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Multi-Target Pharmacological Strategies for Hepatoprotection and Cognitive Enhancement

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Abstract: Hepatic dysfunction and cognitive impairment are increasingly recognized as interrelated conditions mediated through the liver–brain axis, involving complex interactions between metabolic, inflammatory, and neurochemical pathways. Key mechanisms such as hyperammonemia, oxidative stress, neuroinflammation, and cholinergic dysfunction contribute to both hepatocellular damage and neuronal impairment. Conventional single-target therapies often fail to adequately address this multifactorial pathology, highlighting the need for multi-target pharmacological strategies.

This review provides a comprehensive overview of shared pathophysiological mechanisms linking liver and brain dysfunction and discusses emerging therapeutic approaches that simultaneously target oxidative stress, inflammatory cascades, neurotransmitter systems, and gut microbiota. Pharmacological interventions, including antioxidants, anti-inflammatory agents, acetylcholinesterase inhibitors, and ammonia-lowering therapies, have significant potential to improve both hepatic and cognitive outcomes. Additionally, advances in network pharmacology, polypharmacology, microbiome-based interventions, and nanotechnology-driven drug delivery systems are shaping the future of multi-target therapy.

Keywords: Liver–brain axis; Hepatoprotection; Cognitive enhancement; Oxidative stress; Neuroinflammation.

1. Introduction

The liver and brain are connected organs that maintain systemic homeostasis via metabolic, detoxification, and neurochemical processes. Evidence shows that hepatic dysfunction affects brain function, leading to cognitive impairments ranging from mild deficits to severe neuropsychiatric conditions such as hepatic encephalopathy (HE) (Butterworth, 2013). This interaction, known as the liver–brain axis, involves metabolic, inflammatory, and neurochemical signaling pathways (Felipo, 2013).

Hyperammonemia, due to impaired hepatic detoxification, is a main factor in liver-related cognitive dysfunction. Elevated ammonia crosses the blood–brain barrier, leading to astrocyte swelling, oxidative stress, and disturbed neurotransmission (Felipo, 2013). At the same time, systemic inflammation from liver injury triggers neuroinflammation by activating microglia and elevating pro-inflammatory cytokines such as TNF-α and IL-1β, thereby worsening neuronal damage (Montagnese et al., 2015).

Oxidative stress, inflammation, and cholinergic dysfunction are common in both hepatic and neurocognitive disorders. Excessive reactive oxygen species (ROS) cause lipid peroxidation, protein oxidation, and mitochondrial dysfunction in both hepatocytes and neurons (Sies, 2017). Inflammatory pathways such as NF-κB cause tissue injury in the liver and synaptic dysfunction in the brain (Tilg et al., 2016). Additionally, cholinergic dysfunction, marked by reduced acetylcholine levels and increased AChE activity, is critical in cognitive decline and may also affect systemic inflammatory responses (Tracey, 2007).

Because these disorders are complex, single-target therapies often fail. Interest in multi-target strategies is growing. Such therapies target oxidative stress, inflammation, and neurotransmitter systems together. This comprehensive approach can manage both hepatic injury and cognitive impairment. This review discusses shared mechanisms and highlights new multi-target therapeutic strategies for hepatoprotection and cognitive enhancement.

2. Pathophysiological Mechanisms

Hepatic dysfunction and cognitive impairment are linked by metabolic, inflammatory, and neurochemical pathways. Hyperammonemia, oxidative stress, neuro-inflammation, and neurotransmitter imbalance are central to this process. They collectively cause both liver cell and neuronal dysfunction.

2.1. Hyperammonemia and Neurotoxicity

Hyperammonemia is a hallmark of liver dysfunction caused by impaired urea cycle activity. Ammonia crosses the blood–brain barrier and is taken up by astrocytes, which convert it to glutamine. Excess glutamine creates an osmotic imbalance, leading to astrocyte swelling and cerebral edema. This disrupts neuronal signaling and contributes to cognitive impairment and hepatic encephalopathy (Butterworth, 2013; Felipo, 2013). Ammonia also alters glutamatergic and GABAergic neurotransmission, which impairs synaptic function (Felipo, 2013).

2.2 Oxidative Stress

Oxidative stress is key in liver injury and neurodegeneration. Excessive ROS induces lipid peroxidation, protein oxidation, and DNA damage. In the liver, oxidative stress leads to cell death and fibrosis. In the brain, it hurts mitochondria and promotes neuronal death (Sies, 2017). Damaged mitochondria create more ROS, starting a cycle of cellular damage.

2.3 Neuroinflammation and Systemic Inflammation

Liver injury triggers systemic inflammation characterized by elevated circulating cytokines, including tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6). These cytokines can cross the blood–brain barrier or signal across it, activating microglia and inducing neuroinflammation. Sustained microglial activation leads to synaptic dysfunction, neuronal injury, and cognitive decline (Montagnese et al., 2015). In parallel, inflammatory signaling pathways such as nuclear factor-kappa B (NF-κB) exacerbate both hepatic and neuronal damage (Tilg et al., 2016).

2.4 Cholinergic Dysfunction

The cholinergic system is crucial for learning and memory. Cognitive impairment is associated with lower acetylcholine levels and higher AChE activity. Acetylcholine also controls inflammation via the cholinergic anti-inflammatory pathway. Vagal nerve stimulation reduces cytokine release. When this pathway falters, both neuroinflammation and liver injury progress (Tracey, 2002).

2.5 Gut–Liver–Brain Axis

The gut microbiota helps control liver and brain function. In liver disease, dysbiosis increases intestinal permeability, allowing endotoxins (lipopolysaccharides) to enter the bloodstream. These activate hepatic Kupffer cells and systemic inflammation, which, in turn, affect the brain. Changes in gut microbes also influence neurotransmitter levels and neuroinflammatory pathways, connecting gut, liver, and cognitive health (Tripathi et al., 2018).

3. Multi-Target Pharmacological Strategies

The link between liver dysfunction and cognitive problems means therapies should target several disease pathways at once. Single-target drugs often aren't enough, since oxidative stress, inflammation, neurotransmitter imbalance, and metabolism are all involved. Multi-target strategies aim to address these issues together for both liver and brain health.

3.1 Antioxidant-Based Therapies

Antioxidant-based therapies are central to addressing oxidative stress in both liver injury and neurodegeneration. These therapies reduce reactive oxygen species (ROS) and help restore redox balance.

N-acetylcysteine (NAC), a precursor of glutathione, is widely used to treat acetaminophen-induced hepatotoxicity and has been shown to have neuroprotective effects by stabilizing mitochondria and reducing oxidative damage (Atkuri et al., 2007). Similarly, natural antioxidants such as polyphenols and flavonoids exhibit dual protective effects by attenuating oxidative stress in hepatocytes and neurons (Sies, 2017).

3.2 Anti-inflammatory Agents

Chronic inflammation drives the progression of liver diseases and neurodegenerative disorders. Drugs that target inflammatory mediators such as TNF-α, IL-1β, and COX-2 reduce liver injury and neuroinflammation.

NSAIDs and targeted cytokine inhibitors are effective in experimental models, mainly by blocking NF-κB signaling pathways (Tilg et al., 2016). Reducing systemic inflammation also improves cognitive function.

3.3 Cholinergic Modulators

Cognitive dysfunction is closely tied to disrupted cholinergic neurotransmission. AChE inhibitors such as donepezil and rivastigmine increase synaptic acetylcholine, improving memory and cognition. Cholinergic pathways also control systemic inflammation through the vagus nerve's anti-inflammatory pathway. This links cognitive improvement with benefits for the liver (Tracey, 2002).

3.4 Ammonia-Lowering Therapies

Ammonia-lowering therapies are foundational in managing liver-associated cognitive impairment by targeting key mechanisms involved in hyperammonemia. These strategies aim to reduce both ammonia production and absorption:

- Lactulose acidifies the gut lumen, reducing ammonia absorption
- Rifaximin alters gut microbiota to decrease ammonia production

These treatments improve cognitive function in people with hepatic encephalopathy (Bass et al., 2010).

3.5 Gut–Liver–Brain Axis Modulation

The gut microbiome greatly influences liver and brain function. Dysbiosis can cause endotoxemia and inflammation.

Probiotics, prebiotics, and synbiotics restore microbial balance, reduce gut leakiness, and lower inflammatory signals. These changes support better liver and brain function (Tripathi et al., 2018).

4. Emerging Approaches in Multi-Target Therapy

The complexity of interconnected hepatic and neurocognitive disorders has driven the development of innovative therapeutic strategies that move beyond traditional single-target paradigms. Emerging approaches focus on systems-level interventions that modulate multiple molecular pathways simultaneously, thereby improving therapeutic efficacy and translational potential.

4.1 Network Pharmacology and Systems Biology

Network pharmacology integrates systems biology, bioinformatics, and pharmacology to holistically understand drug–target–disease interactions. This approach identifies key nodes and signaling networks involved in both hepatic and neurological disorders, enabling the design of multi-target interventions. By mapping protein–protein interaction networks and signaling pathways, network pharmacology facilitates the identification of compounds that can simultaneously regulate oxidative stress, inflammation, and neurotransmission (Hopkins, 2008).

4.2 Polypharmacology and Multi-Target Drug Design

Polypharmacology involves the rational design or selection of drugs that interact with multiple biological targets. Unlike traditional "one drug–one target" strategies, multi-target-directed ligands (MTDLs) are engineered to exert combined antioxidant, anti-inflammatory, and enzyme-modulating effects. This approach has shown promise in complex diseases such as

Alzheimer's disease and chronic liver disorders, where multiple pathological pathways coexist (Peters, 2013).

4.3 Natural Products as Multi-Target Agents

Natural products are inherently multi-functional due to their diverse chemical composition. Phytochemicals such as flavonoids, alkaloids, and coumarins exhibit antioxidant, anti-inflammatory, and enzyme-inhibitory activities. These compounds can simultaneously modulate hepatic enzymes, reduce oxidative stress, and influence neurotransmitter systems, making them ideal candidates for dual hepatoprotective and cognitive-enhancing therapies (Koehn & Carter, 2005).

4.4 Gut Microbiome-Based Therapeutics

Advances in microbiome research have highlighted the importance of the gut–liver–brain axis in disease progression. Therapeutic strategies targeting the microbiome include probiotics, prebiotics, synbiotics, and faecal microbiota transplantation (FMT). These interventions modulate microbial composition, reduce endotoxin production, and influence neuroactive metabolite synthesis, thereby improving both liver function and cognitive outcomes (Cryan & Dinan, 2012; Tripathi et al., 2018).

4.5 Nanotechnology-Driven Drug Delivery

Nanotechnology offers advanced drug delivery systems that enhance bioavailability, target specificity, and therapeutic efficacy. Nanocarriers such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles can deliver drugs selectively to hepatic or neural tissues while minimizing systemic toxicity. This approach is particularly useful for multi-target therapies requiring precise delivery across biological barriers, including the blood–brain barrier (BBB) (Patra et al., 2018).

5. Conclusion and Future Perspectives

Hepatic dysfunction and cognitive impairment are closely interconnected through shared mechanisms involving oxidative stress, inflammation, hyperammonemia, and neurotransmitter imbalance. The concept of the liver–brain axis provides a unifying framework to understand how liver pathology contributes to neurocognitive decline. Given this complexity, conventional single-target therapies are often inadequate, whereas multi-target pharmacological strategies offer a more comprehensive and mechanistically relevant approach.

Therapeutic interventions that simultaneously modulate redox balance, inflammatory signaling, and cholinergic function have demonstrated significant potential in improving both hepatic and cognitive outcomes. In particular, antioxidants, anti-inflammatory agents, ammonia-lowering therapies, and cholinergic modulators collectively address the core pathological processes underlying these disorders (Butterworth, 2013; Tilg et al., 2016). In addition, modulation of the gut–liver–brain axis has emerged as a promising strategy, highlighting the importance of microbiome-targeted therapies in systemic disease management (Tripathi et al., 2018).

Future research should focus on the development of integrated multi-target therapeutic models, supported by advances in network pharmacology and systems biology. There is a need for well-designed preclinical and clinical studies that simultaneously evaluate hepatic and cognitive endpoints. The identification of reliable biomarkers linking liver function with neurocognitive status will be critical for early diagnosis and therapeutic monitoring. Furthermore, innovative approaches such as nanotechnology-based drug delivery and multi-target-directed ligands (MTDLs) hold promise for improving drug efficacy and tissue-specific targeting.

In conclusion, multi-target pharmacological strategies represent a rational and evolving paradigm for addressing the dual burden of hepatic and cognitive disorders. Translating these approaches into clinical practice will require interdisciplinary efforts integrating pharmacology, neuroscience, hepatology, and systems medicine.

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