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From dried bear bile to molecular investigation: a systematic review of the effect of bile acids on cell apoptosis, oxidative stress and inflammation in the brain, across pre-clinical models of neurological, neurodegenerative and neuropsychiatric disorders

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Abstract

Bile acids, mainly ursodeoxycholic acid (UDCA) and its conjugated species glycoursodeoxycholic acid (GUDCA) and tauroursodeoxycholic acid (TUDCA) have long been known to have anti-apoptotic, anti-oxidant and anti-inflammatory properties. Due to their beneficial actions, recent studies have started to investigate the effect of UDCA, GUDCA, TUDCA on the same mechanisms in pre-clinical models of neurological, neurodegenerative and neuropsychiatric disorders, where increased cell apoptosis, oxidative stress and inflammation in the brain are often observed. A total of thirty-five preclinical studies were identified through PubMed/Medline, Web of Science, Embase, PsychInfo, and CINAHL databases, investigating the role of the UDCA, GUDCA and TUDCA in the regulation of brain apoptosis, oxidative stress and inflammation, in pre-clinical models of neurological, neurodegenerative and neuropsychiatric disorders. Findings show that UDCA reduces apoptosis, reactive oxygen species (ROS) and tumour necrosis factor (TNF)-α production in neurodegenerative models, and reduces nitric oxide (NO) and interleukin (IL)-1β production in neuropsychiatric models; GUDCA decreases lactate dehydrogenase, TNF-α and IL-1β production in neurological models, and also reduces cytochrome c peroxidase production in neurodegenerative models; TUDCA decreases apoptosis in neurological models, reduces ROS and IL-1β production in neurodegenerative models, and decreases apoptosis and TNF-α production, and increases glutathione production in neuropsychiatric models. In addition, findings suggest that all the three bile acids would be equally beneficial in models of Huntington's disease, whereas UDCA and

TUDCA would be more beneficial in models of Parkinson’s disease and Alzheimer's disease, while GUDCA in models of bilirubin encephalopathy and TUDCA in models on depression. Overall, this review confirms the therapeutic potential of UDCA, GUDCA and TUDCA in neurological, neurodegenerative and neuropsychiatric disorders, proposing bile acids as potential alternative therapeutic approaches for patients suffering from these disorders.

Introduction

Ursodeoxycholic acid (UDCA), is a bile acid endogenously produced in small quantities in human bile and in larger quantities in certain species of bear bile (Qiao et al., 2011; Shoda, 1927; Tint et al., 1990). Dried bear bile has been used for centuries in China as a remedy for fever, inflammation, swelling and pain (Feng et al., 2009; Zhou et al., 2015), particularly for several liver conditions (Beuers et al., 1998). From the prospective of traditional Chinese medicine, bear bile shows remarkably abilities to clear 'liver heat' and reduce 'liver fire', which refer to the pathological phenomenon related to the liver (Li et al., 2016). Along with the rising concerns about endangered species, over the decades scientists have developed new ways of producing it through the chemical transformation of cholic acid and chenodeoxycholic acid from bovine bile (Eggert et al., 2014). Currently, UDCA is widely used as the first-line therapy for cholestatic hepatopathies and the only one approved by the United States Food and Drug Administration (FDA) for the treatment of primary biliary cirrhosis (Amaral et al., 2009). Moreover, its use has recently been expanded to other hepatic diseases, like intrahepatic cholestasis (Zhang et al., 2016b), and even to extrahepatic ones, such as inflammatory bowel diseases (Van den Bossche et al., 2017). The versatility is attributed to its multiple mechanisms of action, including reducing cell death, as well as exerting anti-oxidant and anti-inflammatory properties (Roma et al., 2011).

UDCA is a hydrophilic tertiary bile acid, when given orally, unconjugated UDCA is rapidly conjugated in the liver with glycine to form glycoursodeoxycholic acid

(GUDCA) in humans, and to a lesser extent with taurine to form tauroursodeoxycholic acid (TUDCA) (Invernizzi et al., 1999; Rudolph et al., 2002) (Fig.1). Both conjugated and unconjugated UDCA can be detected in the blood and brain of humans and rodents (Chen et al., 2020a; Huang et al., 2015; Pan et al., 2017; Tao et al., 2021; Xie et al., 2013). Accordingly, pre-clinical evidence shows that both UDCA and GUDCA can slowly penetrate in the brain across the blood-brain barrier (BBB) endothelium (Palmela et al., 2015). In humans, UDCA can enter the cerebrospinal fluid after been given orally (Parry et al., 2010), and similarly, TUDCA can easily cross the BBB in mice and improve cerebral blood flow (Chen et al., 2020b). As a result, it is thought that the principal source of conjugated and unconjugated UDCA in the brain comes from peripheral circulation (Kiriyama and Nochi, 2019), but UDCA synthesis in the brain should also not be excluded.

Once in the brain, UDCA and its amidated conjugates, GUDCA and TUDCA, are known to exert neuroprotective properties, which consist on reducing cell apoptosis, oxidative stress and inflammation (Vaz et al., 2019; Zangerolamo et al., 2021a). For instance, UDCA and TUDCA were found to reduce neuronal loss in prion-infected cerebellar slice cultures (Cortez et al., 2015); TUDCA was also able to prevent oxidative stress induced by elevated glucose concentration in cultured retinal neural cells through decreasing reactive oxygen species (ROS) production (Gaspar et al., 2013); while GUDCA was demonstrated to promote resolution of inflammation via reducing tumor necrosis factor (TNF)-α and interleukin (IL-1)-β cytokines expression

in transduced microglial cell line (Vaz et al., 2019).

Interestingly, changes in brain apoptosis, oxidative stress and inflammation have been identified as three of the main pathophysiological mechanisms characterizing neurological (Hilton et al., 2006; Rawat et al., 2018; Xu et al., 2018), neurodegenerative (Cai and Xiao, 2016; Gelders et al., 2018; Hickey and Chesselet, 2003; Jenner, 2003; Liu et al., 2019; Sanchez-Lopez et al., 2012), and neuropsychiatric disorders (Borsini et al., 2020; Jahanbazi Jahan-Abad et al., 2018; Kohler et al., 2016; Liu et al., 2015). For example, several pre-clinical studies observed higher apoptosis in brain cells exposed to 1-methyl-4-phenylpyridinium (MPP)/1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or interferon (IFN)-α models of Parkinson's disease (PD) and depression, respectively (Borsini et al., 2018; Hilton et al., 2006; Sun et al., 2018). Similar to apoptosis, increased production of pro-inflammatory cytokines, such as TNF-α, IL-6 and IFN-γ, as well as excessive levels of oxidative stress products are often observed in at least a sub-group of patients with neurological disorders, such as those experiencing acute encephalitis/encephalopathy (Ichiyama et al., 1998) and cerebral ischemia (Ewelina et al., 2017), or those with neurodegenerative disorders, like PD (Chen et al., 2008) and Alzheimer's disease (AD) (Terranova et al., 2001), or those with neuropsychiatric disorders, such as depression (Maes et al., 1998; Pariante, 2019).

Due to the ability of bile acids in reducing cell apoptosis, oxidative stress and inflammation, recent studies have started to investigate the effect of UDCA, GUDCA

and TUDCA on those aforementioned mechanisms also in the context of neurological, neurodegenerative and neuropsychiatric disorders (Cheng et al., 2019; McMillin and DeMorrow, 2016). This is the first systematic review which summarizes evidence generated so far and demonstrating the role of UDCA, GUDCA and TUDCA in the regulation of apoptosis, oxidative stress and inflammation in the brain, across *in vivo, ex vivo* and *in vitro* models of neurological, neurogenerative and neuropsychiatric disorders, or in homeostatic state.

1. Methods

We searched for studies including keywords related to bile acids, and either cell apoptosis or oxidative stress or inflammation using the following algorithm ((UDCA) OR (ursodeoxycholic acid) OR (GUDCA) OR (glycoursodeoxycholic acid) OR (TUDCA) OR (tauroursodeoxycholic acid)) AND ((apoptosis) OR (oxidative stress) OR (inflammation)). The study protocol was registered on PROSPERO (ID: CRD42021223744) prior to the systematic literature search. The search was carried out using PubMed/Medline, Web of Science, Embase, PsychInfo, and CINAHL databases. We included *in vivo*, *ex vivo* and *in vitro* studies investigating the role of the three bile acids, UDCA, GUDCA and TUDCA in models of neurological, neurogenerative and neuropsychiatric disorders, or in homeostatic state conditions. In addition, studies had to include outcomes of cell apoptosis, oxidative stress or inflammation. Studies excluded from the search were or contained one or more of the following: no markers of cell apoptosis, oxidative stress or inflammation, not published in English language,

or investigated models in the context of conditions out of our scope (gene modification models, surgical models, prion infection models and retinal disease models). A total of 35 studies met the criteria for our review at the end of the selection process (Fig.2), and were assessed for risk of bias following the SYRCLE guidelines for animal studies (Hooijmans et al., 2014) (Suppl. Material 1), and with previously used questionnaires for cellular studies (AlShwaimi et al., 2016; Golbach et al., 2016) (Suppl. Material 2).

2. Results

In this section of the review, we will summarise findings from 34 articles reporting changes in brain cell apoptosis, oxidative stress and inflammation in *in vivo, ex vivo* and *in vitro* studies, nine of which using treatment with UDCA, six using GUDCA, and twenty-one using TUDCA (see Table 1).

2.1 UDCA

2.1.1 Models of neurological disorders

One *ex vivo* study investigated the effect of treatment with UDCA on apoptosis in models of neurological disorders. Findings show that UDCA prevents cell apoptosis in models of encephalopathy. In particular, the *ex vivo* study, conducted in foetal neurons and astrocytes isolated from rats, found that treatment with UDCA prevents the increase in the number of TUNEL positive apoptotic cells induced by treatment with bilirubin, here used as a model of encephalopathy (Silva et al., 2001).

2.1.2 Models of neurodegenerative and neuropsychiatric disorders

One *in vivo*, two *ex vivo* and four *in vitro* studies investigated the effect of treatment with UDCA in models of neurodegenerative disorders, like PD, AD and Huntington's Disease (HD), and one *ex vivo* study in models of neuropsychiatric disorders, particularly depression. Together they show that, independently of the model, treatment with UDCA prevents increase in cell apoptosis, oxidative stress and inflammation induced by the various challenges used to model the aforementioned disorders.

In particular, the first *in vivo* study used a rotenone-induced PD model (Abdelkader et al., 2016), whereas the second *in vitro* study used a sodium nitroprusside (SNP)-induced PD model (Chun and Low, 2012), and the third *in vitro* study used MPP+-induced PD model (Qi et al., 2021). All studies showed that treatment with UDCA prevents activation of the apoptotic marker caspase 9, and decrease in TNF-α and IL-1β production in the striatum of rotenone-treated rats (Abdelkader et al., 2016), and prevents production of ROS in SNP-induced human neuroblastoma cells (Chun and Low, 2012) and MPP+-induced mouse neuroblastoma cells (Qi et al., 2021).

Three other studies used amyloid-β (Aβ) models of AD. The two *ex vivo* study conducted in rats showed that UDCA prevents cell death induced by Aβ in cortical neurons using Hoechst staining (Sola et al., 2006), as well as the production of IL-1β and nitric oxide (NO) in microglia exposed to Aβ (Joo et al., 2003). The other one *in*

196 *vitro* studies found that UDCA prevents production of TNF-α and NO in BV2 microglia
197 previously exposed to Aβ (Joo et al., 2004).
198
199 Another *in vitro* study used treatment with 3-Nitropropionic acid (3-NP) as a
200 model of HD. The study showed that UDCA prevents mitochondrial release of
201 cytochrome c, a well-known indicator of apoptosis, in rat neuronal RN33B cells
202 (Rodrigues et al., 2000). Finally, one aforementioned *ex vivo* study also used
203 lipopolysaccharide (LPS) as a model of inflammation-induced depression and showed
204 that UDCA inhibits the production of IL-1β and NO in rat microglia (Joo et al., 2003).
205
206 ***2.1.3 Homeostatic state***
207 Four *ex vivo* and four *in vitro* studies, six of which previously mentioned (Chun
208 and Low, 2012; Joo et al., 2003; Joo et al., 2004; Rodrigues et al., 2000; Silva et al.,
209 2001; Sola et al., 2006) investigated the effect of UDCA on apoptosis, oxidative stress
210 or inflammation in homeostatic conditions. Overall, studies showed that UDCA does
211 not change cell apoptosis, and levels of oxidative stress and inflammation.
212
213 Five *ex vivo* and *in vitro* studies showed that UDCA does not affect cell
214 apoptosis in neurons (Rodrigues et al., 2000; Silva et al., 2001; Sola et al., 2006),
215 astrocytes (Silva et al., 2001), human neuroblastoma cells (Chun and Low, 2012) and
216 human glioblastoma cells (Yao et al., 2020). However, one *in vitro* study found that
217 treatment with UDCA increases ROS production in glioblastoma cells (Yao et al., 2020),

while another *in vitro* study did not find any changes in ROS production in human neuroblastoma cells (Chun and Low, 2012). In terms of inflammation, one *ex vivo* and one *in vitro* study showed that UDCA does not change levels of NO and IL-1β or inducible nitric oxide synthase (iNOS) production in rat primary microglial cells (Joo et al., 2003) and BV2 microglia (Joo et al., 2004).

2.2 GUDCA

2.2.1 Models of neurological disorders

Five *ex vivo* studies investigated the effect of treatment with GUDCA on apoptosis, oxidative stress or inflammation in a bilirubin model of neurological disorders. Altogether, these studies showed that GUDCA administration has anti-apoptotic and anti-oxidant effects, but no anti-inflammatory effects.

In particular, one *ex vivo* study showed that GUDCA prevents bilirubin-induced expression of caspase 3 and caspase 9 in rat primary neurons (Vaz et al., 2010). In addition, another three *ex vivo* studies found that GUDCA prevents reduction in apoptosis, using Hoechst staining, in rat cortical neurons and organotypic-cultured hippocampal slices (Silva et al., 2012), in neuron monocultures and in rat cortical neuron-astrocyte co-cultures (Falcao et al., 2014), and in rat cortical astrocytes (Fernandes et al., 2007).

With respect to oxidative stress, two aforementioned *ex vivo* studies demonstrated

that GUDCA prevents bilirubin-induced production of lactate dehydrogenase (LDH) (Fernandes et al., 2007), as well as oxygen consumption extracellular adenosine triphosphate (ATP) release (Vaz et al., 2010). Similarly, another *in vitro* study showed that GUDCA prevents bilirubin-induced reduction of glutathione (GSH) in rat neurons (Brito et al., 2008). With respect to inflammation, one aforementioned *ex vivo* study showed that GUDCA prevents TNF-α, IL-1β and IL-6 production induced by bilirubin (Fernandes et al., 2007), while another *ex vivo* study, also previously mentioned, did not find any effect (Falcao et al., 2014).

2.2.2 Models of neurodegenerative disorders

Only one aforementioned *in vitro* study also investigated the effect of GUDCA in a neurodegenerative model of HD, induced by the neurotoxic 3-NP. Results showed that GUDCA prevents release of cytochrome c in rat neuronal RN33B cells (Rodrigues et al., 2000).

2.2.3 Homeostatic state

Five *ex vivo* and one *in vitro* study previously mentioned (Brito et al., 2008; Falcao et al., 2014; Fernandes et al., 2007; Rodrigues et al., 2000; Silva et al., 2012; Vaz et al., 2010) investigated the effect of GUDCA on apoptosis, oxidative stress and inflammation in homeostatic state conditions. Together, these studies showed that, GUDCA treatment has no effect on all three aforementioned mechanisms.

In particular, all studies showed that GUDCA does not affect apoptosis, measured by either propidium iodide (PI), Hoechst or Annexin V+/7-AAD staining; oxidative stress, measured by cytochrome c, ATP, NO or LDH production; and inflammation, measured by TNF-α, IL-1β or IL-6 production,in rat neurons (Brito et al., 2008; Falcao et al., 2014; Silva et al., 2012; Vaz et al., 2010), rat astrocytes (Falcao et al., 2014; Fernandes et al., 2007), rat neuronal RN33B cells (Rodrigues et al., 2000) and rat neurons-astrocytes co-cultured cells (Falcao et al., 2014).

2.3 TUDCA

2.3.1 Models of neurological disorders

One *in vivo* study and one *in vitro* study investigated the anti-apoptotic effect of TUDCA in models of neurological disorders. In the first *in vivo* study, administration of TUDCA before or after stereotaxic collagenase injection, used here as a model of intracerebral hemorrhage, prevented or rescued caspase protein expression, as well as nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) expression in female rat brain (Rodrigues et al., 2003). However, another *in vitro* study found that TUDCA has no effect on apoptosis in human neuroblastoma cells exposed to oxygen-glucose deprivation-reoxygenation (OGD/R) treatment, used here as a model of cerebral ischemia (Cheng et al., 2018).

2.2.2 Models of neurodegenerative disorders

Six *in vivo,* six *ex vivo* and five *in vitro* studies, two of which previously

mentioned (Rodrigues et al., 2000; Sola et al., 2006) investigated the effect of TUDCA on cell apoptosis, oxidative stress and inflammation in HD, AD and PD models of neurodegeneration. Altogether, these studies showed that, treatment with TUDCA exerts anti-apoptotic, antioxidant and anti-inflammatory properties in the various models.

On *in vivo* and one *in vitro* study used 3-NP as model of HD, and showed that TUDCA prevents cell apoptosis, measured by Hoechst staining, in rat striatal (Keene et al., 2001) and in rat neuronal RN33B cells (Rodrigues et al., 2000). Three other *ex vivo* and one *in vitro* study, using an Aβ model of AD, found that TUDCA prevents increase in apoptosis, measured in this case by TUNEL staining, in primary rat cortical neurons (Sola et al., 2006; Sola et al., 2003), rat cortical and hippocampal neurons (Ramalho et al., 2013), and rat neuronal-like PC12 cells (Ramalho et al., 2004; Viana et al., 2010). Similarly, another *ex vivo* study, using glutamate-induced model of acute and chronic neurodegenerative disorders, showed that TUDCA prevents neuronal apoptosis in rat cortical neurons by reducing Hoechst staining (Castro et al., 2004), whereas another study, conducting both *ex vivo* and *in vitro* experiments, showed that TUDCA prevents advanced glycation endproducts (AGEs)-induced expression of the apoptotic marker caspase 9 in rat cortical neurons and in human neuroblastoma cells exposed to AGEs, used here as model of AD (Yin et al., 2012). In addition, one *in vivo* study, using 6-hydroxydopamine (6-OHDA) as model of PD, showed that TUDCA prevents increase in apoptosis, using TUNEL staining, in rat striatum (Duan et al., 2002).

306

307 With respect to oxidative stress, two *in vivo*, one *ex vivo* and two *in vitro* studies,
308 using either MPTP or MPP+-induced model of PD, showed that TUDCA prevents ROS
309 production in mice midbrain and striatum (Moreira et al., 2017), in cortical neurons
310 (Rosa et al., 2017), as well as in human neuroblastoma cells (Moreira et al., 2017; Rosa
311 et al., 2017). Similarly, another *in vivo* study, using the same MPTP model of PD
312 showed that TUDCA prevents increase in glutathione peroxidase (GPx) production in
313 mice cortex(Mendes et al., 2019). With respect to inflammation, the same study showed
314 that TUDCA prevents IL-1β expression in the same mice brain region (Mendes et al.,
315 2019), while another *in vivo* study used streptozotocin as the model of AD, and showed
316 that TUDCA inhibits TNF-α, IL-1β and IFN-γ mRNA expression in the hippocampus
317 of male mice (Zangerolamo et al., 2021b).

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319 ***2.3.3 Models of neuropsychiatric disorders***

320 Four *in vivo*, two *ex vivo* and one *in vitro* studies investigated the effect of
321 TUDCA on cell apoptosis, oxidative stress and inflammation in LPS-induced models
322 of depression. Overall, studies showed that treatment with TUDCA exerts anti-
323 apoptotic, anti-oxidant and anti-inflammatory properties in this model.

324

325 In one *in vivo* study, TUDCA prevents increase in apoptosis, measured by
326 Hoechst staining, in mice hippocampus (Wu et al., 2019). With respect to inflammation,
327 four *in vivo* studies and one *in vitro* study showed that TUDCA prevents increase in

TNF-α and IL-6 production in mice hippocampus (Wu et al., 2019) and prefrontal cortex (Cheng et al., 2019), and in BV2 microglia cells (Kim et al., 2018). In addition, two *ex vivo* studies showed that TUDCA prevents production of iNOS in primary astrocytes (Yanguas-Casas et al., 2014) and microglial cells (Yanguas-Casas et al., 2014, 2017). Similarity, in one *in vitro* study and one *in vivo* study, TUDCA prevents iNOS production in BV2 microglia cells (Kim et al., 2018), and increases GSH production in mice hippocampus and prefrontal cortex (Cheng et al., 2019).

2.3.4 Homeostatic state

Two *in vivo*, eleven *ex vivo* and six *in vitro* studies, fourteen of which previous mentioned (Castro et al., 2004; Cheng et al., 2019; Keene et al., 2001; Kim et al., 2018; Moreira et al., 2017; Ramalho et al., 2013; Ramalho et al., 2004; Rodrigues et al., 2000; Rosa et al., 2017; Sola et al., 2006; Sola et al., 2003; Viana et al., 2010; Yanguas-Casas et al., 2014, 2017) investigated the effect of TUDCA treatment on apoptosis, oxidative stress and inflammation in homeostatic conditions. Overall, these studies showed that TUDCA does not affect cell apoptosis and inflammation, but might regulate oxidative stress products to some extent.

Generally, TUDCA does not affect apoptosis in female rat striata (Keene et al., 2001), in primary rat cortical and hippocampal neurons (Castro et al., 2004; Ramalho et al., 2013; Sola et al., 2006; Sola et al., 2003), in rat neuronal RN33B cells (Rodrigues et al., 2000), and in human neuroblastoma cells and PC12 neuronal cells (Ramalho et

al., 2004; Viana et al., 2010). TUDCA also does not affect inflammation in mice hippocampus and prefrontal cortex (Cheng et al., 2019; Yanguas-Casas et al., 2017), in primary rat cortical and hippocampal cells (Ramalho et al., 2013), in rat primary microglia and astrocytes (Yanguas-Casas et al., 2014, 2017), as well as in BV2 microglia cells (Kim et al., 2018).

With respect to oxidative stress, TCDCA however increases mitochondrial membrane potential ($\Delta\Psi m$) and, surprisingly, also ATP level in primary mouse cortical neurons (Rosa et al., 2017), but increases production of the antioxidant enzyme manganese superoxide dismutase (MnSOD) in (Soares et al., 2018) in rat hippocampal stem/progenitor cells and decreases ATP release in mice primary neural stem cells (Xavier et al., 2014). However, TUDCA has no effect on ROS, LDH, GPx or GSH production in mice hippocampus, striatum, midbrain and prefrontal cortex (Cheng et al., 2019; Moreira et al., 2017), in primary mice cortical neurons (Rosa et al., 2017) and human neuroblastoma cells (Moreira et al., 2017; Rosa et al., 2017).

3. Discussion

This is the first review summarising current evidence for the effects of UDCA and its glycine- and taurine-coupled conjugates GUDCA and TUDCA on brain cell apoptosis, oxidative stress and inflammation in models of neurological, neurodegenerative and neuropsychiatric disorders, as well as in homeostatic state. Overall, these findings suggest that all the three bile acids exert anti-apoptotic, anti-antioxidant and anti-inflammatory effects across neurological, neurodegenerative and

neuropsychiatric models. In particular, UDCA reduces apoptosis, ROS and TNF-α production in neurodegenerative models, and reduces NO and IL-1β production in neuropsychiatric models; GUDCA decreases LDH, TNF-α and IL-1β production in neurological models, and also reduces cytochrome c peroxidase production in neurodegenerative models; TUDCA decreases apoptosis in neurological models, reduces ROS and IL-1β production in neurodegenerative models, and decreases apoptosis and TNF-α production, and increases GSH production in neuropsychiatric models (Fig.3). In addition, findings suggest that all the three bile acids would be equally beneficial in models of HD, whereas UDCA and TUDCA would be more beneficial in models of PD and AD, while GUDCA in models of bilirubin encephalopathy and TUDCA in models on depression.

First of all, the number of studies which investigated the effect of UDCA in neurological models was relatively small, while UDCA properties were well documented in a wide range of neurodegenerative models. In these models the beneficial effects of this bile acid were at least in part mediated by prevention of mitochondrial dysfunction. In particular, treatment with UDCA modulates mitochondrial homeostasis perturbations in the rotenone-induced rat model (Abdelkader et al., 2016), and prevents mitochondria-dependent programmed cell death caused by treatment with SNP and MPP, in both human and mice neuroblastoma cells (Chun and Low, 2012; Qi et al., 2021). These mitochondria-mediated mechanisms are quite relevant in order to understand how this acid exerts its properties, especially in

the context of neurodegenerative conditions. Of relevance, two undergoing clinical trials are now testing UDCA in patients with PD: while the first study primarily investigates safety and tolerability of UDCA in these patients (Clinical Trials registration: NCT03840005), the second one aims to assess whether UDCA can reduce PD progression and ultimately its symptomatology (Clinical Trials registration: NCT02967250) (Zangerolamo et al., 2021a). Findings from these trials will be fundamental to further validate the pre-clinical evidence outlined in this review, and will corroborate knowledge for the beneficial role of UDCA in delaying or reducing PD neurodegeneration.

In contrast with UDCA, studies on GUDCA mainly focused on bilirubin-induced models of encephalopathy. In particular, findings from our review showed that GUDCA can prevent bilirubin-induced mitochondrial energy impairment in rat primary neurons (Vaz et al., 2010), as well as TNF-α and IL-1β production in rat primary astrocytes, ultimately reducing cell apoptosis and inflammation (Fernandes et al., 2007). In addition, evidence suggests that, as a consequence of its anti-inflammatory properties, GUDCA can also indirectly affect other downstream mechanisms, such as synaptic plasticity (Silva et al., 2012), which is indeed very sensitive to inflammation (Golia et al., 2019). Therefore, this confirms the involvement of this bile acid not only in the anti-apoptotic and anti-inflammatory pathways previously identified and discussed in this review, but also in several other downstream mechanisms, such as brain plasticity, which are highly relevant in the context of neurological disorders (Martella et al., 2018).

Instead, TUDCA has been widely investigated in both models of neurodegenerative and neuropsychiatric conditions. In models of neurogenerative disorders, TUDCA decreases Aβ- and 3-NP-induced neuronal cell death (Rodrigues et al., 2000; Sola et al., 2003), whereas in models of neuropsychiatric disorders, the effect of TUDCA mostly results in preventing increased neuroinflammation, such as elevated TNF-α and IL-6, caused by treatment with LPS. Part of TUDCA anti-inflammatory action consists in reducing NF-κB activation and regulating brain-derived neurotrophic factor expression (Wu et al., 2019; Yanguas-Casas et al., 2017), both of which are often identified in both pre-clinical and clinical studies in depression (Bai et al., 2021; Zhang et al., 2016a). Another possible target of TUDCA anti-inflammatory effect may be the G protein-coupled bile acid receptor 1/Takeda G protein-coupled receptor 5 (GPBAR1/TGR5) (Yanguas-Casas et al., 2017), which has been found to mediate anti-inflammatory effect (Keitel et al., 2019) and its agonist have been reported to alleviate delayed neuronal degeneration (Hu et al., 2021) and neurodegeneration (Wu et al., 2018).

Although UDCA, TUDCA and GUDCA have been proven to significantly reduce cell apoptosis, oxidative stress and inflammation in pre-clinical models of neurological, neurodegenerative and neuropsychiatric conditions, each of those has shown its unique properties and level of efficacy, with respect to a specific brain condition. For example, UDCA and GUDCA maybe more effective for bilirubin encephalopathy, whereas UDCA and TUDCA for AD, with TUDCA also effective in

depression. While these pre-clinical findings are quite interesting, more research is needed in clinical context, in order to identify the best acid-specific treatment strategy, also taking also into account their individual bioavailability. In particular, TUDCA is better absorbed by the intestine than GUDCA (Aldini et al., 1996), and undergoes less biotransformation than UDCA (Invernizzi et al., 1999), therefore suggesting that TUDCA has significant metabolic advantages over UDCA and GUDCA. This, together with pre-clinical evidence outlined in our review, will definitely guide future therapeutic approaches.

Surprisingly, in homeostatic state, most of the studies showed that bile acids do not affect cell apoptosis or inflammation, especially when used within a certain range of concentrations (50-800 μM for UDCA; 50 μM for GUDCA; 50-500 μM or 50-400 mg/kg for TUDCA). However, UDCA was able to reduce the cell apoptosis in two different kinds of brain blastoma cells (Chun and Low, 2012; Yao et al., 2020), the dual pro-apoptotic and anti-apoptotic properties of UDCA represent the characteristic traits of bile acids (Goossens and Bailly, 2019). Despite additional experiments are still required to confirm the anticancer activity of UDCA in the brain, it shows promise as a potential therapeutic agent for the therapy of brain cancer. Apart from that, TUDCA was able to regulated the production of oxidative stress molecules across a variety of brain cells (Moreira et al., 2017; Rosa et al., 2017; Soares et al., 2018; Xavier et al., 2014). For example, TUDCA increased $\Delta\Psi m$ in mice primary cortical neurons and HO-1 in human neuroblastoma cells when used at 100 μM (Moreira et al., 2017; Rosa et al.,

2017). ΔΨm forms the transmembrane potential of hydrogen ions which is harnessed to make ATP (Zorova et al., 2018), while HO-1 protects cells by reducing superoxide and other ROS (Uddin et al., 2020). Similarly, TUDCA inhibited production of ROS products in mice neural stem cells, when used both at 50 and 100μM (Soares et al., 2018; Xavier et al., 2014). However, further concentration-dependent experiments are still required to confirm these preliminary findings.

This review has few limitations that should be considered, such as the variety of models and the numerous molecules that were manipulated. Additionally, dosage and route of administration among bile acids also varied significantly across studies. However, so far, our review consistently showed strong beneficial anti-apoptotic, anti-oxidant and anti-inflammatory effects of UDCA and its taurine/glycine conjugated species across a variety of pre-clinical models of neurological, neurodegenerative and neuropsychiatric disorders. Future research will allow to identify which bile acid would be the most effective for each specific disorder, and ultimately to develop more personalized dosages and treatment duration strategies for patients suffering from these conditions.

Declaration of Competing Interest

The authors of this manuscript declare no conflicts of interest.

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