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REVIEW ARTICLE

Plant-Based Anti-inflammatory Interventions for Neuroinflammation in Hepatic Encephalopathy

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Abstract: Hepatic encephalopathy (HE) occurs as a spectrum of neuropsychiatric abnormalities in patients with compromised liver function. While ammonia has traditionally been considered the primary mediator in, HE pathogenesis, recent evidence indicates that inflammation plays a crucial role in disease progression. The liver's impaired function leads to elevated blood ammonia levels, causing neurotoxic effects and contributing to cognitive dysfunction, lethargy, and potential progression to coma. However, clinical observations reveal that ammonia levels alone do not correlate perfectly with disease severity, suggesting the involvement of additional factors. Systemic inflammation and neuroinflammation are attributed as significant contributors to HE progression, working synergistically with ammonia to worsen cognitive impairment and accelerate disease progression. Current therapeutic regimens primarily focus on reducing blood ammonia levels, but these approaches often have notable side effects and may not address all aspects of the disease. Plant-based interventions, with their inherent anti-inflammatory properties, present a promising alternative therapeutic approach. Several plants and their bioactive compounds, including genistein, rutin, chrysin, allicin, and thymoquinone, have demonstrated significant potential in preclinical studies by modulating inflammatory pathways and improving cognitive function in HE models. These natural compounds may offer effective therapeutic options with potentially fewer side effects compared to conventional treatments. Integration of anti-inflammatory strategies, particularly plant-based interventions, into HE management protocols may enhance treatment outcomes and improve patient quality of life.

Keywords: Hepatic encephalopathy; Neuroinflammation; Ammonia toxicity; Plant-based therapy; Cognitive dysfunction.

1. Introduction

Hepatic encephalopathy is a complex neuropsychiatric syndrome that develops when liver function becomes compromised, leading to an accumulation of neurotoxic substances in the bloodstream [1]. The condition occurs through a spectrum of neurological abnormalities, ranging from subtle cognitive changes to severe complications including coma and death [2]. The liver orchestrates numerous physiological processes, including macronutrient metabolism, blood volume regulation, cholesterol homeostasis, immune response mediation, and xenobiotic compound metabolism [3]. When liver function deteriorates, these processes become impaired, potentially leading to conditions such as hepatic encephalopathy [4]. The development of hepatic encephalopathy can occur through various pathways, including acute liver failure, chronic liver disease, or portosystemic shunting [5]. Based on the underlying etiology, HE is categorized into three distinct types: Type A, associated with acute liver failure without pre-existing liver conditions; Type B, linked to portosystemic shunting; and Type C, resulting from chronic liver failure [6]. In cirrhotic patients, HE presents in two forms: covert and overt. Covert HE manifests as subtle neurophysiological and psychomotor abnormalities without obvious clinical signs, while overt HE presents with clear clinical manifestations including lethargy, personality changes, and dyspraxia [7]. While the complete pathogenesis of HE remains to be fully elucidated [8], ammonia has been identified as a central player in disease development. As a potent neurotoxic substance, ammonia's effects on the brain range from cognitive impairment to seizures and death. Multiple mechanisms underlie ammonia's neurotoxicity. In the brain, ammonia metabolism occurs through the conversion of glutamate to glutamine in astrocytes. However, elevated ammonia levels lead to glutamine accumulation, which, due to its osmotic properties, contributes to brain edema development [9].

Despite substantial evidence supporting ammonia's role in HE pathogenesis, recent research suggests that the multifaceted nature of the disease cannot be explained by ammonia alone. While ammonia's contribution remains integral, it appears to work in concert with other factors rather than acting independently [10].

Over the past decade, inflammation has gained recognition as a significant contributor to HE pathogenesis. Studies have shown that inflammatory responses worsen encephalopathy in acute liver failure patients and reduce their transplantation eligibility [11]. Similarly, cirrhotic patients with severe encephalopathy demonstrate heightened systemic inflammatory responses [12, 13]. These

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findings show that addressing inflammatory responses could serve as an effective strategy to alleviate HE symptoms and prevent disease progression [14]. Current HE management primarily relies on medications such as lactulose, rifaximin, metronidazole, and ornithine-aspartate, which focus mainly on reducing blood ammonia levels [15, 16]. While rifaximin and lactulose have shown efficacy in reducing serum inflammatory mediators and improving cognitive function [17, 18], their associated adverse effects can lead to poor patient compliance. The limitations of conventional treatments have sparked interest in alternative therapeutic approaches. Plants and plant-derived compounds, known for their anti-inflammatory properties, could be promising candidates for HE treatment [19]. This review summarizes the significance of inflammatory responses in exacerbating HE and evaluates the potential of plant-based anti-inflammatory interventions based on preclinical evidence

Table 1. Classification and Clinical Features of Hepatic Encephalopathy

Type	Cause	Clinical Manifestations	Features
Type A	Acute liver failure	Rapid onset, cerebral edema	High mortality risk
Type B	Portosystemic bypass	Variable progression	No intrinsic liver disease
Type C	Cirrhosis	Gradual onset	Most common form
Minimal HE	Cirrhosis	Subtle cognitive deficits	Requires specialized testing
Overt HE	Cirrhosis	Clear neurological signs	West Haven criteria grades I-IV

2. Pathophysiological Role of Ammonia in Hepatic Encephalopathy

The relationship between ammonia and its deleterious effects in HE was first documented by Nencki and Hahn in 1890, through their groundbreaking experiments with surgically created portosystemic shunts in dogs [20]. Their work demonstrated that when nitrogen-rich blood bypassed the liver, dogs developed encephalopathic symptoms including ataxia, aggressiveness, and progression to stupor and coma, particularly after ammonia-rich meals [21].

2.1. Clinical Evidence of Ammonia's Role

Clinical studies have reinforced ammonia's significance in HE pathogenesis. A landmark study by Bernal et al., involving 257 patients, established a positive correlation between serum ammonia levels and intracranial pressure, a hallmark of acute hepatic encephalopathy [22]. The mechanism involves ammonia detoxification in brain astrocytes, where glutamine synthetase incorporates ammonia into glutamate to produce glutamine. In hyperammonemic states, excessive glutamine production leads to water accumulation due to glutamine's osmotic properties, resulting in brain edema [23].

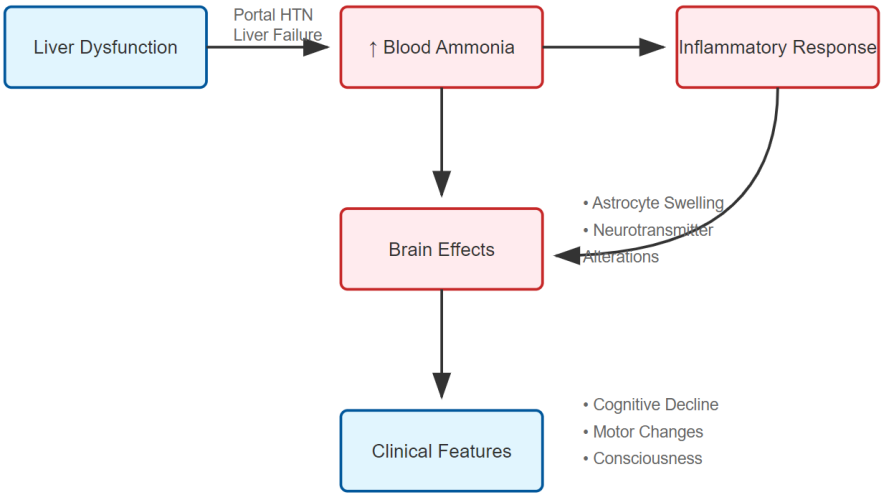

Figure 1. Pathophysiology of Hepatic Encephalopathy

Several experimental studies have validated these mechanisms. Takahashi et al. demonstrated that rats infused with ammonium acetate developed increased brain water content and elevated glutamine levels. Conversely, when treated with L-methionine sulfoxime, a glutamine synthetase inhibitor, prior to ammonium acetate infusion, the rats showed reduced brain water content and glutamine levels [24]. Master et al. corroborated these findings, showing that continuous ammonium acetate administration following portacaval anastomosis resulted in brain edema, which was prevented by methionine-sulfoximine pre-administration [25].

2.2. Cognitive Dysfunction in HE

2.2.1. Animal Model Studies

Cognitive impairment represents a significant manifestation of chronic HE. Mendez et al. evaluated spatial memory changes across three chronic HE models: portal hypertension, portacaval shunt (Type B HE), and thioacetamide intoxication (Type C HE). Using the Morris water maze, they demonstrated significant spatial memory impairment across all models [26].

2.2.2. Ammonia's Impact on Cognitive Function

Aguilar et al. further investigated ammonia's role in cognitive dysfunction through postnatal and pre/neonatal hyperammonemic exposure in rats. Their behavioral assessments using active and passive avoidance tasks revealed that rats with prenatal exposure to ammonia-rich diets showed marked cognitive deficits [27].

2.3. Molecular Mechanisms

The glutamate-nitric oxide-cGMP pathway, crucial for long-term potentiation and memory formation, is significantly affected by hyperammonemia. Hermenegildo et al. used in vivo microdialysis to demonstrate that chronic hyperammonemia impairs this pathway in the cerebellum [28]. Monfort et al. extended these findings to portacaval anastomosis models, showing reduced cGMP formation and guanylate cyclase activation even with NO donor administration [29].

2.4. Limitations of Ammonia-Centric Theory

Despite substantial evidence supporting ammonia's role, clinical observations suggest a more complex pathogenesis. Ong et al.'s study of 121 cirrhotic patients revealed that while ammonia levels correlate with disease severity, 69% of Grade 0 HE patients showed elevated ammonia levels without clinical symptoms [30]. This overlap in ammonia levels between symptomatic and asymptomatic patients indicates that additional factors contribute to disease progression [31, 32]

3. Inflammation in Hepatic Encephalopathy

3.1. Systemic Inflammatory Response in Liver Failure

Systemic Inflammatory Response Syndrome (SIRS) frequently accompanies both acute and chronic liver failure. Characterized by alterations in body temperature, heart rate, respiratory rate, and white blood cell count, SIRS significantly influences HE progression [33]. In acute liver failure patients, Rolando's research revealed that 56.8% of admitted patients developed SIRS, with 54% developing infections. Notably, patients manifesting SIRS components showed accelerated encephalopathy progression and increased intracranial pressure [34].

3.2. Synergistic Effects of Inflammation and Hyperammonemia

The intricate relationship between inflammation and hyperammonemia was elucidated in Shawcross's pivotal study. Cirrhotic patients with SIRS components who received oral amino acid solutions showed worsened neuropsychological function with elevated ammonia levels. Remarkably, when SIRS subsided, neuropsychological deterioration decreased despite persistent hyperammonemia, indicating inflammation's crucial role in exacerbating ammonia-induced cognitive impairment [35].

3.3. Inflammatory Mechanisms in HE Progression

3.3.1. Brain Edema

Brain edema, a major mortality factor in acute liver failure-associated HE, involves complex inflammatory mechanisms. Chung's research demonstrated that portacaval anastomosis followed by ammonia infusion increased brain water content, while indomethacin administration reduced brain edema development, highlighting inflammation's role [36].

3.3.2. Inflammatory Mediators and Disease Progression

Jiang's investigations using hepatic devascularization models revealed progressive increases in serum TNF-α, IL-6, and IL-1β levels, peaking during coma stages. Brain tissue analysis showed enhanced microglial activation and elevated pro-inflammatory cytokine expression, correlating with brain edema development and coma onset [37].

Table 2. Inflammatory Mediators in Hepatic Encephalopathy

Mediator	Primary Source	Effects	Clinical Significance
TNF-α	Kupffer cells, microglia	Neuroinflammation, BBB disruption	Correlates with HE severity
IL-1β	Activated microglia	Astrocyte activation, neuronal dysfunction	Early marker of progression
IL-6	Multiple cell types	Acute phase response, inflammation	Predictor of poor outcomes
IL-18	Inflammasome activation	Microglial activation	Associated with cognitive decline
NF-ϰB	Various cell types	Master regulator of inflammation	Therapeutic target

3.3.3. Genetic Evidence

Chantal's research provided genetic evidence through TNF-α and IL-1β receptor gene deletion studies. Mice lacking these inflammatory mediator genes showed delayed brain edema development and slower progression to coma following azoxymethane administration [38].

3.4. Anti-inflammatory Interventions

3.4.1. TNF-a Modulation

Chastre's work with etanercept, a TNF-α blocking agent, demonstrated significant therapeutic potential. In azoxymethane-induced HE, etanercept reduced plasma TNF-α and IL-6 levels, decreased cerebral IL-6, diminished microglial activation, and delayed coma progression [39].

3.4.2. Chronic HE Management

In chronic HE models, Rodrigo's research showed that portacaval shunting-induced learning and motor impairments corresponded with increased microglial activation and elevated cerebellar IL-1β. Ibuprofen administration improved cognitive and motor function by reducing neuroinflammation [40].

3.4.3. TNF-a Neutralization Effects

Dadsetan's studies with infliximab revealed its efficacy in improving cognitive function through neuroinflammation reduction. The treatment normalized serum IL-6 and IL-10 levels, reduced hippocampal pro-inflammatory cytokine expression, and restored AMPA and NMDA receptor expression crucial for learning and memory [41].

Table 3. Comparison of Anti-inflammatory Interventions in HE

Intervention Type	Efficacy	Safety Profile	Cost	Clinical Implementation
Conventional medications	High	Moderate	High	Well-established
Plant-based compounds	Moderate-High	High	Low-Moderate	Limited clinical data
Combination therapy	High	Moderate	High	Emerging approach
Traditional formulations	Variable	Generally safe	Variable	Region-dependent
Novel plant extracts	Under investigation	Promising	Variable	Research phase

4. Plant-Based Interventions

4.1. Genistein

Genistein, a prominent soy isoflavone, has shown remarkable potential in HE treatment. Ganai's investigations using D-galactosamine-induced HE models demonstrated genistein's ability to improve spatial learning in the Morris water maze test. The compound significantly reduced hippocampal expression of TNF-α, IL-4, and IL-1β mRNA, suggesting its efficacy in modulating neuroinflammatory responses. The improvement in glutamatergic neurotransmission and reduction in ammonia levels further supported genistein's therapeutic potential [42].

Table 4. Plant-Based Compounds with Anti-inflammatory Properties in HE

Compound	Source	Mechanism of Action	Experimental Evidence
Genistein	Soy	NF-ϰB inhibition, TNF-α reduction	Improved spatial learning
Rutin	Citrus fruits	Antioxidant, cytokine modulation	Reduced ammonia levels
Chrysin	Honey, propolis	TLR4/NF-ϰB pathway inhibition	Enhanced cognitive function
Allicin	Garlic	TNF-α/IL-1β reduction	Decreased liver enzymes
Thymoquinone	Black seed	Microglial inhibition	Reduced brain edema

4.2. Rutin

Mansour's research explored rutin's efficacy against thioacetamide and γ-radiation-induced HE. Rutin administration effectively reduced elevated serum levels of liver enzymes and ammonia. The compound demonstrated significant anti-inflammatory properties by reducing pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) while enhancing anti-inflammatory IL-10 levels, suggesting a balanced immunomodulatory approach [43].

4.3. Chrysin

Marasy's investigations into chrysin revealed its effectiveness in thioacetamide-induced HE. The compound improved cognitive and motor function as assessed through novel object recognition and rotarod tests. Chrysin's mechanism involved reducing brain NF-ϰB, TNF-α, and IL-6 levels, along with decreased Toll-like receptor-4 gene expression, indicating its broad anti-inflammatory effects [44]

4.4. Allicin

Allicin, derived from garlic, showed promising results in Saleh's acute liver failure studies. The compound effectively reduced serum liver enzymes, bilirubin, and ammonia levels. Its anti-inflammatory action, demonstrated through reduction of TNF-α and IL-1β levels in both liver and brain tissue, suggests a dual-action therapeutic approach [45].

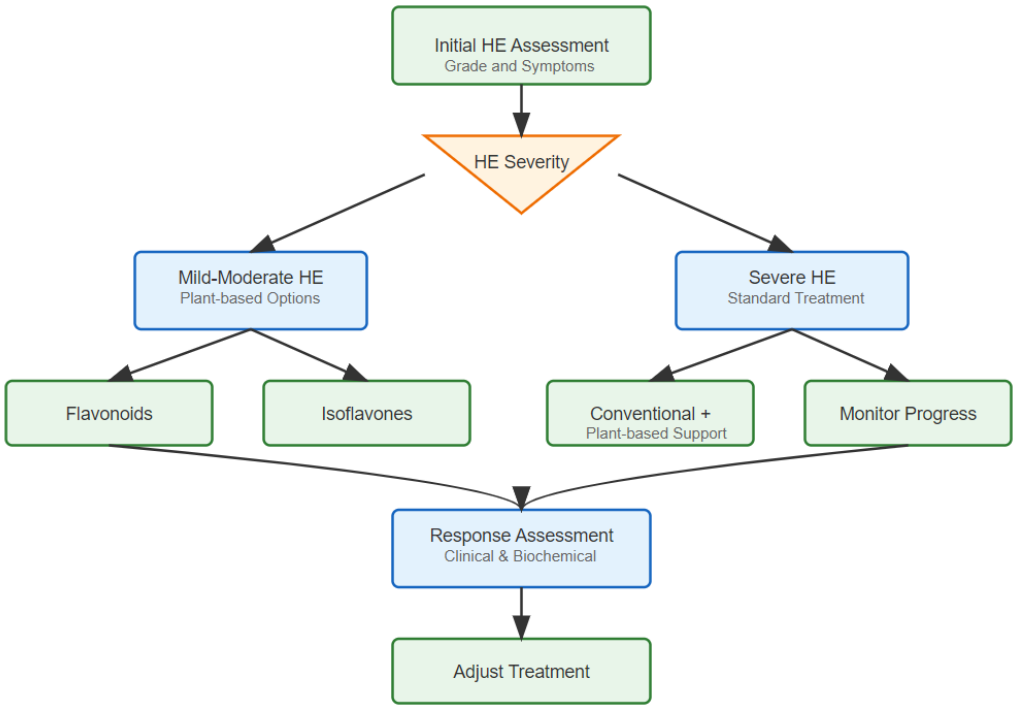

Figure 2. Treatment Algorithm for Plant-Based Interventions

4.5. BabaoDan

Lu Lu's research on BabaoDan demonstrated its effectiveness in both acute and chronic HE models. The formulation improved brain function and reduced liver enzyme levels while inhibiting inflammatory mediator expression. Its ability to modulate TNF-α, IL-1β, IL-6, NF-ϰB, and Toll-like receptor-4 gene expression in both liver and brain tissue suggests comprehensive anti-inflammatory effects [46].

4.6. Barnebydendron Flavonoids

Baraka's studies on Barnebydendron riedelii leaf extract flavonoids showed significant improvement in thioacetamide-induced HE. The treatment enhanced memory and motor function while reducing inflammatory markers through NF-ϰB/IL-6 pathway modulation [47].

Table 5. Clinical Markers and Their Significance in HE Monitoring

Marker	Normal Range	Significance in HE	Monitoring Frequency
Ammonia	15-45 µmol/L	Disease severity	Every 4-6 hours in acute cases
CRP	<10 mg/L	Inflammatory status	Daily in hospitalized patients
IL-6	<7 pg/mL	Prognosis indicator	As clinically indicated
TNF-α	<15.6 pg/mL	Treatment response	Research settings
Liver enzymes	Variable	Underlying condition	Weekly in stable patients

4.7. Ashwagandha

Khalil's research on Ashwagandha root extract demonstrated its effectiveness in improving cognitive function and reducing neuroinflammation. The extract significantly improved performance in memory-related tasks and reduced NF-ϰB and TNF-α expression in brain and liver tissues [48].

4.8. Thymoquinone

Hajipour's investigations of thymoquinone revealed its ability to improve cognitive function and reduce blood-brain barrier disruption in HE. The compound effectively reduced brain water content and inflammatory mediators in the hippocampus [49].

4.9. Frankincense

Marziehsadat's research demonstrated frankincense's ability to improve cognitive function in bile duct ligation-induced HE. The treatment reduced escape latency time in the Morris water maze and decreased hippocampal TNF-α mRNA expression [50].

4.10. Ginseng Berry Extract

Choi's studies showed ginseng berry extract's effectiveness in improving both reference and working memory in mild bile duct ligation-induced HE. The extract reduced microglial activation and TNF-α levels, demonstrating its anti-neuroinflammatory properties [51]

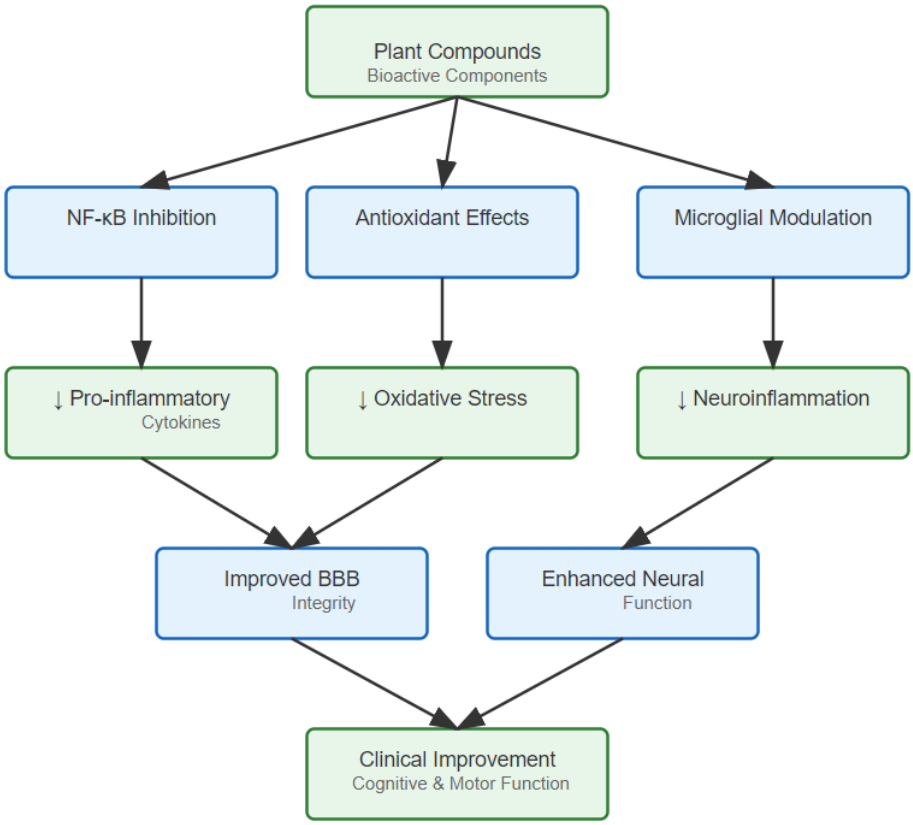

Figure 3. Mechanistic Pathway of Plant-Based Anti-inflammatory Effects in HE

5. Conclusion

Hepatic encephalopathy presents a complex neuropsychiatric syndrome where both hyperammonemia and inflammation play pivotal roles in disease progression. While ammonia has long been recognized as a primary mediator in HE pathogenesis, current evidence indicates that inflammatory processes significantly influence disease severity and progression. The interaction between hyperammonemia and inflammation suggests that therapeutic strategies targeting both pathways may yield superior clinical outcomes. Plant-based interventions, with their diverse array of bioactive compounds, offer promising therapeutic alternatives for HE management. These natural compounds demonstrate multiple mechanisms of action, including modulation of inflammatory pathways, reduction of oxidative stress, and improvement of cognitive function. The preclinical evidence presented in this review supports their potential as therapeutic agents, with several key advantages: First, many plant-based compounds exhibit dual action, simultaneously addressing both inflammatory responses and ammonia-related toxicity. Second, these natural interventions generally demonstrate favorable safety profiles compared to conventional synthetic drugs. Third, the diverse molecular targets of plant-based compounds suggest potential for developing combination therapies that might enhance therapeutic efficacy. Plant-based anti-inflammatory interventions represent a valuable therapeutic approach that merits further exploration and development. Their capability to provide effective treatment options with fewer side effects makes them particularly attractive for long-term HE management.

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