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Review Article

The neuroprotective effect of ursodeoxycholic acid in different neurological diseases

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ABSTRACT

Bile acids are amphipathic molecules generated by the liver to act as detergents in which fat-soluble vitamins and dietary lipids are dissolved. They are a group of diverse molecules that differ in some properties, including hydrophilicity. The hydrophilic member, ursodeoxycholic acid (UDCA), is known for its cytoprotective characteristics. It has been authorized to be used as a first-line therapy for primary biliary cholangitis by the US Food and Drug Administration (FDA). Recently, its application has expanded to include extrahepatic conditions. Its several modes of action, which include lowering cell death and exhibiting anti-oxidant and anti-inflammatory properties, are responsible for this adaptability. A considerable number of studies have been conducted in recent years on how bile acids affect brain function, offering insightful information and creating new research opportunities. In this review, we outlined the potential use of UDCA as a treatment for various neurological diseases such as seizures, alzheimer's disease, parkinson's disease, Huntington's disease, and stroke, and for psychiatric conditions such as depression and anxiety.

Keywords: *Bile acids; ursodeoxycholic acid; cytoprotective, neurological diseases; seizures.*

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1. Bile acids

Bile acids, which are amphipathic molecules produced by the liver during digestion, are retained in the gall bladder and released into the intestinal lumen in response to meal consumption **[1, 2]**. Before being released into bile, bile acids are usually conjugated to amino acids, glycine, or taurine. It is significant to note that this conversion increases the polarity and, consequently, the solubility of these molecules **[3]**. The primary function of bile acids is to serve as detergents during the solubilization of dietary lipids and fat-soluble vitamins **[4]**. A significant amount of bile acids are either actively or passively retrieved throughout the gastrointestinal system before being recycled by the enterohepatic circulation in the liver, with a minor portion being eliminated as waste **[1]**. In addition, bile acids contribute to getting rid of excess cholesterol since they are produced in the liver using cholesterol as the precursor molecule **[5]**. Since the bile acids are diverse compounds, their effects on cells vary depending on how hydrophilic they are; although the hydrophobic ones may cause apoptosis, the hydrophilic ones have cytoprotective properties **[6, 7, 8]**.

1.1. Ursodeoxycholic acid (UDCA)

Ursodeoxycholic acid (UDCA) makes up only 3% of all bile acids, so it is found in trace concentrations in human bile. UDCA is

considered a 7-hydroxy epimer of the primary bile acid chenodeoxycholic acid (CDCA) **[9]**. UDCA is a hydrophilic bile acid that, when taken orally, quickly produces glycoursodeoxycholic acid (GUDCA) or tauroursodeoxycholic acid (TUDCA) by conjugation with glycine or taurine, respectively **[10]**. UDCA, also known by its brand name Ursodiol, is currently a commonly used medication for cholestatic hepatopathies and has been authorized by the US Food and Drug Administration (FDA) to be used as a first-line treatment for primary biliary cholangitis **[11, 12]**. Recently, its application has expanded to include extrahepatic conditions such as sensory neuropathy and inflammatory bowel disease. Its several modes of action, which include lowering cell death and exhibiting anti-oxidant and anti-inflammatory qualities besides inhibition of endoplasmic reticulum (ER) stress, are all responsible for this adaptability as shown in **Fig.1. [13,14]**.

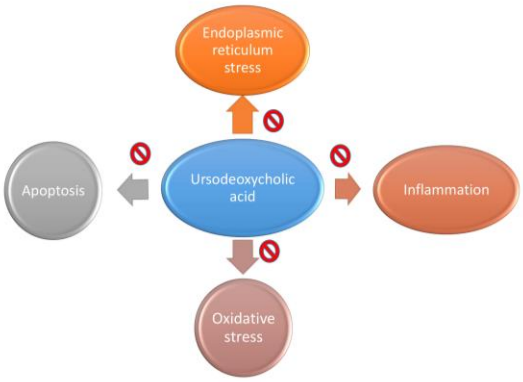

Fig. 1. Several modes of action of Ursodeoxycholic acid

2. Bile acids and neurological diseases

There are several causes of neurodegenerative disorders. Although the precise mechanism behind the pathophysiology of each disease state differs, they are all similar in the following ways: Misfolded or mutant protein accumulation, abnormal ER stress, and exaggerated neuroinflammation, causing extensive neuronal death and brain atrophy **[1,15]**. A considerable number of studies have been conducted in recent years on how bile acids affect brain function, offering insightful information and creating new research opportunities. Bile acids are believed to enter the brain through the systemic circulation, besides their production inside the brain. Therefore, there may be a connection between bile acids and both neurological function and neurological illness **[16, 17]**. As a result of the numerous positive results indicating that bile acids are advantageous in neurodegenerative models, several registered clinical trials were carried out to show their efficacy in humans. The clinical trials encompassed several neurological diseases such as Alzheimer's disease, Parkinson's disease, Huntington's disease, and amyotrophic lateral sclerosis **[18]**.

In this review, we outlined the bile acids' potential as a treatment for various neurological and psychiatric conditions, as shown in **Fig. 2**, taking into consideration the experimental model used and the putative underlying mechanisms.

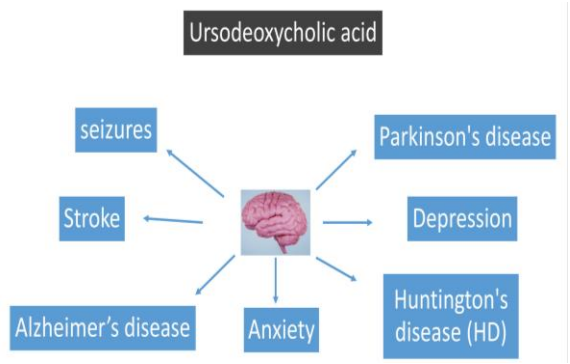

Fig. 2. Ursodeoxycholic acid's potential use as a treatment for various neurological and psychiatric conditions

2.1. Seizures

For thousands of years, Nature bear's bile powder (NBBP) has been used to treat febrile seizures in traditional Chinese therapeutic practice; however, due to ethical concerns, its use

is currently limited. The biotransformation-produced cultured bear bile powder (CBBP) could be an adequate alternative for NBBP. CBBP proved its anticonvulsant property in the rat model of febrile seizure through augmenting the GABAergic transmission and attenuating the neuroinflammation **[19]**. The TUDCA was used specifically to inhibit the ER stress in the pilocarpine model of status epilepticus in mice, which causes a subsequent reduction of nod-like receptor protein 3 (NLRP3) inflammasome activation, demonstrating the relationship between ER stress and NLRP3 inflammasome activation **[20]**. In the pentylenetetrazole (PTZ) model of epilepsy, the TUDCA showed protective effects in respiratory and cardiovascular conditions coexisting with seizures through controlling oxidative damage, inflammation, and cellular viability **[21]**. The vulnerability to PTZ-induced seizures increases with repeated exposure to stress. In the meantime, oxidative stress, hippocampal endoplasmic reticulum stress, and neuronal loss are triggered by repetitive restraint stress. Findings have demonstrated that TUDCA inhibits ER stress, which, in turn, prevents recurrent restraint stress-induced hippocampal neurotoxicity **[22]**. Moreover, the ER stress process in epileptic seizures can be suppressed by TUDCA and 4-phenyl-butyric acid combinatorial therapy **[23]**. A summary of the use of bile acids in experimental models of seizures is demonstrated in **Table 1**. However, to the best of our knowledge, no clinical trials involving seizures have been conducted on this medication.

2.2. Alzheimer’s disease

In an in vitro study, the UDCA reduced the production of nitric oxide and interleukin-1β in rat microglia exposed to amyloid-β (Aβ), a model for Alzheimer's disease **[24]**. In addition, in Alzheimer's disease model APP/PS1 double-knockout mice, TUDCA reduces amyloid β peptides and alleviates memory loss **[25, 26]**. Moreover, the TUDCA was able to reverse the metabolic changes and memory impairment in a mouse model of Alzheimer's disease caused by streptozotocin, as evidenced by the observed decrease in neuroinflammation and the brain's amyloid oligomer protein level **[27]**. According to recent clinical research, the levels of hydrophobic bile acids are significantly raised in the serum of alzheimer’s disease patients compared to the control individuals **[28]**. The pathological consequences of this alteration could be manifested by the disruption of blood-brain barrier integrity and an increase in the oxidation of docosahexaenoic acid to encourage the development of amyloid-β plaques **[29]**. One of the proposed therapeutic approaches is the use of UDCA to stimulate the biliary secretion of bile acids, thus lowering the serum levels of harmful bile acids **[9]**. A phase 2a clinical trial on TUDCA treatment showed a reduction in AD biomarkers, including phosphorylated tau-181. However, due to the small sample size and relatively short treatment duration, the therapy did not significantly improve the cognitive impairment **[30]**.

2.3. Parkinson's disease

According to the findings of both in vitro and in vivo studies, UDCA protected dopaminergic neurons and enhanced behavioral performance in MPTP mice; it also enhanced cell viability and reduced cell death in cells treated with MPP^+; it prevented ATP depletion, collapse of mitochondrial membrane potential, and reactive oxygen species accumulation in mouse neuroblastoma cells. Moreover, it regulated the autophagic flux and reduced apoptosis **[31]**. In a rotenone-induced parkinson's disease model, rats given daily intraperitoneal injections of UDCA had striatal dopamine levels that were nearly identical to those of the control group. Additionally, the levels of nuclear factor-

κB (NF-κB), Bax, and caspase-9 mRNA were significantly reduced. The group that received UDCA had lower levels of striatal cytokines than the group that received rotenone. Additionally, this UDCA therapy reduced rotenone-induced alterations of mitochondria in striatal neurons **[32]**. Furthermore, a phase II, randomized, double-blind, placebo-controlled study with UDCA (30 mg/kg daily) in individuals with parkinson's disease demonstrated that this rather high dosage was safe and tolerable. However, further extensive studies are required to assess UDCA's disease-modifying potential in parkinson's disease **[33]**.

Table 1. Summary for the use of bile acids in seizures and the possible mechanisms underlying the neuroprotective effect

Model	Drug	Effect	Reference
Warm water bath immersion model for febrile seizure	Cultured bear bile powder	CBBP prolonged the latency of FS, decreased the incidence rate of FS, decreased hippocampal degeneration decreased expression of inflammatory markers. Also, CBBP elevated GABA content and the expression of $GABA_AR$.	**[19]**
Pilocarpine model	TUDCA	TUDCA treatment significantly decreased the ER stress markers in the hippocampus, which causes a subsequent reduction of NLRP3 inflammasome activation	**[20]**
PTZ-kindling model	TUDCA	TUDCA reduced the seizure-related histological damage, inflammatory and hypoxic markers in brain stem, heart, and lung tissues	**[21]**
Repeated restraint stress followed by PTZ induced seizures	TUDCA	TUDCA reduced repeated restraint stress seizure susceptibility. Also reduced ER stress markers, oxidative stress markers, and neuronal loss	**[22]**
PTZ-kindling model	TUDCA+4-PBA	TUDCA+ 4-PBA reduced ER stress markers, oxidative stress markers, and apoptosis.	**[23]**

CBBP, Cultured bear bile powder; ER, Endoplasmic reticulum; GABA, γ-aminobutyric acid; $GABA_AR$, γ-aminobutyric acid receptor; NLRP3, Nod-like receptor protein 3; NF-κB, Nuclear factor-κB; PTZ, Pentylenetetrazole; TUDCA, Tauroursodeoxycholic acid; 4-PBA, 4-phenyl-butyric acid.

2.4. Huntington's disease (HD)

Findings revealed that systemically administered TUDCA significantly subsided the neuropathology in the striatum of the R6/2 transgenic HD mouse model. Particularly, R6/2 mice that began to take TUDCA at 6 weeks of age presented less striatal atrophy and apoptosis, together with scarcer and smaller ubiquitinated intranuclear huntingtin masses in the neurons. A significant correction in sensory and locomotor impairments was obvious in mice treated with TUDCA **[34]**. Moreover, in the 3-nitropropionic acid model of HD, TUDCA upgraded the cognitive and locomotor impairments and evaded striatal atrophy **[35]**.

2.5. Stroke

A retrospective cohort follow-up study found that stroke risk was associated with lower levels of excretion of total bile acid, deoxycholic acid, and lithocholic acid; low bile acid excretion remained a significant risk factor even after controlling for major potential determinants and could be a risk factor for stroke on its own **[36]**. Moreover, in a metabolomic study involving 50 young patients with a diagnosis of ischemic stroke, total bile acid levels were comparable between the stroke and healthy groups, but there was a substantial difference in the bile acid component. The stroke patients showed a significant increase in glycochenodeoxycholic acid, which in turn promotes oxidative stress and apoptosis, revealing that it could be associated with the pathogenesis of ischemic stroke **[37]**. Therefore, we can conclude from these studies that the accumulation of hydrophobic bile acids has detrimental consequences that contribute to the stroke pathophysiology. In addition, in a mouse model of hemorrhagic stroke, the TUDCA, being a hydrophilic bile acid, effectively decreased the brain edema, suppressed the endoplasmic reticulum stress, inhibited the pyroptotic cell death, and diminished the deficits in spatial memory **[38]**.

2.6. Depression

In a rodent model of depression, chronic unpredictable stress, the TUDCA treatment was able to reduce the abnormalities in many behavioral tests, such as the tail suspension test, forced swimming test, open field test, and sucrose preference test. Besides, the TUDCA attenuated multiple pathological processes such as neuroinflammation, oxidative stress, and endoplasmic reticulum stress that strongly contribute to the pathogenesis of depression **[39]**. In another study, using - induced depression like behviour model, the TUDCA also exhibited an antidepressant effect **[40]**.

2.7. Anxiety

TUDCA demonstrated protection to neurons and subsequent alleviation of anxious behaviors through its interaction with TGR5 receptor to regulate the NF-κB/BDNF signaling cascade **[41, 42]**. There is a negative association between NF-KB and BDNF, in which the reduction in NF-KB results in BDNF increase, thus fostering neurogenesis and synaptic plasticity **[43,44]**.

3. Safety, tolerability, and adverse effects

An excellent safety profile was demonstrated by UDCA, which reported mostly mild gastrointestinal adverse effects, including nausea, vomiting, abdominal discomfort, diarrhea, and, less commonly, rashes and itching **[45]**. Moreover, early controlled clinical trials in patients with gallstone disease and long-term, large-scale, placebo-controlled trials in patients with cholestatic liver disease did not report any significant side effects from the administration of UDCA **[46]**.

Conclusion

Urosodeoxycholic acid's use in a variety of neurological and psychiatric conditions produced encouraging experimental results, paving the way for further testing of the drug's effectiveness in human clinical settings.

Abbreviations

Amyloid-β (Aβ); Cultured bear bile powder (CBBP); Chenodeoxycholic acid (CDCA); Endoplasmic reticulum (ER); Food and Drug Administration (FDA); Glycoursodeoxycholic acid (GUDCA); Huntington's disease (HD); Nature bear's bile powder (NBBP); Nuclear factor-κB (NF-κB); Pentylenetetrazole (PTZ); Tauroursodeoxycholic acid (TUDCA); Ursodeoxycholic acid (UDCA).

Declarations

Ethics approval and consent to participate

Not applicable

Consent to publish

Not applicable

Availability of data and materials

Data will be made available on reasonable request.

Competing interests

The authors declare that no competing interests exist.

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Author's Contribution

Nourhan Sayed Radwan: Conception and design, acquisition of data, writing the initial draft of the article, and reviewing and approving the final version of the paper.

Alaa Emam Sadek, Doaa Elsherbiny, and Samar S. Azab: Conception and design and reviewing, and approving the final version of the paper.

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