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PHARMACOLOGY OF HERBAL COGNITIVE ENHANCERS: A GUT–BRAIN AXIS PERSPECTIVE

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ABSTRACT :

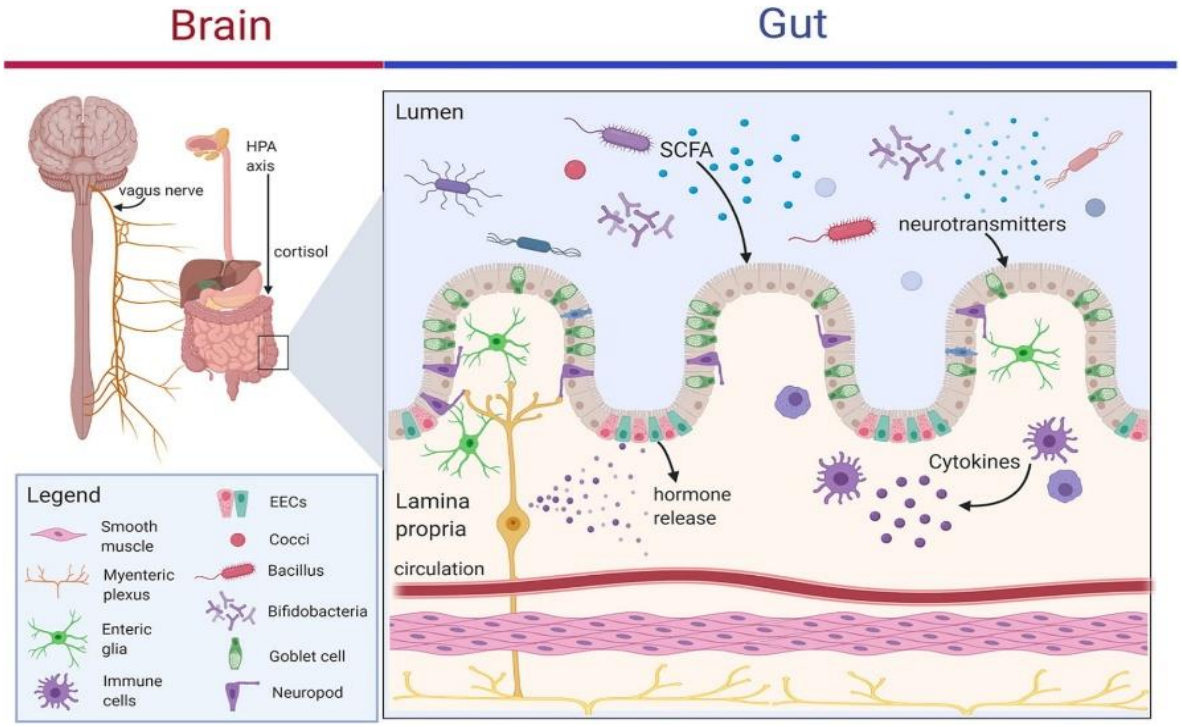
Cognitive decline associated with aging and neurodegenerative diseases is a major global health challenge. Herbal cognitive enhancers such as Bacopa monnieri, Withania somnifera, Panax ginseng, Curcuma longa, and Ginkgo biloba have been traditionally used for memory enhancement and neuroprotection. Recent research highlights the gut–brain axis (GBA) as a critical mediator linking gut microbiota with central nervous system (CNS) functions. The pharmacological activity of herbal compounds is increasingly recognized to depend on gut microbiome-mediated metabolism, modulation of neurotransmitter systems, and attenuation of neuroinflammation. This review summarizes current insights into the pharmacology of major herbal cognitive enhancers from a GBA perspective, emphasizing their mechanisms, clinical relevance, and future therapeutic potential.

1. Introduction

Cognitive functions, such as memory, learning, and attention, are essential for maintaining a good quality of life. Neurodegenerative conditions like Alzheimer's and Parkinson's diseases, along with age-related cognitive decline, are not effectively treated with existing synthetic medications. As a result, there has been a resurgence of interest in herbal remedies, grounded in Ayurvedic, Chinese, and other traditional practices, as potential cognitive enhancers.

The gut-brain axis (GBA) is a two-way communication system connecting the gut and the brain, playing a crucial role in neurological health through neural, endocrine, immune, and microbial channels. The gut microbiota is key in processing phytochemicals, improving their bioavailability, and producing neuroactive compounds. Exploring herbal pharmacology through the lens of the GBA could lead to new strategies for preventing and addressing cognitive decline.

Fig no:1 Gut Brain Axis



2. The Gut-Brain Axis and Cognition:

The GBA involves several pathways:

Neural: The vagus nerve transmits signals from the gut to the brain.
Endocrine: Gut microbiota influences the production of neurotransmitter precursors, such as tryptophan to serotonin.
Immune: Imbalances in microbiota can cause systemic inflammation, impacting neuroinflammation.
Metabolite: Microbial byproducts, like short-chain fatty acids (SCFAs), play a role in synaptic plasticity and the growth of new neurons.

Disruption of the GBA is linked to anxiety, depression, and cognitive dysfunction. Herbal cognitive enhancers may function as neuromodulators, in part through the regulation of the GBA.

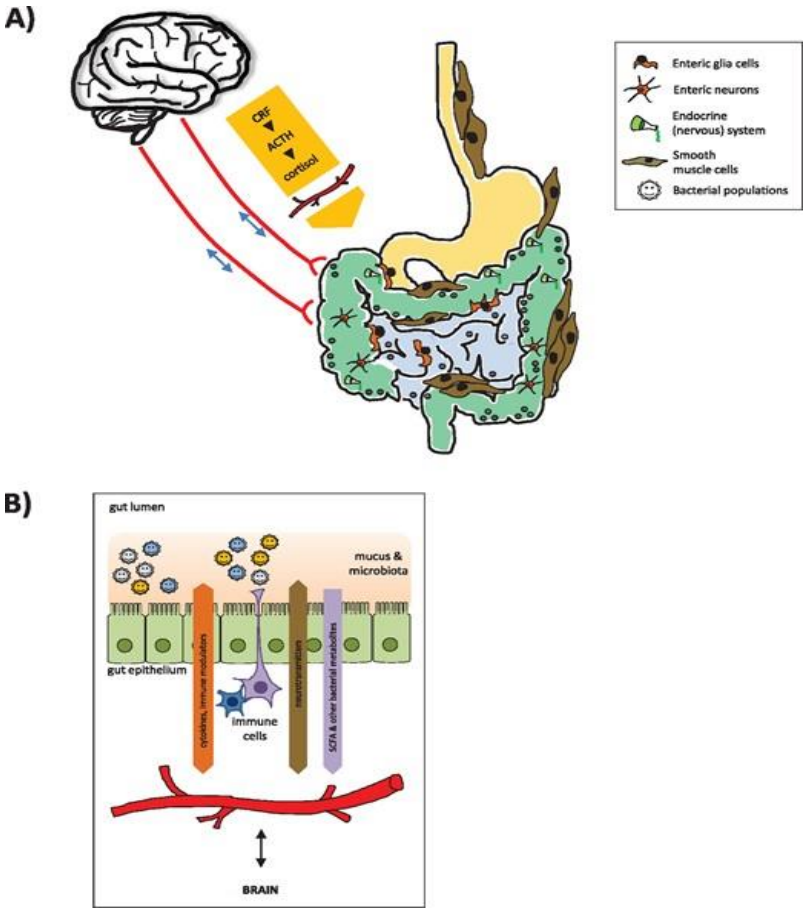


Fig.. no:2 Schematic Overview of the Gut-Brain Axis

Schematic Overview of the Gut-Brain Axis:
The illustration shows the gastrointestinal tract with the upper section (esophagus and stomach) highlighted in yellow. The small intestine (duodenum, jejunum, ileum) is depicted in light blue, while the large intestine (cecum and the ascending, transverse, and descending colon) is shown in green. The interactions between the gastrointestinal tract and both the autonomous and central nervous systems are represented by red lines. Short blue arrows indicate bidirectional communication, and the hypothalamic-pituitary-adrenal (HPA) axis is illustrated in dark yellow.

3. Herbal Cognitive Enhancers: Pharmacology and GBA Interactions

3.1 Bacopa monnieri (Brahmi)

- Active compounds: Bacosides.
- Pharmacology: Promotes synaptic plasticity, supports antioxidant defenses, and regulates serotonin and dopamine.
- GBA role: Boosts gut microbial diversity, facilitating the passage of bacoside metabolites across the blood–brain barrier.

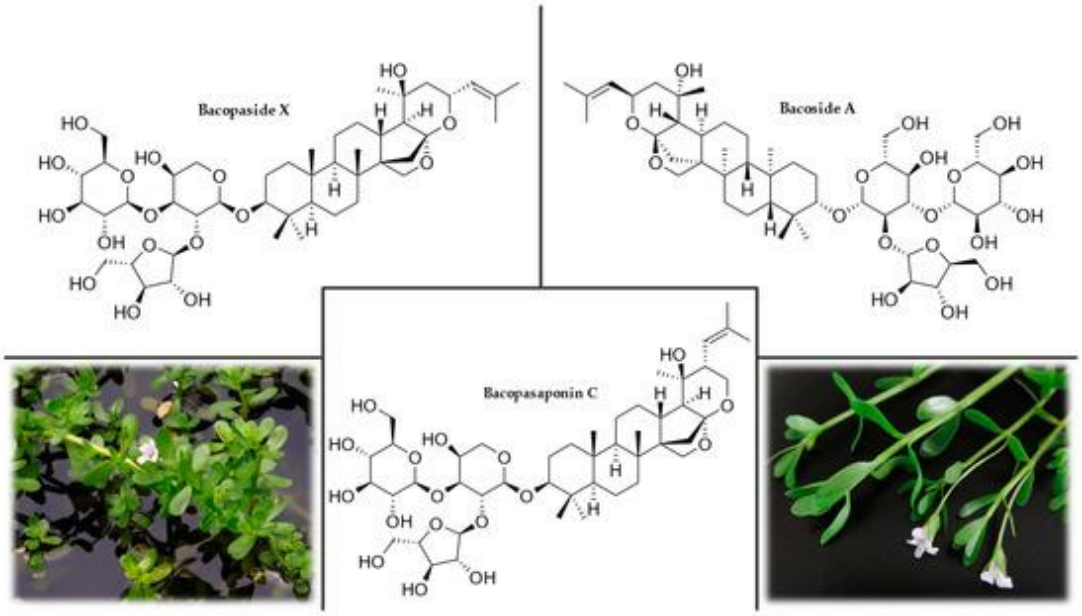


Fig. no.3 Bacopa monnieri (Brahmi) Main bioactive compound chemical structure

3.2 Withania somnifera (Ashwagandha)

- Active compounds: Withanolides.
- Pharmacology: Acts as an adaptogen, reduces stress, mimics GABA activity, and suppresses neuroinflammation.
- GBA role: Addresses stress-related gut dysbiosis, reinforces the gut barrier, and indirectly reduces neuroinflammation.

3.3 Panax ginseng

- Active compounds: Ginsenosides.
- Pharmacology: Enhances cholinergic signaling and stimulates neurotrophic factors.
- GBA role: Gut microbiota transforms ginsenosides into active metabolites, such as compound K, which boost cognitive functions.

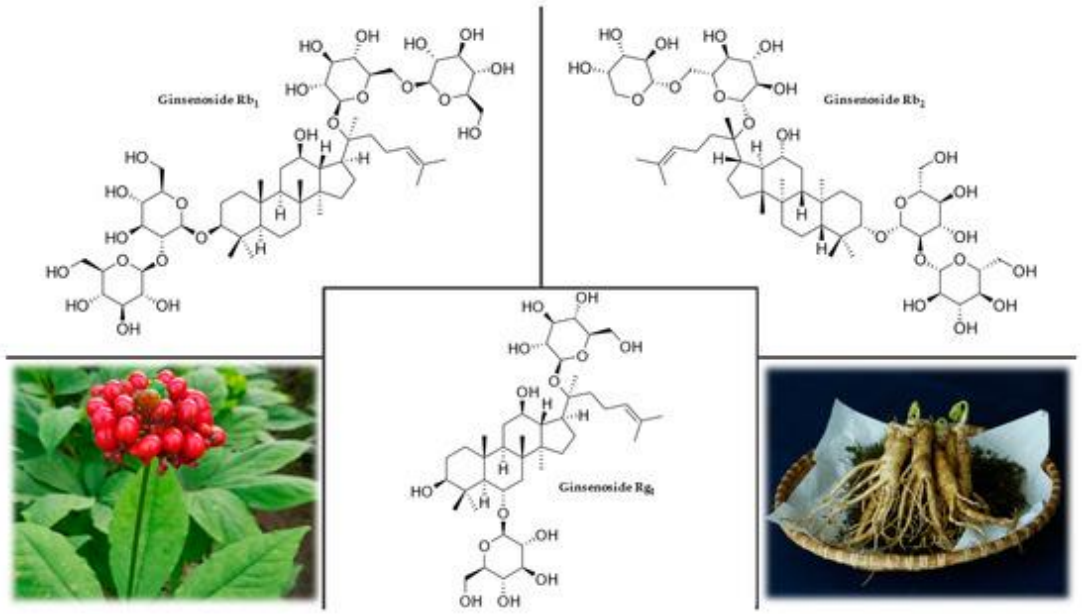


Fig. no.5 Panax ginseng Main bioactive compound chemical structure

3.4 Curcuma longa (Turmeric)

- Active compound: Curcumin.
- Pharmacology: Acts as an antioxidant and anti-inflammatory agent, and promotes BDNF and CREB signaling.
- GBA role: Serves as a prebiotic-like substance, with gut microbes increasing curcumin's bioavailability.

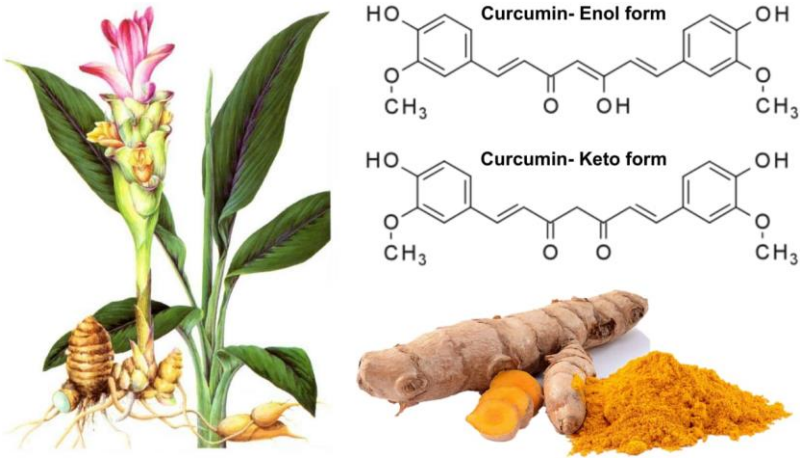


Fig. no.6 Curcuma longa (Turmeric)Main bioactive compound chemical structure

3.5 Ginkgo biloba

- Active compounds: Flavonoids and terpenoids.
- Pharmacology: Improves blood flow in the brain, modulates NMDA receptors, and has antioxidant properties.
- GBA role: Gut microbiota metabolizes flavonoids, enhancing neuroactivity

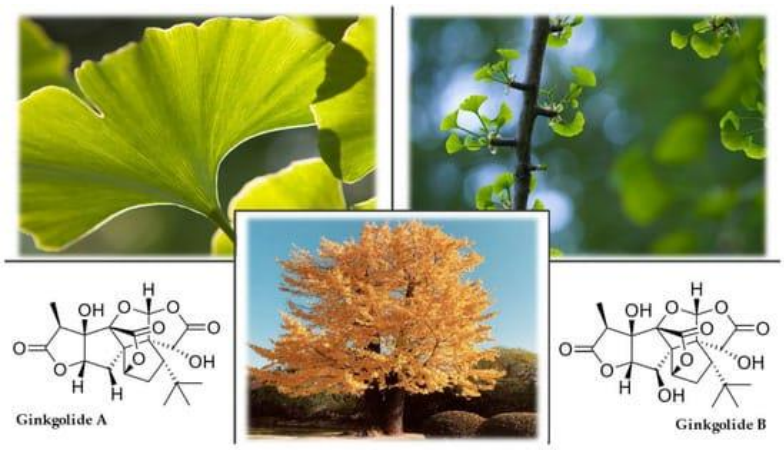


Fig. no.7 Ginkgo biloba Main bioactive compound chemical structure

4. Modulation of Gut Microbiota by Herbal Extracts

- Herbal components often function as prebiotics, encouraging beneficial bacteria like Lactobacillus and Bifidobacterium.
- Microbial fermentation enhances the bioavailability of polyphenols, alkaloids, and terpenoids.
- Correcting gut dysbiosis can reduce systemic inflammation and improve cognitive function.

5. Pharmacological Pathways via GBA

Herbal cognitive enhancers influence multiple interconnected pathways through the gut–brain axis:

- Neurotransmitter modulation: Herbal metabolites regulate cholinergic (acetylcholine), serotonergic, dopaminergic, and GABAergic systems. For example, Bacopa monnieri supports serotonin and dopamine regulation, while Ashwagandha enhances GABA signaling.
- Neuroprotection: Antioxidant phytochemicals mitigate oxidative stress, prevent lipid peroxidation, and protect against amyloid beta-induced neurotoxicity.
- Synaptic plasticity and neurogenesis: Curcumin and Ginseng increase BDNF and CREB levels, improving learning and memory.

- Microbial biotransformation: The gut microbiota converts poorly absorbable phytochemicals like ginsenosides, curcumin, and flavonoids into active metabolites with stronger CNS effects.

6. Clinical Evidence

Several clinical studies support the use of herbal cognitive enhancers:

- Bacopa monnieri: RCTs show improvements in memory, processing speed, and attention in healthy elderly adults.
- Withania somnifera: Clinical trials report enhanced cognitive performance, reduced stress, and better executive function in those with mild cognitive impairment.
- Panax ginseng: Found to improve working memory, attention, and fatigue resistance; effects vary based on individual microbiome composition.
- Curcumin: Chronic supplementation in older adults improves attention, working memory, and mood.
- Ginkgo biloba: Offers modest benefits in dementia and age-related decline, especially when combined with other nootropics.

7. Challenges and Future Directions

Despite promising results, challenges remain:

- Variability between individuals: Gut microbiota differences affect how herbal compounds are processed and their effectiveness.
- Standardization issues: Variability in plant sources, extraction techniques, and active ingredient concentrations hinder reproducibility.
- Bioavailability problems: Many herbal compounds, like curcumin, are poorly absorbed and rapidly metabolized.
- Clinical trial limitations: Small sample sizes, brief durations, and inconsistent outcomes limit generalization.

Future outlook:

- Integrating pharmacometabolomics with microbiome analysis can offer insights into individual responses.
- Combining synbiotics/psychobiotics with herbal extracts may enhance cognitive effects.
- Developing standardized formulas with nanocarrier systems could improve bioavailability.

8. Conclusion

Herbal cognitive enhancers hold significant promise for managing cognitive decline, as they act on multiple physiological areas. Moreover, their benefits extend beyond the brain by modulating the gut–brain axis, which activates key metabolites, balances neurotransmitters, and reduces neuroinflammation. Future strategies that combine herbal medicine with microbiome-focused treatments could lead to innovative, personalized approaches to support cognitive health.

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