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Hepatic Encephalopathy and The Emerging Role of Medicinal Plants: An Integrative Approach to Neuro Metabolic Dysfunction

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Abstract

A multifaceted neurological condition, hepatic encephalopathy (HE) is complex that arises as a result of severe liver damage. Traditionally viewed as a reversible metabolic condition, recent findings highlight the part of neuroinflammation, oxidative stress, and disturbed blood-brain barrier in its progression. Current treatment approaches largely focus on ammonia reduction but fail to fully address underlying neuronal and inflammatory imbalances. Emerging evidence supports the use of medicinal plants with neuroprotective, antioxidant, and anti-inflammatory properties as complementary therapies in HE. Various phytochemicals derived from plants like *Moringa oleifera*, Ashwagandha, and Berberine have demonstrated promising effects in animal models, improving cognitive function and reducing biochemical and histopathological damage. This review synthesizes current insights into HE pathophysiology and highlights the integrative role of plant-based interventions as a future therapeutic strategy.

Keywords: Antioxidant therapy, Cognitive dysfunction, Herbal medicine, Neuroinflammation, Oxidative stress, Phytotherapy.

Introduction

Hepatic encephalopathy (HE) is classified as a metabolic disorder and is generally viewed as reversible after liver transplantation. However, our understanding is shifting. Research now reveals that neuroinflammation and neuronal damage are hallmarks of HE, and severe cases can lead to lasting harm. It presents as a diverse array of mental or neurological conditions, varying from subtle shifts to a coma [(1)]. The clinical manifestations of HE can vary significantly, presenting a wide array of signs and symptoms. These may include cognitive, personality, and intellectual deficits, as well as changes in consciousness and neuromuscular impairments like asterixis and hyperreflexia. The diverse symptoms of HE differs not only among patients but can also fluctuate over time in a single patient. Additionally, it's noteworthy that cirrhotic patients who seem clinically "normal" may still exhibit abnormalities on electroencephalography [(2)]. Even in its least severe form, HE diminishes quality of life in relation to health and increases the likelihood of experiencing episodes of severe HE [(3)].

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HE can be broadly classified into two main types: Overt HE (OHE), which is more noticeable, and Covert HE (CHE), which is less apparent [4]. For a variety of causes, the high prevalence of CHE varies throughout research and environments. First, the testing strategy affects the prevalence. The majority fall under the category of psychometric exams. These consist of the computerised EncephalApp Stroop, the one-minute Animal Naming test, and the gold standard timed paper pencil Psychometric Hepatic Encephalopathy Score (PHES) test [5]. Later stages of cirrhosis are when CHE is more common. Cirrhosis affects close to half of all patients in children [6].

Clinical Risk Factors

The incidence of HE was recorded near to 10% of 100 cases per person-years of observation, with a median duration to diagnosis of 25 months. Among the patients, 508 (<1%) underwent liver transplantation, 2,806 (2%) passed away before developing HE, and 27,620 (15%) were lost to follow-up. HE was more frequently observed in humans with alcoholic cirrhosis compared to those with cirrhosis due to hepatitis C virus (HCV) or nonalcoholic/nonviral causes. Additionally, the highest incidence was noted in patients with portal hypertension. These findings emphasize the significant burden of HE in patients with cirrhosis, particularly among those with alcohol related liver disease. The study also highlights significance of early identification and management approaches to mitigate HE related complications. Given the aging population and the increasing prevalence of nonalcoholic fatty liver disease (NAFLD), understanding HE risk factors is crucial for improving patient outcomes. Further research is needed to explore preventive measures and optimize treatment approaches for HE in this vulnerable group [7].

Causes

- Systemic infections such as sepsis
- Bleeding within the gastrointestinal tract
- Persistent constipation
- Excessive intake of dietary proteins
- Fluid loss or inadequate hydration
- Central nervous system modulators
- Low potassium levels and/or presence of alkalosis
- Irregular or improper use of lactulose therapy
- History of undergoing anesthesia
- Previous portal decompression interventions
- Intestinal blockage or lack of bowel movement
- Presence of uremia
- Additional liver damage on top of existing conditions
- Emergence of hepatocellular carcinoma [14].

Consequences

- Falls
- Diminished mobility
- Driving restrictions
- Hospital admissions
- Burden on Healthcare resources
- Caregiver strain
- Financial difficulties [8].

Symptoms

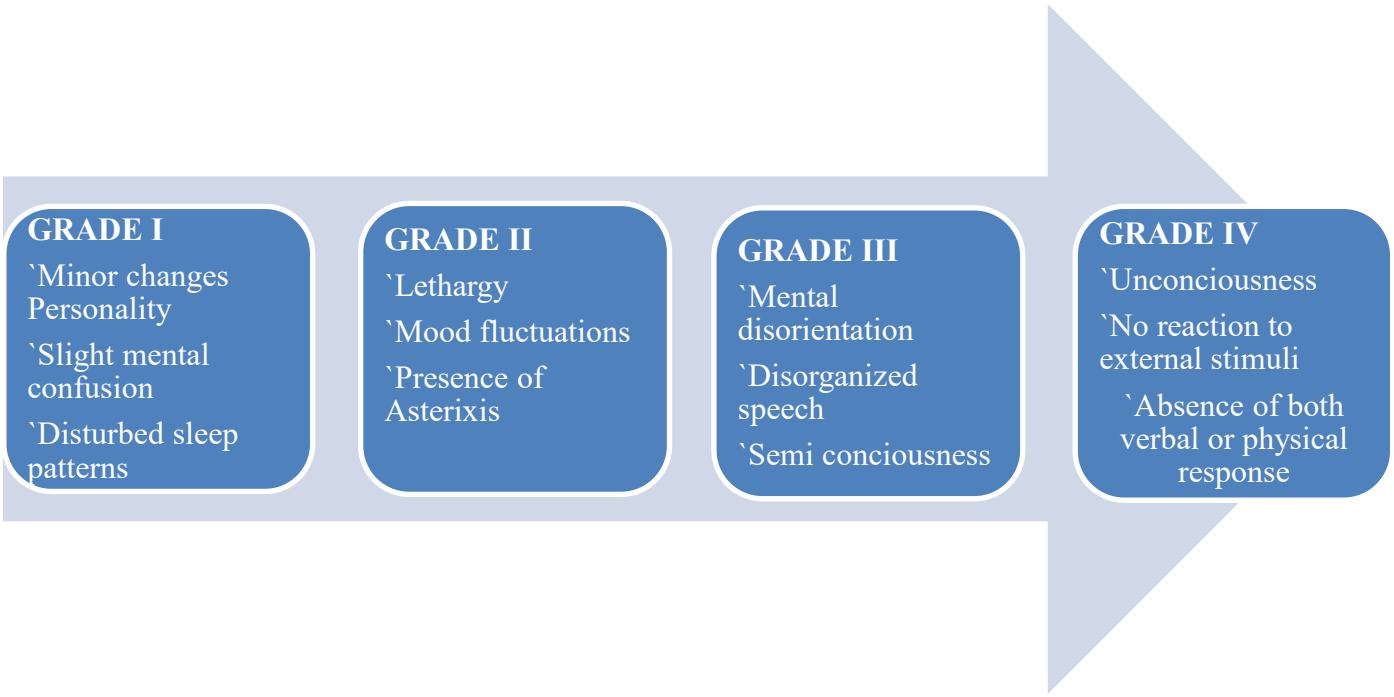

Figure 1: Clinical grading of Hepatic encephalopathy based on symptom severity [2]

Diagnosis

A diagnosis of HE should only be established after ruling out other neurological disorders. Although increased ammonia levels are associated with the severity of HE, a reduction in these levels has been linked to an improvement in encephalopathic symptoms. Measuring ammonia concentrations can be useful in supporting the identification and guiding therapy, particularly in health effected person with a known history of liver cirrhosis. Venous blood samples are sufficient for assessing ammonia levels, as there is no significant benefit in measuring ammonia partial pressures. While ammonia testing aids in clinical evaluation, it should always be interpreted alongside other diagnostic parameters to ensure accurate assessment and effective management of HE [9,10].

A comprehensive evaluation, including patient history and subtle cognitive changes, is essential for accurately identifying MHE, ensuring timely intervention and neuropsychological assessment is considered the most reliable method for detecting cognitive deficits and diagnosing MHE. This evaluation involves a series of standardized neuropsychologist-analyzed test outcomes compared to normative data. Test results should preferably be changed depending on age, gender, and educational background to guarantee correctness. The assessment typically begins with a core battery of psychometric tests that evaluate key cognitive domains, with a greater emphasis on areas expected to be impaired in MHE. Although no universally standardized test battery exists for MHE, most evaluations prioritize assessments of attention, frontal lobe function, perceptual-motor skills, and information processing speed. Clinical correlation and a thorough assessment of contributing factors are essential for accurate diagnosis and management [11,12].

Electroencephalography (EEG) serves as an important technique for identifying HE, especially in research-based evaluations [13]. HE is characterized by a reduction in the mean frequency of electrical brain activity, which can be detected through EEG recordings. Studies have reported a wide range of diagnostic sensitivity for this finding, varying between 43% and 100%. This variation is likely influenced by differences in patient populations, disease severity, and EEG interpretation criteria [14]. Blood must be drawn from a vein without stasis, meaning no tourniquet should be used, and care must be taken to prevent turbulence or hemolysis. Furthermore, the sample To guarantee, it has to be examined within 20 minutes and carried on ice for reliable outcome. Given these limitations and the lack of direct impact on treatment strategies, ammonia testing is

generally not considered essential in routine HE evaluation but may still be useful in specific cases or research settings [15].

Progression Arising Out of MHE To OHE

Cirrhotic patients diagnosed with MHE are at a higher risk of progressing to OHE compared to those without MHE. The presence of MHE indicates early neurological impairment, which can gradually worsen as liver dysfunction progresses. Studies suggest that patients with MHE experience more frequent episodes of OHE, highlighting the importance of early detection and management. Identifying and treating MHE in cirrhotic patients may help delay or prevent the transition to more severe forms of encephalopathy, eventually enhancing the quality of life and results for patients [16,17].

A study assessing the progression of HE found that MHE effected person had a significantly more risk of evolving OHE over time. The actuarial probability of OHE within three years was reported to be 56% in MHE effected people, compared to only 8% in those with no MHE. This striking difference highlights the role of MHE as an early predictor of disease progression. Identifying and managing MHE at an early stage may help reduce the likelihood of developing severe neurological complications, emphasizing the need for regular monitoring and timely intervention in cirrhotic patients. MHE is often considered an indicator of advanced liver dysfunction, as it has been linked to a reduced survival time in affected patients. Its presence suggests a worsening hepatic condition, making it a potential marker for disease severity. While treatment strategies for MHE aim to improve reasoning ability and quality of life, further research is needed to determine whether early intervention can significantly alter the long-term progression of liver disease and delay the onset of more severe neurological complications [16,18,19,20].

Pathophysiological Mechanisms of HE

Ammonia function and neuroinflammation

The exact pathogenesis of this disease remains incompletely informed. However, everyone agrees that elevated ammonia levels and systemic inflammation play a synergistic role in its development. These factors contribute to astrocyte swelling and excessive fluid accumulation, leading to swelling of brain, that is thought to reside beneath the neurological signs of HE. Despite this general understanding, the precise molecular pathways responsible for these structural brain changes to until point have remained unclear. Ongoing research aims to clarify the complex interactions between ammonia toxicity, neuroinflammation, and astrocyte dysfunction to develop more effective therapeutic strategies for HE management [15,21].

Helicobacter pylori and hepatic encephalopathy

Some researchers have investigated a potential link in cirrhotic patients infected with Helicobacter pylori and developing HE. The hypothesis is based on the urease activity of H. pylori, which leads to ammonia production in the stomach, potentially increasing systemic ammonia levels through intestinal absorption. However, findings from various studies have been inconsistent, with most research failing to support this theory. Eliminating H. pylori failed to lead to any measurable changes in ammonia levels or cognitive function. These findings suggest that H. pylori infection may not play a significant role in the pathogenesis of HE, although further studies may be needed to confirm this conclusively.

Hyperammonemia and its role in hepatic encephalopathy

In HE, the liver's diminished capacity to detoxify ammonia leads to its excessive accumulation in the bloodstream, a condition known as hyperammonemia. Once ammonia crosses the blood brain barrier (BBB), it disrupts normal neurotransmission and triggers astrocyte swelling, contributing to cerebral edema. This swelling is a key factor in the neurological symptoms associated with HE. Ammonia induced neurotoxicity also affects various neurotransmitter systems. It enhances GABAergic activity while impairing glutamatergic neurotransmission, leading to an imbalance that further worsens neuronal dysfunction. Additionally, ammonia exposure generates oxidative and nitrosative stress, damaging cellular components and contributing to

mitochondrial dysfunction. This impairment in mitochondrial energy production results in neuronal energy deficits, further exacerbating cognitive decline and motor disturbances. The cumulative effects of ammonia toxicity including neurotransmitter imbalances, oxidative damage, and disrupted cellular metabolism serve as a crucial role in the developing of HE. Comprehension of these mechanisms highlights the importance various treatment plans that attempt to reduce levels of ammonia and mitigating its neurotoxic effects [22].

Neuroinflammation and oxidative stress in hepatic encephalopathy

Liver failure not only disrupts metabolic functions but also triggers systemic inflammation, eventually leading neuroinflammation. An increase of inflammatory markers by secretion activates microglial cells in the brain, which intensifies neuronal dysfunction and has a role in causing cognitive decline as a characteristic of HE. Neuroinflammation is closely linked to oxidative stress, which exacerbates neuronal injury and disrupts neurotransmission. The bidirectional relationship between systemic and neuroinflammation emphasises the importance of developing treatment strategies to slow the course of HE by targeting inflammatory pathways. The pathophysiology of HE is influenced by inflammation as well as oxidative and nitrosative stress. Reactive oxygen and nitrogen species are overproduced as a result of inflammatory markers, excessive manganese buildup, and increased ammonia. These reactive molecules cause nitration and inactivation of critical brain proteins, further impairing neuronal function. Moreover, oxidative stress contributes to mitochondrial dysfunction, reducing neuronal energy production and worsening cognitive and motor deficits. Given the damaging effects of oxidative and nitrosative stress, researchers are exploring antioxidant therapies as potential treatments for HE. Targeting these stress pathways may help protect neuronal function, reduce disease progression, and improve patient outcomes [23].

Manganese neurotoxicity and neurotransmitter imbalance in hepatic encephalopathy

Liver failure impairs the normal hepatobiliary excretion of manganese, leading to its accumulation in the basal ganglia. This excessive manganese buildup is linked to neurological symptoms resembling parkinsonism, adding further complexity to HE. Manganese induced neurotoxicity primarily affects dopaminergic pathways, disrupting neurotransmission and contributing to motor dysfunctions observed in HE patients. Neuroimaging studies, particularly T1 weighted MRI, have revealed hyperintensities in the basal ganglia, indicating manganese deposition. These findings emphasize the role of manganese toxicity in HE pathogenesis, prompting research into chelation therapies as a potential treatment approach to reduce manganese accumulation and its associated neurological effects. Alterations in neurotransmitter levels significantly contribute to the advancement of hepatic encephalopathy. Altered neurotransmission, including increased GABAergic activity and impaired glutamatergic function, disrupts normal neuronal communication, leading to both cognitive and motor impairments. Ammonia induced changes in neurotransmitter receptor expression and function further exacerbate these disturbances, worsening HE symptoms. Researchers are investigating therapeutic strategies aimed at restoring neurotransmitter balance, such as GABA receptor antagonists and modulators of glutamatergic transmission, to improve neuronal function and alleviate HE related neurological deficits. Addressing these neurochemical alterations could provide a promising avenue for more effective HE management [24].

Blood brain barrier dysfunction in hepatic encephalopathy

Liver dysfunction can impair the reliability of the BBB, increasing its permeability to neurotoxic chemicals like ammonia. Under normal conditions, the BBB acts as a protective filter, restricting harmful compounds from entering the central nervous system. However, in HE, liver failure induced systemic inflammation and oxidative stress weaken this barrier, allowing neurotoxins to cross more easily. The increased permeability of the BBB leads to higher ammonia concentrations in the brain, worsening damage to neurones and adding to motor and cognitive deficits. Additionally, other harmful substances, including inflammatory mediators and metabolic byproducts, may also infiltrate the brain, compounding the neurological damage.

Understanding the mechanisms behind BBB disruption in HE has led to growing interest in therapeutic strategies aimed at strengthening barrier integrity. Potential treatments, such as anti-inflammatory agents and BBB stabilizers, are being explored to mitigate neurotoxic infiltration and reduce HE progression [25].

Treatment of Hepatic Encephalopathy

The management of HE primarily focuses on reducing blood ammonia levels, with non-absorbable disaccharides like lactulose being the standard treatment for this purpose [26]. Beyond lactulose, rifaximin is widely used as an adjunct therapy to regulate gut microbiota and suppress the growth of ammonia producing bacteria, thereby lowering systemic ammonia levels [4]. The stable molecule L-ornithine L-aspartate, or LOLA for short, synthesized from the combination of two specific amino acids, plays a pivotal role in mitigating ammonia levels within the body. The L-ornithine component of LOLA stimulates the urea cycle, a critical metabolic pathway responsible for the detoxification and elimination of excess nitrogen. Concurrently, the enzyme glutamate transaminase uses both L-ornithine and L-aspartate as precursors, facilitating the conversion of these amino acids into glutamate. The resultant increase in glutamate concentrations enables the enzyme glutamine synthetase (GS) to efficiently catalyze the conversion of ammonia into glutamine, thereby reducing ammonia levels and promoting a more balanced nitrogen metabolism, LOLA, facilitates ammonia detoxification by enhancing urea cycle activity and promoting glutamine synthesis, further aiding in metabolic balance [27,28].

Probiotics are gaining attention for their role in restoring gut microbiome equilibrium, which in turn helps reduce systemic inflammation and supports overall gut health [29]. Additionally, albumin infusions have demonstrated benefits in improving circulatory function and exerting anti-inflammatory effects, making them a valuable therapeutic option in HE management [30]. To address metabolic imbalances, branched chain amino acids are administered to support protein metabolism and correct nutritional deficiencies commonly seen in HE patients [31]. Dietary modifications, including carefully regulated protein intake, are also recommended to minimize excessive ammonia production from gut derived sources [32]. Transplanting the microbiota from the faeces is an emerging therapy to rebalance gut flora and mitigating endotoxemia, potentially offering long-term benefits in HE treatment [33]. Adjunct therapies such as zinc supplementation play a crucial role in ammonia metabolism by acting as cofactors for essential enzymes in the urea cycle, thereby improving detoxification efficiency [34].

In some cases, antibiotics like neomycin are utilized to control bacterial overgrowth and subsequently decrease intestinal ammonia production, though their use is more limited compared to other pharmacological agents [35]. Effective HE management requires a multidisciplinary approach that integrates pharmacological interventions, dietary strategies, and supportive care to optimize patient outcomes [36]. Ongoing research is exploring individualized treatment plans tailored to variations in gut microbiota and metabolic profiles, offering a more personalized approach to HE therapies [37].

Complications of Hepatic Encephalopathy

Hepatic encephalopathy is linked to recurrent episodes of cognitive dysfunction, which over time can contribute to persistent memory deficits, ultimately diminishing patients' quality of life [38]. Neuromuscular complications, including asterixis and impaired motor coordination, are frequently observed in HE patients, further affecting their ability to perform daily activities and maintain independence [39]. Recurrent HE episodes are a significant concern, leading to frequent hospital readmissions and imposing a substantial economic burden on healthcare systems due to increased treatment costs and prolonged hospital stays [40]. Moreover, the condition predisposes affected individuals to additional complications, such as infections and gastrointestinal bleeding, which arise from systemic inflammation and the body's weakened immune response. As liver dysfunction progresses in HE patients, it may result in brain swelling and disturbances in blood flow of brain,

worsening neurological symptoms and potentially leading to more severe cognitive and motor impairments [40, 41,42].

Drawbacks In Present Treatment and Strategies to Overcome Them

Although multiple treatment options exist, current therapies often fail to provide complete resolution of HE symptoms, resulting in a high likelihood of recurrence and ongoing disease progression [43]. One major challenge is the adverse effects associated with commonly used treatments, such as lactulose, which can cause gastrointestinal discomfort, including diarrhea and bloating, thereby reducing patient adherence and limiting treatment effectiveness [44]. Additionally, standard treatment approaches primarily focus on reducing ammonia levels but do not adequately target the underlying neuroinflammatory and metabolic imbalances that contribute to HE pathogenesis, leaving critical aspects of disease progression unaddressed [45].

To overcome these therapeutic limitations, researchers are exploring novel strategies, including the development of targeted anti-inflammatory agents and neuroprotective compounds, which aim to modulate inflammation and preserve neuronal function, potentially improving long-term treatment outcomes [46]. Personalized medicine approaches, such as microbiome profiling and individualized nutritional interventions, are currently being investigated as potential strategies to enhance treatment effectiveness and improve long-term outcomes for HE patients [47].

Role of Alternative Systems of Medicine in The Management Of HE

Alternative medicine approaches, including Ayurvedic herbal formulations, have been examined for their potential benefits in HE management, particularly owing to the anti-inflammatory and antioxidant abilities of these, which may help mitigate disease progression [48]. Complementary therapies such as acupuncture, yoga, and mindfulness-based practices have been reported to contribute to overall well-being, and some studies suggest they may support cognitive function and improve mental clarity in individuals affected by HE [49]. In light of these potential benefits, integrative treatment models that combine conventional pharmacological interventions with alternative medicine practices are being explored as a holistic approach to HE management. However, further clinical research is necessary to validate their efficacy and establish standardized protocols for their implementation [50].

Plants Based Interventions in Hepatic Encephalopathy

Mahmoud *et al.,* (2022) evaluated the role of ***Moringa oleifera Lam.*** leaf ethanolic extract (MOLE) in a Carbon tetrachloride (CCl_4) caused HE mouse model, MOLE was evaluated for its effects. It has been found that MOLE reduced ALT, AST, corticosterone, and ammonia levels, increased antioxidant capacity in the hippocampus and cerebral cortex, downregulated TLR4, TLR2, MYD88, and NF-κB gene expression and reduced levels of cytokines that promote inflammation and caspase-3. It also prevented histopathological damage and alleviated anxiety and depression like behaviors [51].

Baek *et al*., (2020) evaluated role of ***Glycyrrhiza uralensis*** (RG) as well as ***Rheum undulatum*** in a CCl_4 caused HE mouse model. Systems based pharmacological analysis identified seven bioactive compounds with 40 potential neurological targets. RG improved HE symptoms by maintaining BBB integrity via downregulation of MMP-9 and upregulation of claudin-5. It also reduced mRNA expression of IL-1β and TGF-β1, indicating anti-neuroinflammatory effects [52].

El-Baz *et al*., (2021) evaluated the role of ***Dunaliella salina*** (D. salina) microalgae in a thioacetamide (TAA) induced HE rat model. D. salina improved liver function, reduced oxidative stress and neuroinflammation, downregulated TLR4 expression, and increased HSP-25 and IGF-1 levels. It also ameliorated behavioral deficits and brain histopathological damage, demonstrating antioxidant, anti-inflammatory, and cytoprotective effects [53].

Du *et al*., (2023) employed a CCl_4 and TAA induced MHE rat model to evaluate **Rhubarb decoction** (RD) administered via retention enema. RD enhanced liver activity, decline ammonia in blood, decreased cerebral edema, and restored cognitive function. It also increased microbial diversity, corrected imbalances in Bifidobacterium and Bacteroides, and modulated bile acid metabolism, particularly taurine related synthesis, highlighting its therapeutic potential through gut microbiota and bile acid regulation [(54)].

Hajipour *et al*., (2023) evaluated the role of **berberine** (Ber) on spatial cognition. It was investigated using a TAA induced rat model of liver cirrhosis. Ber significantly improved spatial memory, restored BBB integrity, reduced brain edema, oxidative stress, and neuroinflammation. It also normalized liver enzyme levels and hippocampal cytokines. These results suggest Ber as a potential therapeutic agent for cognitive enhancement in LC-associated HE [(55)].

Shirmohammadi *et al*., (2024) evaluated the role of **Beta myrcene** (β-myrcene) in a TAA induced acute HE rat model, it was tested at doses of 10, 25, and 50 mg/kg. β-myrcene, particularly at 25 and 50 mg/kg, significantly reduced brain water content, improved serum liver enzyme and ammonia levels, decreased malondialdehyde (MDA) levels, and increased antioxidant enzyme activity (SOD, CAT, GPx). These results indicate its dose dependent protective effects against oxidative stress and brain edema in acute HE [(56)].

El-Hagrassi *et al*., (2022) used TAA induced HE rat model to evaluate methanolic extract of ***Schefflera arboricola L***. leaves. They were administered at doses of 100 and 200 mg/kg for evaluation. The extract, rich in bioactive and phenolic compounds, significantly restored altered levels of liver enzymes, ammonia, oxidative stress, and inflammatory markers. It also reduced histopathological damage. The higher dose showed stronger antifibrotic, anti-inflammatory, and antioxidant effects, indicating notable protective potential against HE [(57)].

Sun *et al*., (2020) evaluated the role ***Lycium barbarum*** polysaccharides (LBP) at 5 mg/kg orally in TAA induced acute HE mouse model, it showed protective effects by reducing oxidative stress, apoptosis, inflammation, ammonia levels, and improving locomotor function. These effects were mediated via MAPK pathway modulation in the liver and brain. In vitro, LBP (50 μg/ml) also protected microglial cells from TNF-α, IL-6, and ammonia induced injury. Findings highlight LBP's therapeutic potential through MAPK pathway regulation and inflammatory cytokine suppression [(58)].

Abozaid *et al*., (2015) explored the protective role of ***Fructus Piperis Longi*** extract (Plfext) against HE in a TAA induced rat model. Rats received oral Plfext (50 mg/kg) for seven days before and during TAA exposure (200 mg/kg *i.p*., twice weekly for four weeks). TAA induced HE caused elevated liver enzymes, plasma ammonia, and lipid peroxidation, along with decreased serum albumin, total protein, glutathione (GSH), and catalase activity. Plfext administration significantly improved liver function, reduced oxidative stress in liver and brain tissues, and restored antioxidant levels, indicating its hepatoprotective and neuroprotective potential through antioxidant mechanisms [(59)].

Deniz *et al*., (2018) investigated investigate the possible neuroprotective effects of *Urtica dioica* (UD) in rats with CCl_4-induced HE. For eight weeks, male Sprague Dawley rats were given CCl_4 injections (1 mL/kg, i.p.) in order to induce HE. UD extracts were given to the subjects and their protective effects were evaluated through serum biochemical markers and brain histopathology. UD treatment significantly normalized elevated levels of AST, ALT, GGT, and ammonia. Histopathological analysis and c-Fos immunostaining revealed reduced brain damage in UD treated rats. [(60)].

Mostafa *et al*., (2017) evaluated the hepatoprotective and neuroprotective potential of **biopropolis** in a TAA induced model of acute HE in Wistar rats. HE was induced using a single TAA dose (300 mg/kg), while treatment groups received either vitamin E or biopropolis (100 to 200 mg/kg) for 30 days. TAA group showed elevated serum ammonia, liver dysfunction, DNA breakage during cell death, increased expression of the iNOS

gene in the brain, and oxidative stress in the liver and brain. Biopropolis treatment, particularly at 200 mg/kg, significantly reversed these pathological changes, improved liver function, reduced oxidative stress and apoptosis, and suppressed iNOS overexpression. These findings highlight biopropolis as a ensuring natural agent for treating HE, with potent antioxidant and antiapoptotic effects [61].

Hajipour *et al*., (2021) explored the neuroprotective potential of **thymoquinone** (TQ) in a TAA induced HE rat model. HE was induced via intraperitoneal TAA injections (200 mg/kg every 48 hours for 14 days), while TQ was administered at 5, 10, and 20 mg/kg *i.p*. for ten days. TQ treatment improved cognitive function, enhanced neural activity, stabilized BBB integrity, and reduced brain edema. On a biochemical level, TQ reduced hippocampal levels of pro-inflammatory cytokines (TNF-α, IL-1β), enhanced GSH concentrations, and elevated the anti-inflammatory cytokine IL-10. Histologically, TQ mitigated structural damage in the brain. These findings highlight TQ's promising therapeutic potential in managing HE by reducing neuroinflammation, oxidative stress, and cognitive dysfunction [62].

Lu *et al*., (2020) investigated the possibility of Babaodan's (BBD) medicinal and preventative effects, a traditional Chinese medicine, against HE in both chronic hepatic encephalopathy and acute hepatic encephalopathy rat models induced by CCl_4 and TAA. BBD pretreatment significantly improved liver function, reduced neurological deficits, and enhanced locomotor activity. It lowered serum ammonia, ALT, AST, TBil, and TBA levels while increasing total protein and albumin. BBD also downregulated inflammatory markers and inhibited the TLR4/MyD88/NF-κB pathway in liver and brain tissues. Furthermore, in LPS-activated macrophages, BBD suppressed inflammatory cytokines and NF-κB activation. These findings suggest that BBD's hepatoprotective and neuroprotective effects in HE is mediated through anti-inflammatory and ammonia lowering mechanisms [63].

Khalil *et al*., (2021) explored the shielding potential of **Ashwagandha** (ASH) extract, against TAA caused HE. ASH was administered orally by dose of 200 mg/kg as well as 400 mg/kg for 29 days before a single TAA injection (350 mg/kg, *i.p*.,). The extract improved locomotor activity, cognitive performance, and significantly reduced serum ammonia and hepatotoxicity markers. Oxidative stress parameters revealed that ASH decreased MDA, GS, and Induction of nitric oxide synthase (iNOS), lead to more GSH, Nrf2, and HO-1 levels. It also downregulated mRNA expression of p38 and ERK½ and reduced NF-κB and TNF-α levels in liver and brain tissues. Histopathological findings supported these biochemical improvements. ASH suggesting its therapeutic potential in HE through antioxidant, anti-inflammatory, and cognitive enhancing pathways [64].

Sedik *et al*., (2024) evaluated the neuroprotective potential of **herbacetin**, a glycosylated flavonoid, in a TAA induced rat model of HE. Herbacetin was administered orally at doses of 20 and 40 mg/kg for 30 days, with a TAA injection (350 mg/kg, *i.p*.,) given on the final day. Herbacetin significantly improved behavioral performance, including locomotor activity and cognitive function. Additionally, it improved liver function and lowered serum ammonia concentrations. Biochemically, herbacetin decreased MDA levels in the brain, GS, TNF-α, IL-1β, and annexin V, while increasing GSH, SIRT1, and AMPK expression. Overall, herbacetin demonstrated strong antioxidant, anti-inflammatory, and antiapoptotic effects, suggesting its therapeutic promise in protecting against HE induced cognitive impairments [65].

Baraka *et al*., (2020) investigated the protective effects of two natural flavonoid-based compounds ***Barnebydendron riedelii*** butanol fraction (BUF) and chrysin against TAA induced HE in rats. BUF, rich in flavonoid glycosides, showed promising interactions with NF-κB and Nrf2 in molecular docking studies. Pre-treatment with BUF (70–280 mg/kg) improved motor and cognitive functions, reduced inflammation (IL-6, NF-κB), ammonia, and oxidative stress, while upregulating Nrf2/HO-1 signaling and protecting liver-brain tissues histologically [66].

El-Marasy *et al*., (2019) employed a TAA induced HE model in Wistar rats, **chrysin** (25, 50, and 100 mg/kg orally for 21 days) showed significant neuroprotective effects. It improved motor coordination and cognitive function, reduced serum ammonia, and lowered liver enzymes (AST, ALT). Chrysin also decreased oxidative stress markers while increasing GSH levels. Furthermore, it downregulated pro-inflammatory markers, TLR-4 gene expression, and caspase-3 protein levels. Histological analysis confirmed reduced hepatic necrosis and astrocyte swelling, suggesting that chrysin acts via antioxidant, anti-inflammatory, and anti-apoptotic pathways to mitigate HE symptoms [67].

Sathyasaikumar *et al*., (2007) evaluated **C Phycocyanin** (CPC), a natural antioxidant, was used for its protective effects against TAA induced fulminant hepatic failure in rats. Administered at 50 mg/kg (*i.p*.) alongside TAA, CPC improved survival, reduced serum ammonia and liver enzymes (AAT, AST), and enhanced prothrombin time. Histological analysis showed decreased liver damage and astrocytic edema. In the brain, CPC reduced lipid peroxidation and tryptophan levels while increasing catalase and glutathione peroxidase activity. These results suggest CPC effectively mitigates TAA-induced HE via antioxidant and neuroprotective mechanisms [68].

Ali *et al*., (2024) used ***Tinospora cordifolia*** (TC), known for its traditional use and liver protective effects, was evaluated for its potential in treating TAA induced HE in rats. Oral pre-treatment with TC extract (30 & 100 mg/kg) improved behavioral deficits, reduced liver enzymes, and lowered oxidative stress in liver and brain tissues. TC also mitigated hyperammonemia, cerebral edema, and preserved BBB integrity. Histological and molecular analysis showed that TC suppressed inflammation, fibrosis, glial activation, and apoptosis via inhibition of MAPK/NF-κB and NLRP3 signaling. These findings highlight TC's dual neuroprotective and hepatoprotective action in HE [69].

Abdelghffar *et al*., (2022) evaluated the neuroprotective and hepatoprotective effects of ***Origanum vulgare*** (O. vulgare) leaf extract in TAA induced HE in rats. GC-MS analysis identified cholesten-3-one, γ-tocopherol, and α-/β-amyrin as major components. TAA caused behavioral deficits, elevated ammonia, inflammatory markers, and oxidative stress, along with reduced neurotransmitter and antioxidant levels. Treatment with O. vulgare (100/200 mg/kg) significantly improved behavioral, biochemical, and histological outcomes, showing effects comparable to silymarin. These results suggest O. vulgare's potential as a natural therapeutic agent against HE via antioxidant and anti-inflammatory pathways [70].

Table 1: Overview of medicinal plants used in hepatic encephalopathy research

S. No.	Plant Name	Part Used	Type of Extract	Model Used to Induce HE	Outcome	Reference
1	*Moringa oleifera*	Leaf	Ethanolic extract	CCl_4	Improved cognitive function, reduced oxidative stress, and neuroinflammation	51
2	*Rheum undulatum* + *Glycyrrhiza uralensis*	Root	Herbal extract mixture	CCl_4	Improved BBB integrity, reduced neuroinflammation	52
3	*Dunaliella salina*	Microalgae	Crude powder	TAA	Reduced oxidative stress, improved histopathology	53

4	Rhubarb, dark plum	Dried rhizome, dried fruit	Water extract	CCl_4 + TAA	Improved liver function, reduced cerebral edema	54
5	Berberine	Fruit	Crude powder	TAA	Improved spatial cognition, reduced oxidative stress	55
6	Beta-myrcene	-	Crude powder	TAA	Reduced oxidative stress, improved antioxidant levels	56
7	*Schefflera arboricola*	Leaves	Methanolic extract	TAA	Established to exert anti fibrotic, anti-inflammatory, and antioxidants characteristics	57
8	*Lycium barbarum* (Goji berry)	Fruits	Ethanolic extract	TAA	Reduced liver and brain damage, modulated MAPK pathway	58
9	*Fructus Piperis Longi*	Fruit	Ethanolic extract	TAA	Improved liver function, reduced oxidative stress	59
10	*Urtica dioica*	Whole plant	Dichloromethane Extract	CCl_4	Neuroprotection, improved biochemical markers	60
11	Biopropolis	-	Active molecule	TAA	Reduced oxidative stress, suppressed iNOS gene	61
12	*Nigella sativa*	Seed	Crude powder	TAA	Reduced inflammation, improved memory	62
13	BabaoDan	-	Crude Powder	CCl_4 + TAA	Reduced ammonia levels, suppressed inflammation	63
14	Ashwagandha (*Withania somnifera*)	Root	Water Extract	TAA	Reduced neuroinflammation, improved cognitive function	64
15	Herbacetin	-	Active molecule	TAA	Reduced oxidative stress, improved cognitive function	65
16	*Barnebydendron riedelii*	Leaf	Methanolic extract	TAA	Reduced neuroinflammation, improved neurotransmitter levels	66

17	Chrysin	-	Active molecule	TAA	Improved cognitive function, reduced apoptosis	67
18	C Phycocyanin (*Spirulina platensis*)	Algae	Active molecule	TAA	Improved survival rate, reduced astrocytic edema	68
19	*Tinospora cordifolia*	Stem	Water extract	TAA	Reduced hyperammonemia, improved neurobehavioral function	69
20	*Origanum vulgare*	Leaves	Hexane extract	TAA	Reduced oxidative stress, comparable to silymarin	70

Conclusion

Hepatic encephalopathy remains a formidable clinical challenge intricately linked to the complex interplay between liver dysfunction and neurocognitive impairment. The burgeoning body of evidence underscores the inadequacy of conventional therapies in fully addressing the multifactorial nature of this condition. In this context, the exploration of medicinal plants offers a compelling adjunctive strategy harnessing the neuroprotective, anti-inflammatory, antioxidant, and hepatoprotective properties inherent in phytochemicals. Integrating such botanical therapeutics into the broader framework of HE management not only reflects a paradigm shift towards a more holistic, patient-centered approach but also holds the promise of mitigating disease burden while enhancing quality of life. Continued interdisciplinary research is imperative to validate efficacy, elucidate mechanisms, and establish standardized formulations, ultimately paving the way for phytotherapy to become a cornerstone in managing hepatic encephalopathy holistically.

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