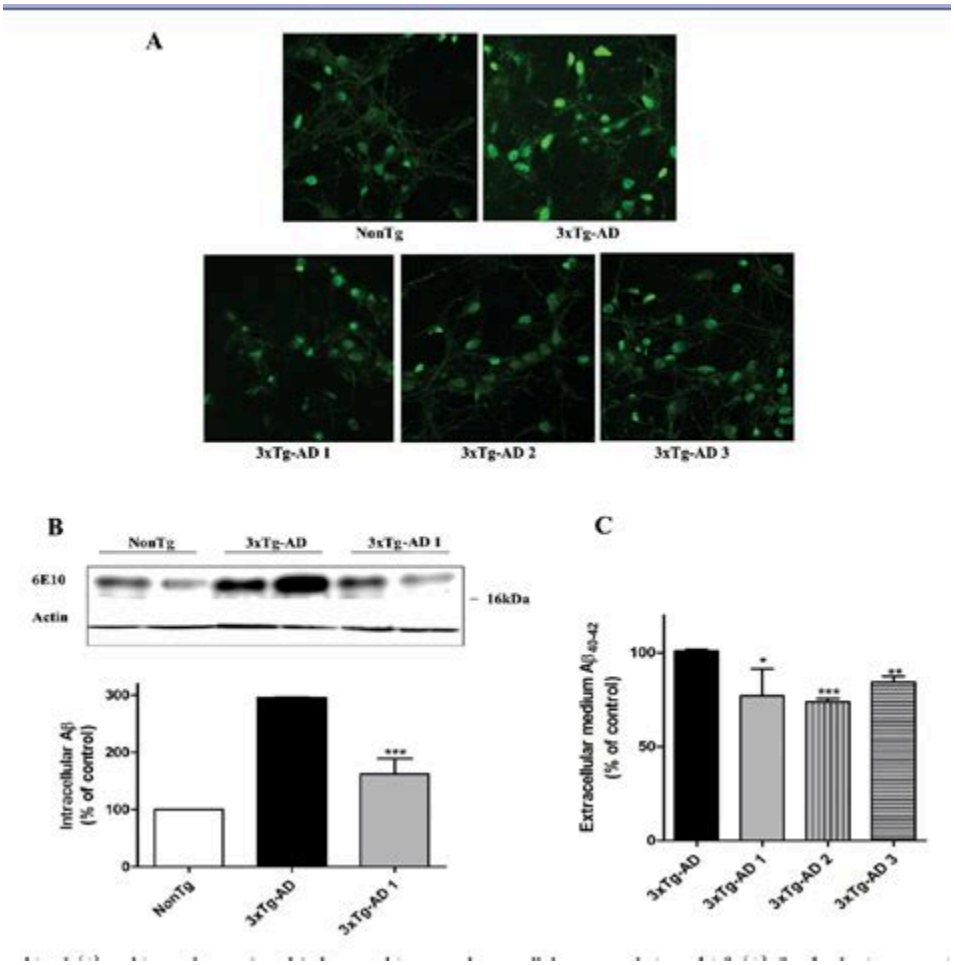
The TUDCA-ALS trial is a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial. The study aims to enroll 320 patients in 25 centers across seven countries in Europe. Enrolled patients are randomized to one of two treatment arms: TUDCA or identical placebo by oral route.

**TUDCA benefits, dosage, and side effects - Examine**



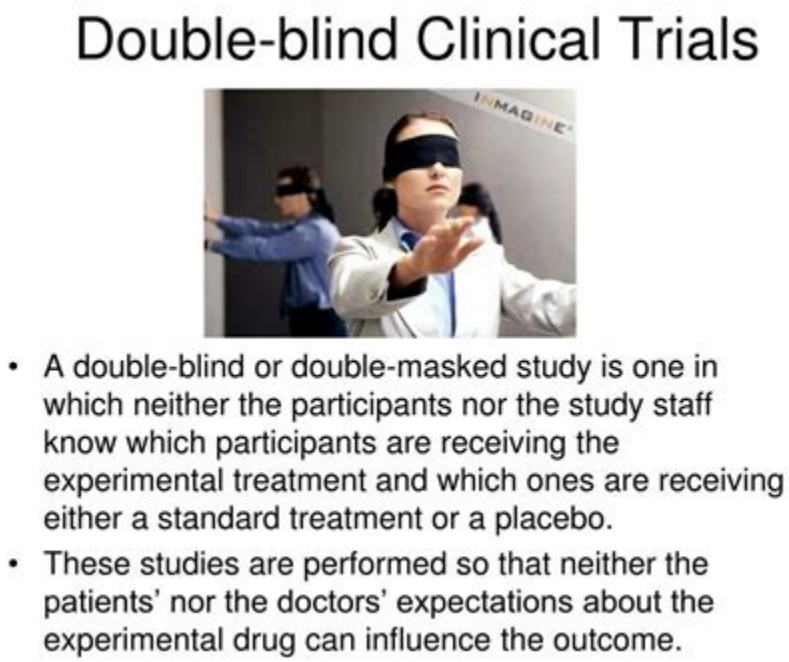

Tauroursodeoxycholic acid (TUDCA), an endogenous bile acid, modulates cell death by interrupting classic pathways of apoptosis. Intracerebral hemorrhage (ICH) is a devastating acute neurological disorder, without effective treatment, in which a significant loss of neuronal cells is thought to occur by apoptosis.

**Amyloid-β pathology is attenuated by tauroursodeoxycholic acid .**



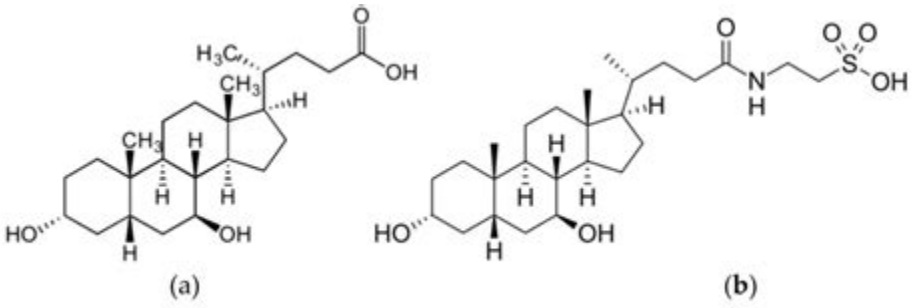

In contrast, after 6 days of TUDCA treatment, the cumulative food intake curve for Stz + TUDCA group was below the respective untreated group (Fig. 1G), showing a clear significant effect at the .

**A randomized double-blind clinical trial on safety and efficacy of .**




TUDCA: Tauroursodeoxycholic Acid By Stephanie Liou 29 Jun, 2010 Abnormalities in energy metabolism What in the world do black bears have to do with treating Huntington's disease? Believe it or not, a compound found in large quantities in the bile (a digestive fluid) of black bears may help prevent the death of brain cells in people with HD.

## Tauroursodeoxycholate—Bile Acid with Chaperoning Activity: Molecular .




TUDCA-treated aged mice also displayed increased energy expenditure and metabolic flexibility, as well as a better cognitive ability. . however, the half-life of c-peptide is longer than that of .

# Tauroursodeoxycholic Acid (TUDCA)—Lipid Interactions and Antioxidant .

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Article

## Tauroursodeoxycholic Acid (TUDCA)—Lipid Interactions and Antioxidant Properties of TUDCA Studied in Model of Photoreceptor Membranes

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[2] Department of Computational Biophysics and Bioinformatics, Faculty of Biochemistry, Biophysics and Biotechnology, Jagiellonian University, 30-387 Krakow, Poland; m.markiewicz@uj.edu.pl
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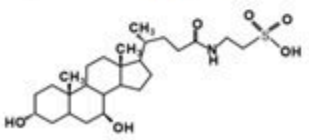
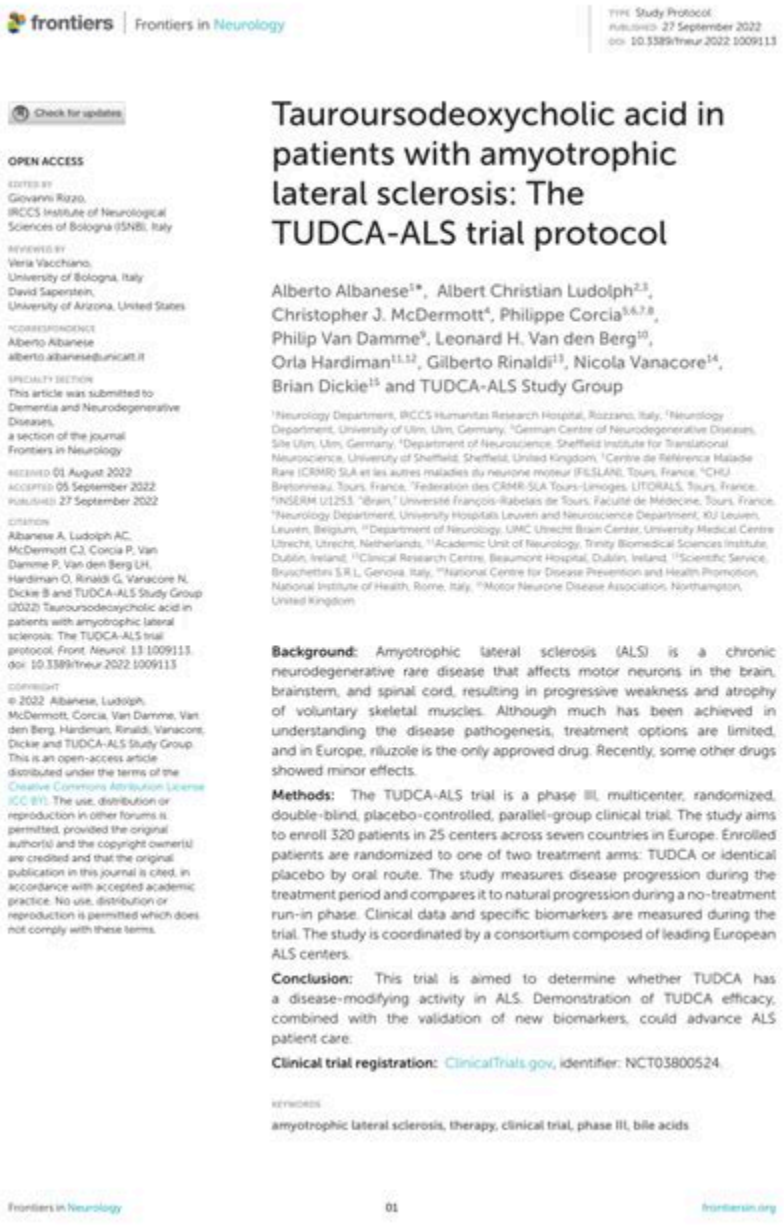



**Figure 1.** Chemical structure of tauroursodeoxycholic acid, TUDCA.



Tauroursodeoxycholic acid (TUDCA) is an endogenous anti-apoptotic bile acid with potent neuroprotective properties in several experimental models of AD. We have previously reported the therapeutic efficacy of TUDCA treatment before amyloid plaque deposition in APP/PS1 double-transgenic mice.

**Tauroursodeoxycholic acid in patients with amyotrophic lateral .**



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# Tauroursodeoxycholic acid in patients with amyotrophic lateral sclerosis: The TUDCA-ALS trial protocol

Alberto Albanese[1]*, Albert Christian Ludolph[2,3], Christopher J. McDermott[4], Philippe Corcia[5,6,7,8], Philip Van Damme[9], Leonard H. Van den Berg[10], Orla Hardiman[11,12], Gilberto Rinaldi[13], Nicola Vanacore[14], Brian Dickie[15] and TUDCA-ALS Study Group

[1]Neurology Department, IRCCS Humanitas Research Hospital, Rozzano, Italy, [2]Neurology Department, University of Ulm, Ulm, Germany, [3]German Centre of Neurodegenerative Diseases, Site Ulm, Ulm, Germany, [4]Department of Neuroscience, Sheffield Institute for Translational Neuroscience, University of Sheffield, Sheffield, United Kingdom, [5]Centre de Référence Maladie Rare (CRMR) SLA et les autres maladies du neurone moteur (FILSLAN), Tours, France, [6]CHU Bretonneau, Tours, France, [7]Federation des CRMR SLA Tours-Limoges, LITORALS, Tours, France, [8]INSERM U1253, "iBrain," Université François-Rabelais de Tours, Faculté de Médecine, Tours, France, [9]Neurology Department, University Hospitals Leuven and Neuroscience Department, KU Leuven, Leuven, Belgium, [10]Department of Neurology, UMC Utrecht Brain Center, University Medical Centre Utrecht, Utrecht, Netherlands, [11]Academic Unit of Neurology, Trinity Biomedical Sciences Institute, Dublin, Ireland, [12]Clinical Research Centre, Beaumont Hospital, Dublin, Ireland, [13]Scientific Service, Brusichettini S.R.L, Genova, Italy, [14]National Centre for Disease Prevention and Health Promotion, National Institute of Health, Rome, Italy, [15]Motor Neurone Disease Association, Northampton, United Kingdom

**Background:** Amyotrophic lateral sclerosis (ALS) is a chronic neurodegenerative rare disease that affects motor neurons in the brain, brainstem, and spinal cord, resulting in progressive weakness and atrophy of voluntary skeletal muscles. Although much has been achieved in understanding the disease pathogenesis, treatment options are limited, and in Europe, riluzole is the only approved drug. Recently, some other drugs showed minor effects.

**Methods:** The TUDCA-ALS trial is a phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group clinical trial. The study aims to enroll 320 patients in 25 centers across seven countries in Europe. Enrolled patients are randomized to one of two treatment arms: TUDCA or identical placebo by oral route. The study measures disease progression during the treatment period and compares it to natural progression during a no-treatment run-in phase. Clinical data and specific biomarkers are measured during the trial. The study is coordinated by a consortium composed of leading European ALS centers.

**Conclusion:** This trial is aimed to determine whether TUDCA has a disease-modifying activity in ALS. Demonstration of TUDCA efficacy, combined with the validation of new biomarkers, could advance ALS patient care.

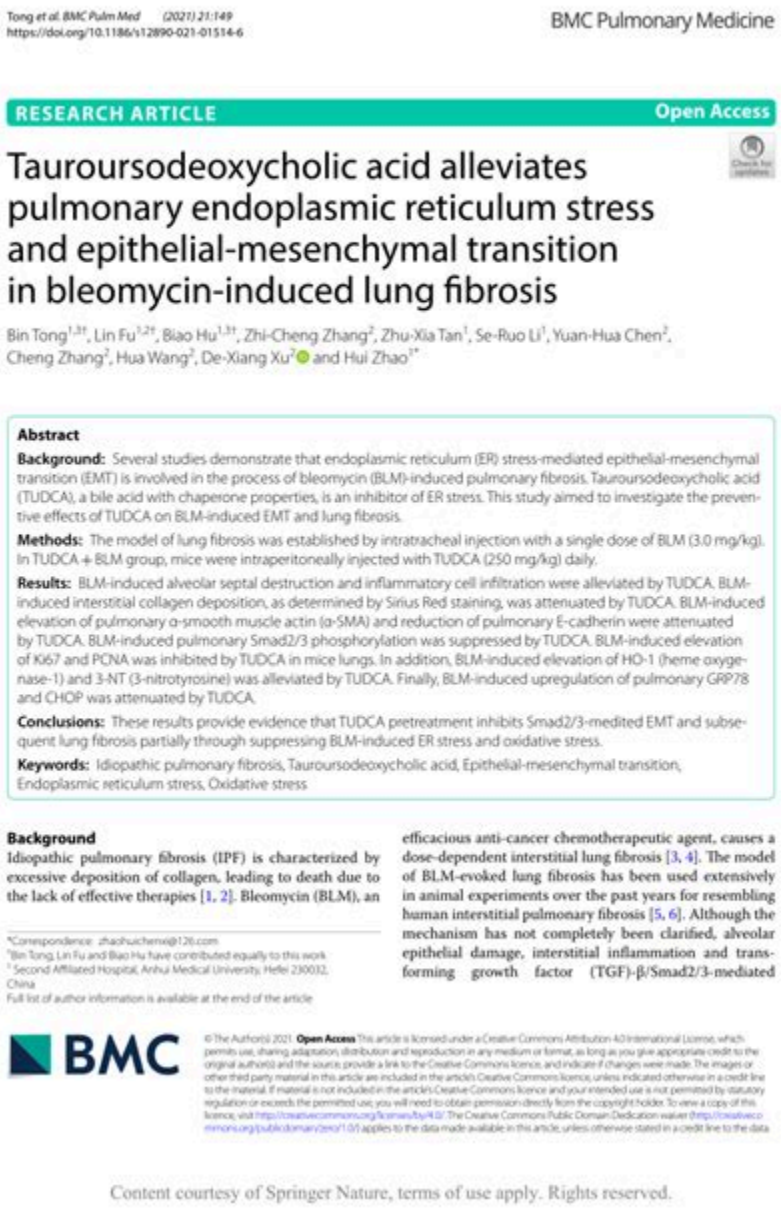
**Clinical trial registration:** ClinicalTrials.gov, identifier: NCT03800524.

KEYWORDS
amyotrophic lateral sclerosis, therapy, clinical trial, phase III, bile acids



TUDCA treatment (500 mg/kg, i. p. , every 3 days) for 3 months significantly decreased Aβ deposition (Aβ40 and Aβ42) in the frontal cortex and hippocampus (Dionisio et al. , 2015). The amyloidogenic processing of amyloid precursor protein was also reduced, indicating that TUDCA interferes with Aβ production.

# Tauroursodeoxycholic acid alleviates pulmonary endoplasmic reticulum .



Tong et al. BMC Pulm Med (2021) 21:149
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BMC Pulmonary Medicine

RESEARCH ARTICLE Open Access

## Tauroursodeoxycholic acid alleviates pulmonary endoplasmic reticulum stress and epithelial-mesenchymal transition in bleomycin-induced lung fibrosis

Bin Tong[1,3†], Lin Fu[1,2†], Biao Hu[1,3†], Zhi-Cheng Zhang[2], Zhu-Xia Tan[1], Se-Ruo Li[1], Yuan-Hua Chen[2], Cheng Zhang[2], Hua Wang[2], De-Xiang Xu[2] and Hui Zhao[1*]

**Abstract**

**Background:** Several studies demonstrate that endoplasmic reticulum (ER) stress-mediated epithelial-mesenchymal transition (EMT) is involved in the process of bleomycin (BLM)-induced pulmonary fibrosis. Tauroursodeoxycholic acid (TUDCA), a bile acid with chaperone properties, is an inhibitor of ER stress. This study aimed to investigate the preventive effects of TUDCA on BLM-induced EMT and lung fibrosis.

**Methods:** The model of lung fibrosis was established by intratracheal injection with a single dose of BLM (3.0 mg/kg). In TUDCA + BLM group, mice were intraperitoneally injected with TUDCA (250 mg/kg) daily.

**Results:** BLM-induced alveolar septal destruction and inflammatory cell infiltration were alleviated by TUDCA. BLM-induced interstitial collagen deposition, as determined by Sirius Red staining, was attenuated by TUDCA. BLM-induced elevation of pulmonary α-smooth muscle actin (α-SMA) and reduction of pulmonary E-cadherin were attenuated by TUDCA. BLM-induced pulmonary Smad2/3 phosphorylation was suppressed by TUDCA. BLM-induced elevation of Ki67 and PCNA was inhibited by TUDCA in mice lungs. In addition, BLM-induced elevation of HO-1 (heme oxygenase-1) and 3-NT (3-nitrotyrosine) was alleviated by TUDCA. Finally, BLM-induced upregulation of pulmonary GRP78 and CHOP was attenuated by TUDCA.

**Conclusions:** These results provide evidence that TUDCA pretreatment inhibits Smad2/3-medited EMT and subsequent lung fibrosis partially through suppressing BLM-induced ER stress and oxidative stress.

**Keywords:** Idiopathic pulmonary fibrosis, Tauroursodeoxycholic acid, Epithelial-mesenchymal transition, Endoplasmic reticulum stress, Oxidative stress

### Background

Idiopathic pulmonary fibrosis (IPF) is characterized by excessive deposition of collagen, leading to death due to the lack of effective therapies [1, 2]. Bleomycin (BLM), an efficacious anti-cancer chemotherapeutic agent, causes a dose-dependent interstitial lung fibrosis [3, 4]. The model of BLM-evoked lung fibrosis has been used extensively in animal experiments over the past years for resembling human interstitial pulmonary fibrosis [5, 6]. Although the mechanism has not completely been clarified, alveolar epithelial damage, interstitial inflammation and transforming growth factor (TGF)-β/Smad2/3-mediated

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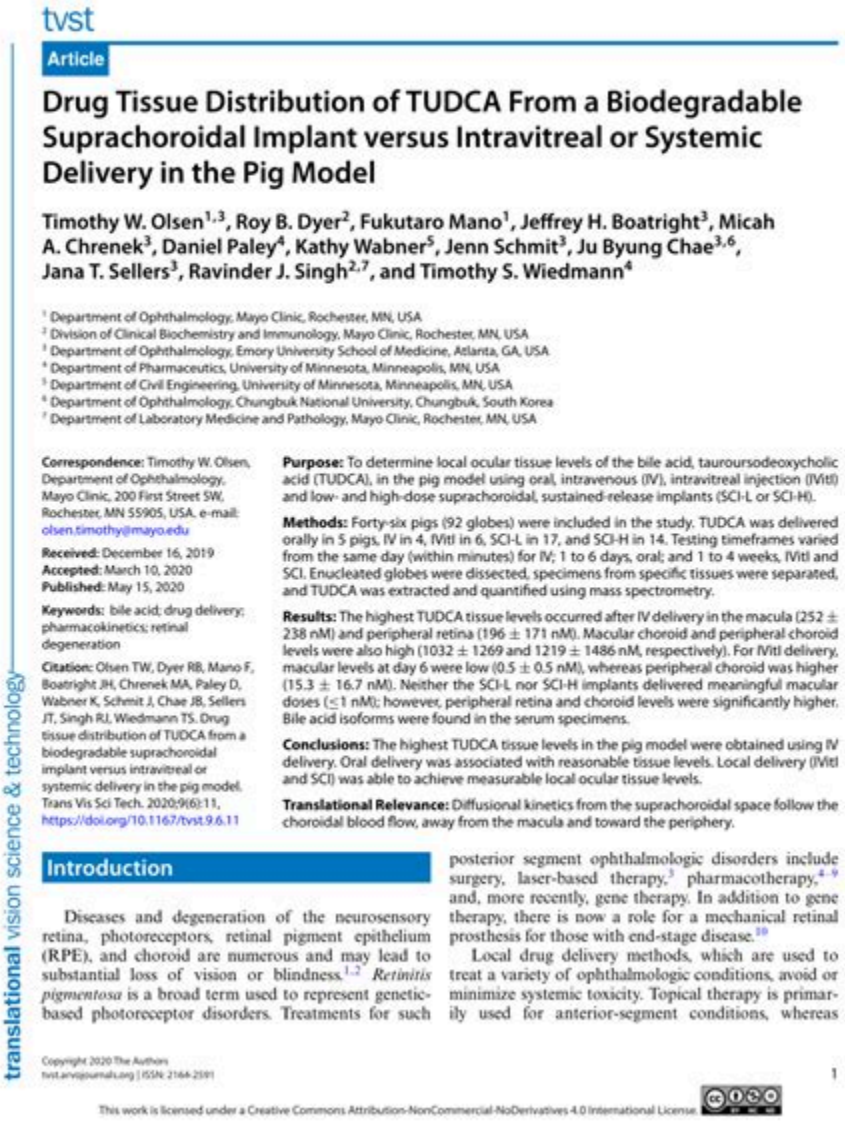
†Bin Tong, Lin Fu and Biao Hu have contributed equally to this work
[1] Second Affiliated Hospital, Anhui Medical University, Hefei 230032, China
Full list of author information is available at the end of the article



Tauroursodeoxycholic acid (TUDCA), a bile acid with chaperone properties, is an inhibitor of ER stress. This study aimed to investigate the preventive effects of TUDCA on BLM-induced EMT and lung fibrosis. Methods. The model of lung fibrosis was established by intratracheal injection with a single dose of BLM (3. 0 mg/kg). In TUDCA + BLM group .

**Drug Tissue Distribution of TUDCA From a Biodegradable Suprachoroidal .**



tvst

Article

# Drug Tissue Distribution of TUDCA From a Biodegradable Suprachoroidal Implant versus Intravitreal or Systemic Delivery in the Pig Model

Timothy W. Olsen[1,3], Roy B. Dyer[2], Fukutaro Mano[1], Jeffrey H. Boatright[3], Micah A. Chrenek[3], Daniel Paley[4], Kathy Wabner[5], Jenn Schmit[3], Ju Byung Chae[3,6], Jana T. Sellers[3], Ravinder J. Singh[2,7], and Timothy S. Wiedmann[4]

[1] Department of Ophthalmology, Mayo Clinic, Rochester, MN, USA
[2] Division of Clinical Biochemistry and Immunology, Mayo Clinic, Rochester, MN, USA
[3] Department of Ophthalmology, Emory University School of Medicine, Atlanta, GA, USA
[4] Department of Pharmaceutics, University of Minnesota, Minneapolis, MN, USA
[5] Department of Civil Engineering, University of Minnesota, Minneapolis, MN, USA
[6] Department of Ophthalmology, Chungbuk National University, Chungbuk, South Korea
[7] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA

**Correspondence:** Timothy W. Olsen, Department of Ophthalmology, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA. e-mail: olsen.timothy@mayo.edu

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**Accepted:** March 10, 2020
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**Keywords:** bile acid; drug delivery; pharmacokinetics; retinal degeneration

**Citation:** Olsen TW, Dyer RB, Mano F, Boatright JH, Chrenek MA, Paley D, Wabner K, Schmit J, Chae JB, Sellers JT, Singh RJ, Wiedmann TS. Drug tissue distribution of TUDCA from a biodegradable suprachoroidal implant versus intravitreal or systemic delivery in the pig model. Trans Vis Sci Tech. 2020;9(6):11, https://doi.org/10.1167/tvst.9.6.11

**Purpose:** To determine local ocular tissue levels of the bile acid, tauroursodeoxycholic acid (TUDCA), in the pig model using oral, intravenous (IV), intravitreal injection (IVitI) and low- and high-dose suprachoroidal, sustained-release implants (SCI-L or SCI-H).

**Methods:** Forty-six pigs (92 globes) were included in the study. TUDCA was delivered orally in 5 pigs, IV in 4, IVitI in 6, SCI-L in 17, and SCI-H in 14. Testing timeframes varied from the same day (within minutes) for IV; 1 to 6 days, oral; and 1 to 4 weeks, IVitI and SCI. Enucleated globes were dissected, specimens from specific tissues were separated, and TUDCA was extracted and quantified using mass spectrometry.

**Results:** The highest TUDCA tissue levels occurred after IV delivery in the macula (252 ± 238 nM) and peripheral retina (196 ± 171 nM). Macular choroid and peripheral choroid levels were also high (1032 ± 1269 and 1219 ± 1486 nM, respectively). For IVitI delivery, macular levels at day 6 were low (0.5 ± 0.5 nM), whereas peripheral choroid was higher (15.3 ± 16.7 nM). Neither the SCI-L nor SCI-H implants delivered meaningful macular doses (≤1 nM); however, peripheral retina and choroid levels were significantly higher. Bile acid isoforms were found in the serum specimens.

**Conclusions:** The highest TUDCA tissue levels in the pig model were obtained using IV delivery. Oral delivery was associated with reasonable tissue levels. Local delivery (IVitI and SCI) was able to achieve measurable local ocular tissue levels.

**Translational Relevance:** Diffusional kinetics from the suprachoroidal space follow the choroidal blood flow, away from the macula and toward the periphery.

## Introduction

Diseases and degeneration of the neurosensory retina, photoreceptors, retinal pigment epithelium (RPE), and choroid are numerous and may lead to substantial loss of vision or blindness.[1,2] *Retinitis pigmentosa* is a broad term used to represent genetic-based photoreceptor disorders. Treatments for such posterior segment ophthalmologic disorders include surgery, laser-based therapy,[3] pharmacotherapy,[4–9] and, more recently, gene therapy. In addition to gene therapy, there is now a role for a mechanical retinal prosthesis for those with end-stage disease.[10]

Local drug delivery methods, which are used to treat a variety of ophthalmologic conditions, avoid or minimize systemic toxicity. Topical therapy is primarily used for anterior-segment conditions, whereas


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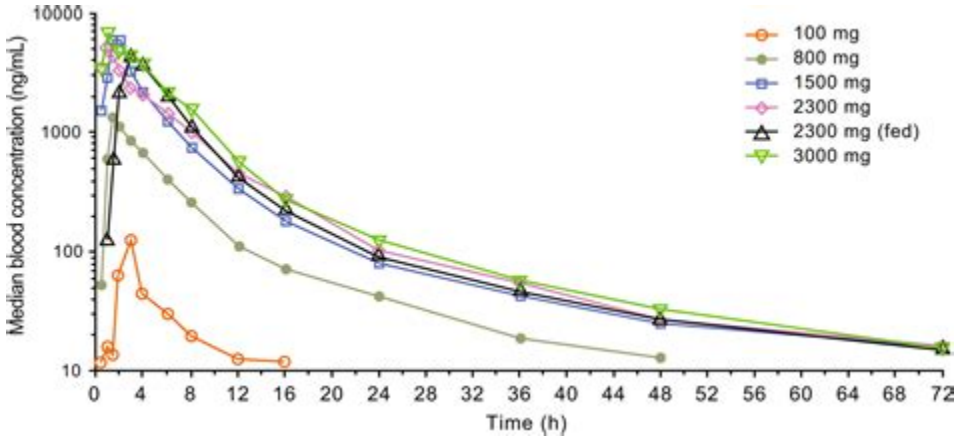
translational vision science & technology

Star 1 Summary Tauroursodeoxycholic acid is the taurine conjugate of ursodeoxycholic acid with antiapoptotic and ER stress response dampening effects used in some countries to treat gallstones. It is also being investigated for a wide variety of other conditions. Brand Names Relyvrio Generic Name Tauroursodeoxycholic acid DrugBank Accession Number

## Pharmacokinetics, Safety, and Tolerability of Orally Administered .

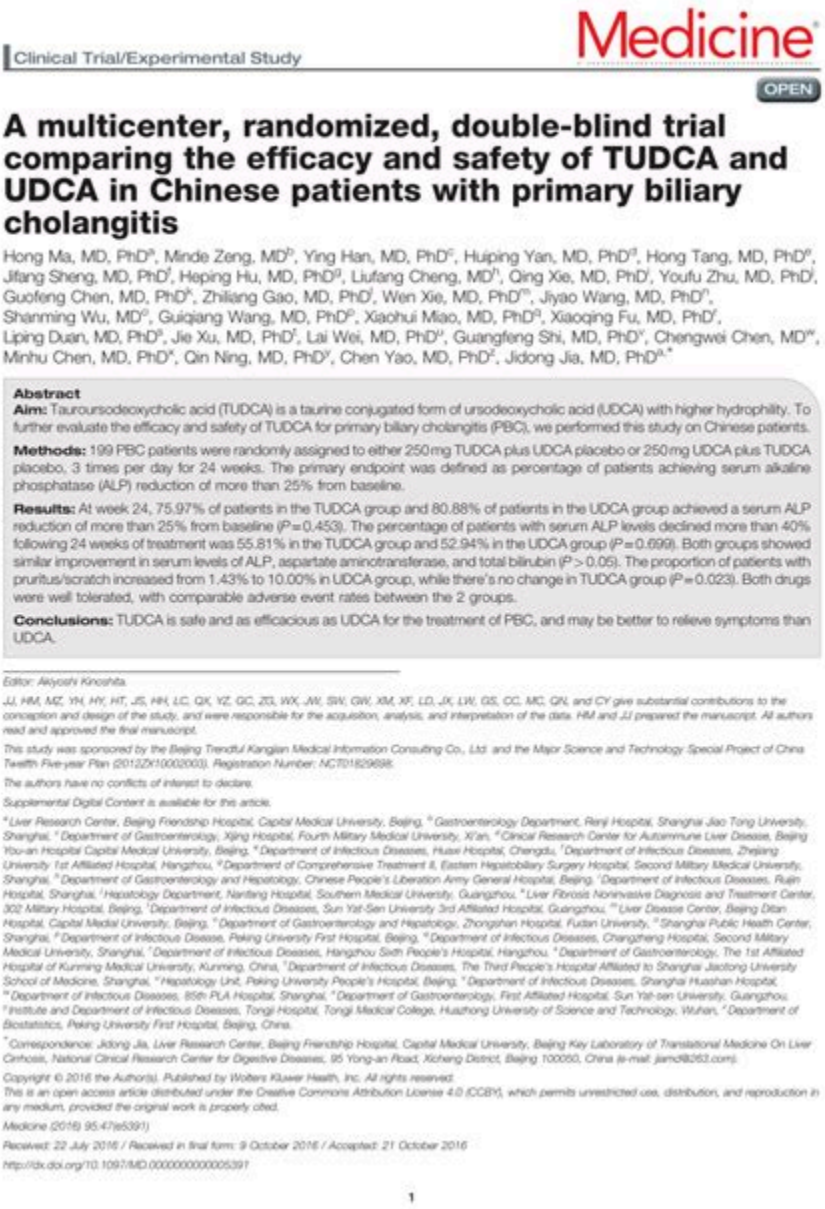



Written by Dr. Frederick J. Marshall Published on October 13, 2022 Contents hide What is TUDCA? TUDCA for Bodybuilding How does TUDCA Work? TUDCA Benefits 1) Reduces Cholestasis Caused by liver injury 2) Improves liver enzyme levels 3) Ameliorates liver cirrhosis symptoms 4) Improves Hepatitis C symptoms 5) Reduces disability in ALS patients

## TUDCA 101: The Ultimate A-Z Guide for Beginners (2022) - Nanotech Project


Tauroursodeoxycholic acid is a naturally occurring hydrophilic bile acid which is the taurine conjugated form of ursodeoxycholic acid (UDCA). Humans have only trace amounts of tauroursodeoxycholic acid but bears have large amounts of tauroursodeoxycholic acid and ursodeoxycholic acid in their bile. [1] Synthesis

**Trial: Safety and Efficacy of TUDCA as add-on Treatment in Patients .**



Clinical Trial/Experimental Study

Medicine

OPEN

# A multicenter, randomized, double-blind trial comparing the efficacy and safety of TUDCA and UDCA in Chinese patients with primary biliary cholangitis

Hong Ma, MD, PhD[a], Minde Zeng, MD[b], Ying Han, MD, PhD[c], Huiping Yan, MD, PhD[d], Hong Tang, MD, PhD[e], Jifang Sheng, MD, PhD[f], Heping Hu, MD, PhD[g], Liufang Cheng, MD[h], Qing Xie, MD, PhD[i], Youfu Zhu, MD, PhD[j], Guofeng Chen, MD, PhD[k], Zhiliang Gao, MD, PhD[l], Wen Xie, MD, PhD[m], Jiyao Wang, MD, PhD[n], Shanming Wu, MD[o], Guiqiang Wang, MD, PhD[p], Xiaohui Miao, MD, PhD[q], Xiaoqing Fu, MD, PhD[r], Liping Duan, MD, PhD[s], Jie Xu, MD, PhD[t], Lai Wei, MD, PhD[u], Guangfeng Shi, MD, PhD[v], Chengwei Chen, MD[w], Minhu Chen, MD, PhD[x], Qin Ning, MD, PhD[y], Chen Yao, MD, PhD[z], Jidong Jia, MD, PhD[a,*]

**Abstract**

**Aim:** Tauroursodeoxycholic acid (TUDCA) is a taurine conjugated form of ursodeoxycholic acid (UDCA) with higher hydrophility. To further evaluate the efficacy and safety of TUDCA for primary biliary cholangitis (PBC), we performed this study on Chinese patients.

**Methods:** 199 PBC patients were randomly assigned to either 250 mg TUDCA plus UDCA placebo or 250 mg UDCA plus TUDCA placebo, 3 times per day for 24 weeks. The primary endpoint was defined as percentage of patients achieving serum alkaline phosphatase (ALP) reduction of more than 25% from baseline.

**Results:** At week 24, 75.97% of patients in the TUDCA group and 80.88% of patients in the UDCA group achieved a serum ALP reduction of more than 25% from baseline ($P = 0.453$). The percentage of patients with serum ALP levels declined more than 40% following 24 weeks of treatment was 55.81% in the TUDCA group and 52.94% in the UDCA group ($P = 0.699$). Both groups showed similar improvement in serum levels of ALP, aspartate aminotransferase, and total bilirubin ($P > 0.05$). The proportion of patients with pruritus/scratch increased from 1.43% to 10.00% in UDCA group, while there's no change in TUDCA group ($P = 0.023$). Both drugs were well tolerated, with comparable adverse event rates between the 2 groups.

**Conclusions:** TUDCA is safe and as efficacious as UDCA for the treatment of PBC, and may be better to relieve symptoms than UDCA.

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JJ, HM, MZ, YH, HY, HT, JS, HH, LC, QX, YZ, GC, ZG, WX, JW, SW, GW, XM, XF, LD, JX, LW, GS, CC, MC, QN, and CY give substantial contributions to the conception and design of the study, and were responsible for the acquisition, analysis, and interpretation of the data. HM and JJ prepared the manuscript. All authors read and approved the final manuscript.

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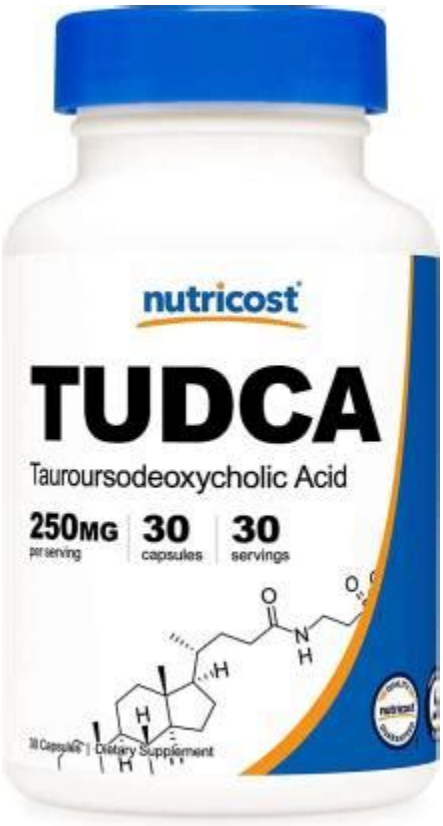
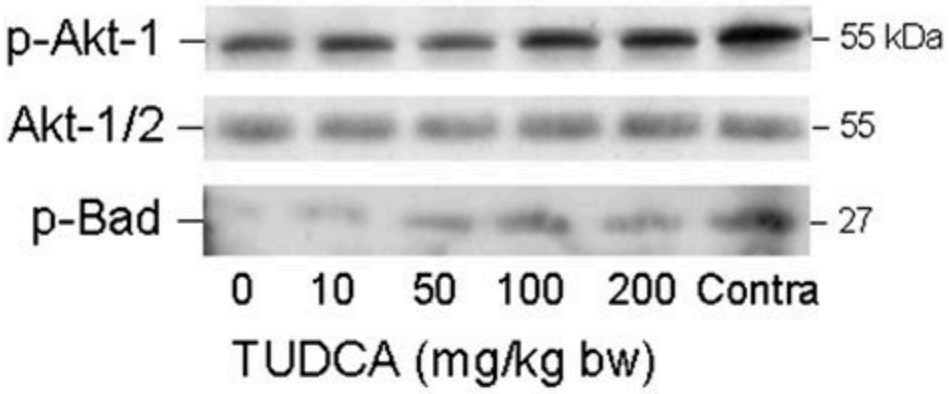
Dr. Eric Berg 08/31/2023 The benefits of TUDCA (tauroursodeoxycholic acid) are numerous it is a potent bile salt that's naturally found in the body. As a supplement, it has a wide range of health benefits, from improving digestion to reducing inflammation. Find out why TUDCA is so powerful and learn the best ways to use it. What is TUDCA?

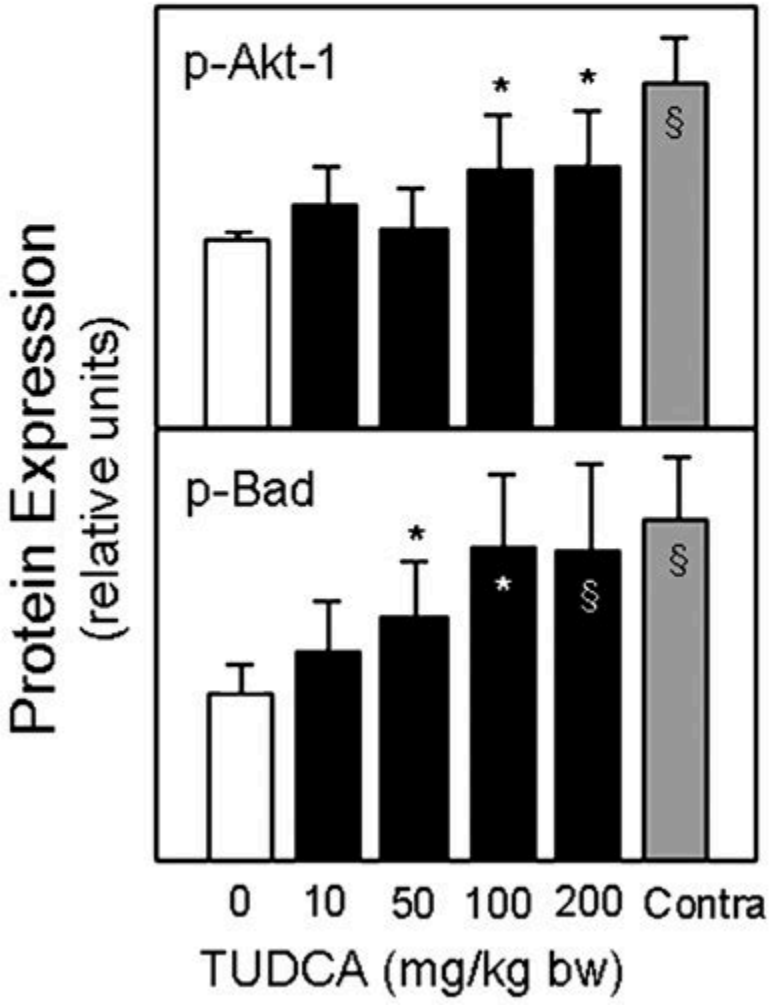
## Tauroursodeoxycholic acid - DrugBank Online




TUDCA. TUDCA is a water soluble bile acid. It shows great potency in treating cholestasis (bile acid backup in the liver) as the water soluble bile acids counteract the toxicity of regular bile acids. Can also protect and rehabilitate the liver, and general protects cells; very promising molecule. TUDCA is most often used for Liver Health and .

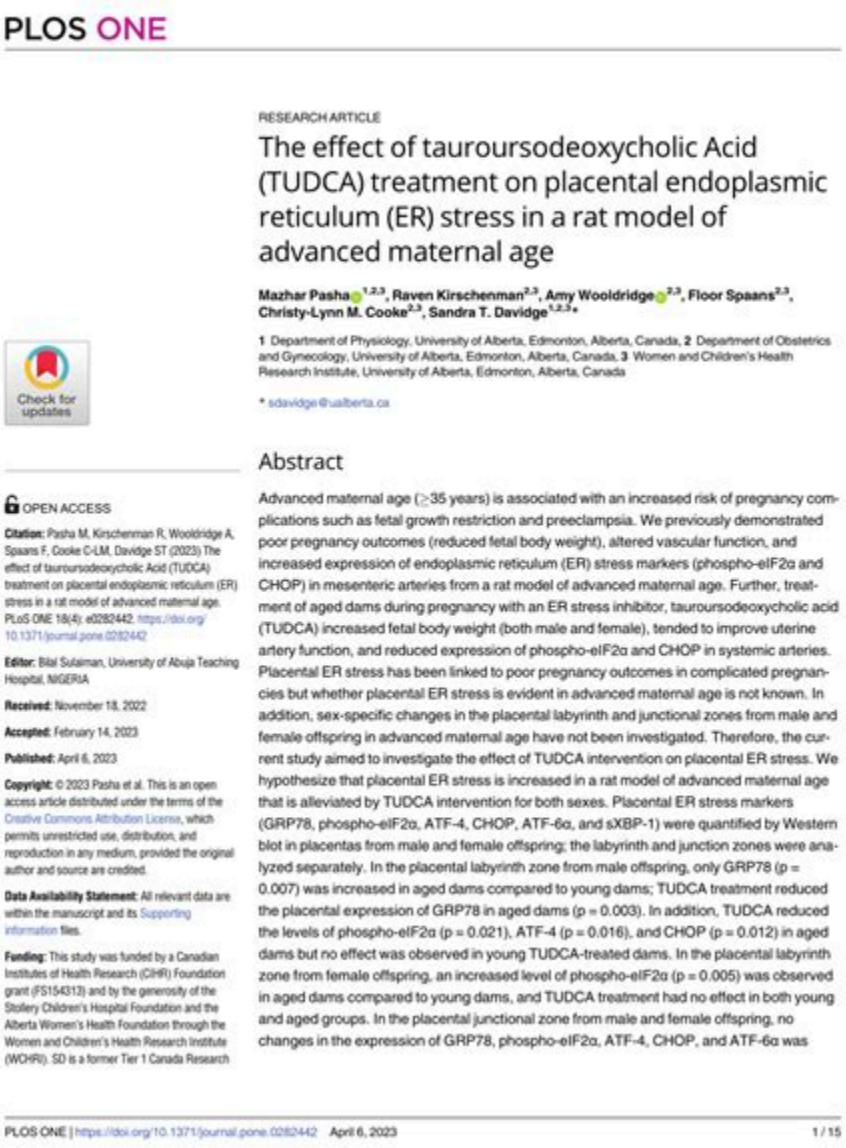
**Tauroursodeoxycholic acid reduces apoptosis and protects against . - PNAS**




TUDCA is one such compound that is known for its chaperoning activity [12,13,14,15]. Until now, various studies have demonstrated good efficiency of TUDCA in alleviating or resolving ER stress, playing a role as a chemical chaperone; however, the exact chemical interactions involved in such activity are still debatable [18,19,20,21,22,23].

**Effect of tauroursodeoxycholic acid on survival and safety in .**



PLOS ONE

RESEARCH ARTICLE

# The effect of tauroursodeoxycholic Acid (TUDCA) treatment on placental endoplasmic reticulum (ER) stress in a rat model of advanced maternal age

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## Abstract

Advanced maternal age (≥35 years) is associated with an increased risk of pregnancy complications such as fetal growth restriction and preeclampsia. We previously demonstrated poor pregnancy outcomes (reduced fetal body weight), altered vascular function, and increased expression of endoplasmic reticulum (ER) stress markers (phospho-eIF2α and CHOP) in mesenteric arteries from a rat model of advanced maternal age. Further, treatment of aged dams during pregnancy with an ER stress inhibitor, tauroursodeoxycholic acid (TUDCA) increased fetal body weight (both male and female), tended to improve uterine artery function, and reduced expression of phospho-eIF2α and CHOP in systemic arteries. Placental ER stress has been linked to poor pregnancy outcomes in complicated pregnancies but whether placental ER stress is evident in advanced maternal age is not known. In addition, sex-specific changes in the placental labyrinth and junctional zones from male and female offspring in advanced maternal age have not been investigated. Therefore, the current study aimed to investigate the effect of TUDCA intervention on placental ER stress. We hypothesize that placental ER stress is increased in a rat model of advanced maternal age that is alleviated by TUDCA intervention for both sexes. Placental ER stress markers (GRP78, phospho-eIF2α, ATF-4, CHOP, ATF-6α, and sXBP-1) were quantified by Western blot in placentas from male and female offspring; the labyrinth and junction zones were analyzed separately. In the placental labyrinth zone from male offspring, only GRP78 ($p = 0.007$) was increased in aged dams compared to young dams; TUDCA treatment reduced the placental expression of GRP78 in aged dams ($p = 0.003$). In addition, TUDCA reduced the levels of phospho-eIF2α ($p = 0.021$), ATF-4 ($p = 0.016$), and CHOP ($p = 0.012$) in aged dams but no effect was observed in young TUDCA-treated dams. In the placental labyrinth zone from female offspring, an increased level of phospho-eIF2α ($p = 0.005$) was observed in aged dams compared to young dams, and TUDCA treatment had no effect in both young and aged groups. In the placental junctional zone from male and female offspring, no changes in the expression of GRP78, phospho-eIF2α, ATF-4, CHOP, and ATF-6α was



Noncompartmental pharmacokinetic analysis resulted in (mean ± standard deviation) a maximum concentration of 8749 ± 2840 ng/mL and half-life of 2. 1 ± 0. 71 hr. Magnetic resonance spectroscopy data were obtained in 3 individuals with Parkinson's disease and showed modest increases in ATP and decreases in ATPase activity.

## The Unexpected Uses of Urso- and Tauroursodeoxycholic Acid in the .

The median overall survival was 49. 6 months (95% CI 41. 7-93. 5) among those treated with TUDCA and 36. 2 months (95% CI 32. 7-41. 6) in the control group, with a reduced risk of death observed in patients exposed to a higher dosage (defined as ≥ 1000 mg/day) of TUDCA (HR 0. 56; 95% CI 0. 38-0. 83; p = 0. 0042) compared to both the control group and thos.

**The bile acid TUDCA reduces age-related hyperinsulinemia in mice - Nature**

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# The bile acid TUDCA reduces age-related hyperinsulinemia in mice

Lucas Zangerolamo, Marina Carvalho, Leticia Barssotti, Gabriela M. Soares, Carine Marmentini, Antonio C. Boschero & Helena Cristina L. Barbosa

Aging is associated with glucose metabolism disturbances, such as insulin resistance and hyperinsulinemia, which contribute to the increased prevalence of type 2 diabetes (T2D) and its complications in the elderly population. In this sense, some bile acids have emerged as new therapeutic targets to treat TD2, as well as associated metabolic disorders. The taurine conjugated bile acid, tauroursodeoxycholic acid (TUDCA) improves glucose homeostasis in T2D, obesity, and Alzheimer's disease mice model. However, its effects in aged mice have not been explored yet. Here, we evaluated the actions of TUDCA upon glucose-insulin homeostasis in aged C57BL/6 male mice (18-month-old) treated with 300 mg/kg of TUDCA or its vehicle. TUDCA attenuated hyperinsulinemia and improved glucose homeostasis in aged mice, by enhancing liver insulin-degrading enzyme (IDE) expression and insulin clearance. Furthermore, the improvement in glucose-insulin homeostasis in these mice was accompanied by a reduction in adiposity, associated with adipocyte hypertrophy, and lipids accumulation in the liver. TUDCA-treated aged mice also displayed increased energy expenditure and metabolic flexibility, as well as a better cognitive ability. Taken together, our data highlight TUDCA as an interesting target for the attenuation of age-related hyperinsulinemia and its deleterious effects on metabolism.

**Abbreviations**

| | |
|---|---|
| AD | Alzheimer's disease |
| ANOVA | One-way analysis of variance |
| AUC | Area under the curve |
| CIDEA | Cell death-inducing DNA fragmentation factor alpha-like effector A |
| CHOL | Cholesterol |
| CNS | Central nervous system |
| COX7A1 | Cytochrome c oxidase subunit 7A1 |
| COX8B | Cytochrome c oxidase subunit 8B |
| DIO2 | Iodothyronine deiodinase 2 |
| EE | Energy expenditure |
| ELISA | Enzyme-linked immunosorbent assay |
| ER | Endoplasmic reticulum |
| eWAT | Epididymal white adipose tissue |
| FXR | Farnesoid X receptor |
| GAPDH | Glyceraldehyde-3-phosphate dehydrogenase |
| GSIS | Glucose-stimulated insulin secretion |
| GTT | Glucose tolerance test |
| H&E | Hematoxylin and eosin |
| iBAT | Interscapular brown adipose tissue |
| IDE | Insulin-degrading enzyme |
| ITT | Insulin tolerance test |
| iWAT | Inguinal white adipose tissue |
| kITT | Constant rate for glucose disappearance |
| PBS | Phosphate buffer saline |
| PPARGC1a | Peroxisome proliferator-activated receptor gamma coactivator 1 alpha |

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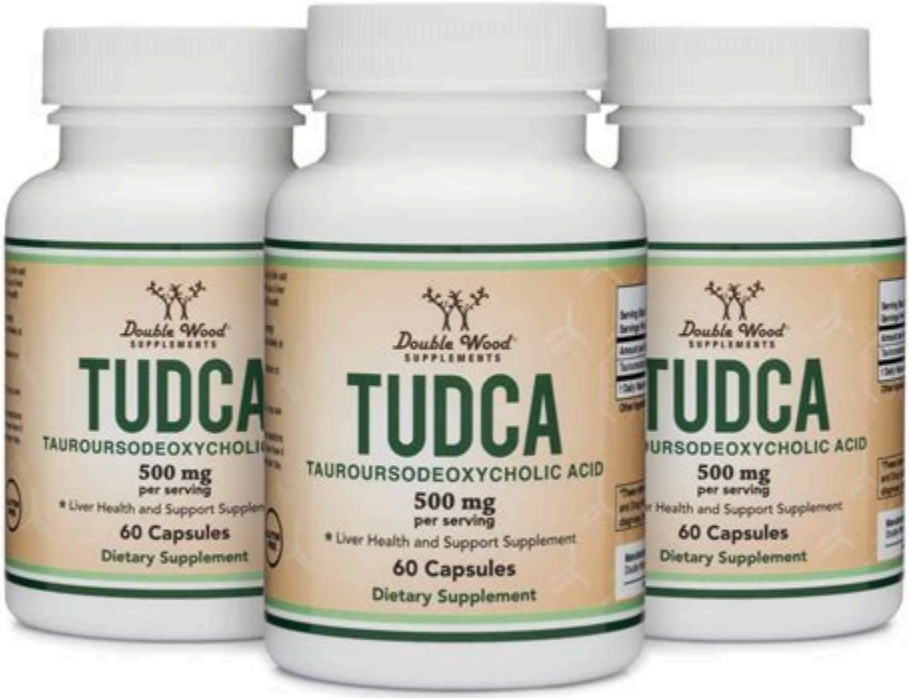
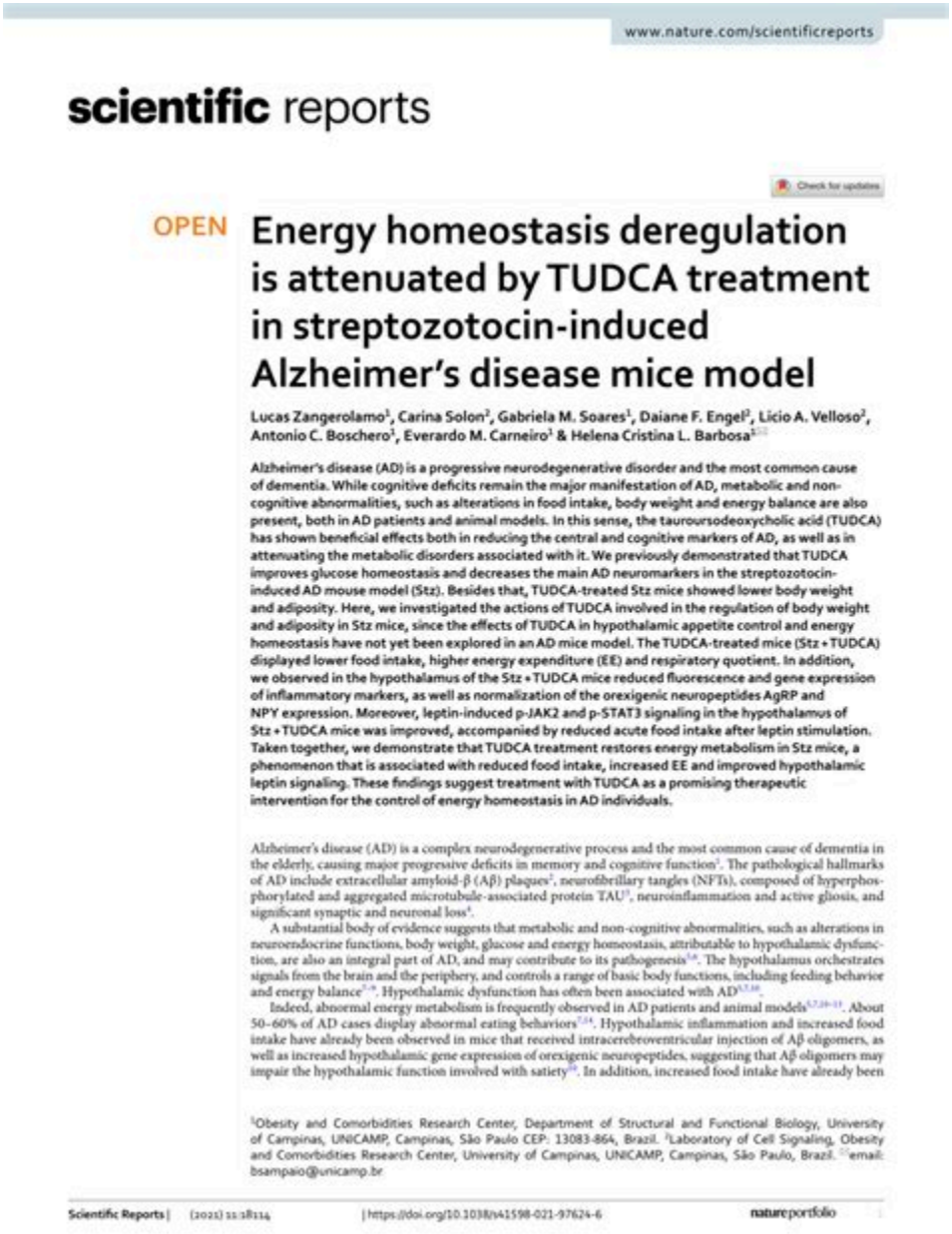
Tauroursodeoxycholic acid (TUDCA) is the taurine conjugate of ursodeoxycholic acid (UDCA), a US Food and Drug Administration-approved hydrophilic bile acid for the treatment of certain cholestatic liver diseases.

# TUDCA: Tauroursodeoxycholic Acid - HOPES Huntington's Disease




TUDCA is taken up by the liver and excreted directly into bile, thus entering the enterohepatic circulation; in part, it is excreted with feces. Bile salts, including TUDCA, play a role in intestinal homeostasis by controlling the size and the composition of the intestinal microbiota (5, 12). Clinical studies performed on patients with .

**Energy homeostasis deregulation is attenuated by TUDCA . - Nature**



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# Energy homeostasis deregulation is attenuated by TUDCA treatment in streptozotocin-induced Alzheimer's disease mice model

Lucas Zangerolamo[1], Carina Solon[2], Gabriela M. Soares[1], Daiane F. Engel[2], Licio A. Velloso[2], Antonio C. Boschero[1], Everardo M. Carneiro[1] & Helena Cristina L. Barbosa[1,2]

**Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most common cause of dementia. While cognitive deficits remain the major manifestation of AD, metabolic and non-cognitive abnormalities, such as alterations in food intake, body weight and energy balance are also present, both in AD patients and animal models. In this sense, the tauroursodeoxycholic acid (TUDCA) has shown beneficial effects both in reducing the central and cognitive markers of AD, as well as in attenuating the metabolic disorders associated with it. We previously demonstrated that TUDCA improves glucose homeostasis and decreases the main AD neuromarkers in the streptozotocin-induced AD mouse model (Stz). Besides that, TUDCA-treated Stz mice showed lower body weight and adiposity. Here, we investigated the actions of TUDCA involved in the regulation of body weight and adiposity in Stz mice, since the effects of TUDCA in hypothalamic appetite control and energy homeostasis have not yet been explored in an AD mice model. The TUDCA-treated mice (Stz + TUDCA) displayed lower food intake, higher energy expenditure (EE) and respiratory quotient. In addition, we observed in the hypothalamus of the Stz + TUDCA mice reduced fluorescence and gene expression of inflammatory markers, as well as normalization of the orexigenic neuropeptides AgRP and NPY expression. Moreover, leptin-induced p-JAK2 and p-STAT3 signaling in the hypothalamus of Stz + TUDCA mice was improved, accompanied by reduced acute food intake after leptin stimulation. Taken together, we demonstrate that TUDCA treatment restores energy metabolism in Stz mice, a phenomenon that is associated with reduced food intake, increased EE and improved hypothalamic leptin signaling. These findings suggest treatment with TUDCA as a promising therapeutic intervention for the control of energy homeostasis in AD individuals.**

Alzheimer's disease (AD) is a complex neurodegenerative process and the most common cause of dementia in the elderly, causing major progressive deficits in memory and cognitive function[1]. The pathological hallmarks of AD include extracellular amyloid-β (Aβ) plaques[2], neurofibrillary tangles (NFTs), composed of hyperphosphorylated and aggregated microtubule-associated protein TAU[3], neuroinflammation and active gliosis, and significant synaptic and neuronal loss[4].

A substantial body of evidence suggests that metabolic and non-cognitive abnormalities, such as alterations in neuroendocrine functions, body weight, glucose and energy homeostasis, attributable to hypothalamic dysfunction, are also an integral part of AD, and may contribute to its pathogenesis[5,6]. The hypothalamus orchestrates signals from the brain and the periphery, and controls a range of basic body functions, including feeding behavior and energy balance[7–9]. Hypothalamic dysfunction has often been associated with AD[5,7,10].

Indeed, abnormal energy metabolism is frequently observed in AD patients and animal models[5,7,10–13]. About 50–60% of AD cases display abnormal eating behaviors[7,14]. Hypothalamic inflammation and increased food intake have already been observed in mice that received intracerebroventricular injection of Aβ oligomers, as well as increased hypothalamic gene expression of orexigenic neuropeptides, suggesting that Aβ oligomers may impair the hypothalamic function involved with satiety[10]. In addition, increased food intake have already been

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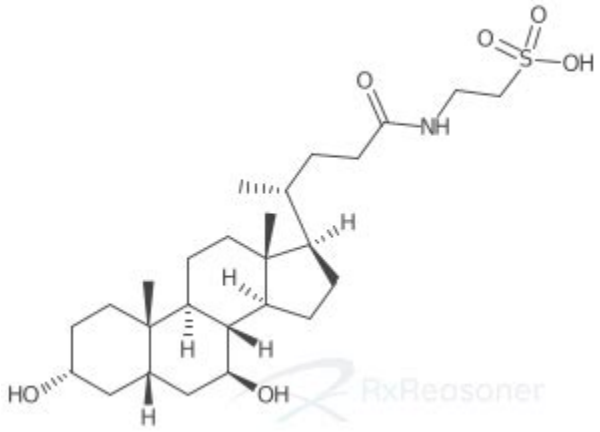
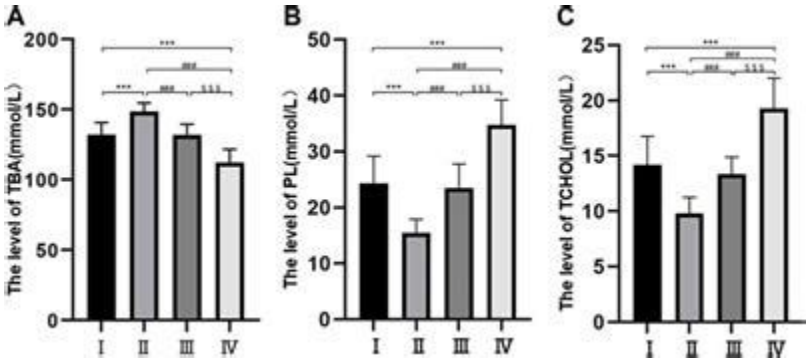
TUDCA will be administered orally at the dose of 1 g twice daily (2 g daily) for 18 months. Patients will be taking also riluzole at the dose of 50 mg twice daily (100 mg daily). Patient randomization will take place after a screening (lead-in) period of 12 weeks (3 months) with 3 assessments at 6-week intervals. .

## Ursodoxicoltaurine - Wikipedia




The ongoing TUDCA-ALS study is a double-blinded, parallel arms, placebo-controlled, randomized multicenter phase III trial with the aim to assess the efficacy and safety of TUDCA as add-on therapy to riluzole in patients with ALS.

## Frontiers | Tauroursodeoxycholic acid in patients with amyotrophic .




UDCA toxicity is related to its interference with drug detoxification, being hydrophilic and anti-apoptotic, has a long half-life, has transcriptional mutational abilities, down-regulates cellular functions, has a very narrow difference between the recommended (13 mg/kg/day) and toxic dose (28 mg/kg/day), and it typically transforms into lithoch.

- https://publiclab.org/notes/print/43150
- https://groups.google.com/g/musclemaestros/c/uYG2MY-vVTg
- https://drive.google.com/file/d/1Ndqm-DxdiI_T2XxHsC-_XUxlXTfZA_Vh/view?usp=sharing