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Phytoconstituents enhancing learning and cognition by targeting the gut-brain axis

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Abstract: The gut-brain axis, a sophisticated network of communication that links the brain and the gastrointestinal tract, plays a critical part in preserving cognitive function and overall mental health. A recent study has brought to light the ability of phytoconstituents bioactive substances derived from plants to modify this axis and improve cognitive function. These organic substances are present in fruits, vegetables, herbs, and other plant-based foods and work through different pathways to produce their effects, such as those of antioxidants, neuroprotectants, and anti-inflammatory agents. Phytoconstituents provide a promising natural strategy to promote brain health and mitigate cognitive decline by boosting the generation of beneficial metabolites, lowering systemic inflammation, and altering the gut microbiota composition. This review highlights the potential of some phytoconstituents to enhance cognitive processes by examining our current understanding of how they affect the gut-brain axis.

Keywords: Gut microbiota • Microbiome • Neuroinflammation • Phytoconstituents • Cognition • Brain

Introduction

The processes by which individuals analyse, store, and use information from their surroundings including perception, learning, memory, and decision-making are referred to as cognitive processes (Balkrishna et al 2020). It includes all of an organism's sensory and other information-processing systems for recognizing, appreciating, and engaging in constructive interactions with elements of its surroundings to satisfy existential demands such as growth, reproduction, and survival. Any autonomous biological system, from prokaryotes to complex creatures like humans, needs cognition to survive, thrive, and procreate. The foundation of cognition comprises control mechanisms, which control the activity of production mechanisms in response to shifting internal and external circumstances (Balkrishna et al 2020). The gut-brain axis (GBA), a bidirectional communication mechanism between the central nervous system (CNS) and the gut microbiota, plays a vital role in enhancing cognition through its effects on a variety of physiological and cognitive processes. Signalling molecules secreted by the GBA include neurotransmitters, Hormones, and cytokines, which can impact cognitive processes as they travel from the gut to the brain. The gut microbiome's synthesis of short-chain fatty acids (SCFAs) can positively impact mood, cognition, and inflammation by interacting with brain receptors and crossing the blood-brain barrier (BBB) (Guo et al 2022). Cognitive impairment may arise from alterations in the GBA; obesity or overnutrition alters the gut microbiota, affecting cognitive performance. This can decrease gut barrier permeability, leading to endotoxin release and cognitive decline. Chronic low-grade inflammation from high-nutrition diets can spread from peripheral tissues to the CNS, worsening cognitive impairment (Pferschy et al 2020). Probiotics may be able to treat cognitive decline and inflammation in the gut-brain axis. Rats given probiotics showed improvements in microglial activation, cerebral and synaptic neuronal damage, and memory impairments. Plant extracts can affect cognition and the microbiome-gut-brain axis. Plant extracts containing triterpenes, including ginsenosides, improve mental and cognitive function by modifying the gut-brain connection. These

compounds, broken down by gut microbiota, reduce inflammation, boost neurotrophic factors, and lower stress, positively affecting cognitive function (Bruce et al 2020). The reciprocal interaction and mutual association between the immune system and neurological system may be the source of aging-related changes in immunological function. These variations could be connected to the start of neurological illnesses like Alzheimer's disease (AD) via gut microbiota-induced neuroinflammation pathways (Mohapatra et al 2023). In this review, we will analyse the effects of phytoconstituents and plant extracts on enhancing cognition through focusing on the Gut-Brain-Axis.

Methodology

A collection of relevant research and review articles about the Phytoconstituents enhancing learning and cognition by targeting the gut-brain axis, was compiled from various resources such as PubMed (https://pubmed.ncbi.nlm.nih.gov), Scopus (https://www.scopus.com), and Google Scholar (https://scholar.google.com). Terms such as “gut-brain axis,” “cognition,” “phytoconstituents,” “herbal,” and “neuroinflammation” were employed. IMPPAT database (https://cb.imsc.res.in/imppat/home) was utilized to search various plants and their phytoconstituents that improves brain functions.

Results and Discussion

Regulation of brain activities by gut microbiota

"Gut-microbiota-brain axis" describes a complex network of relationships encompassing several biological systems that permit the brain and gut bacteria to communicate in both directions (Appleton 2018). The gastrointestinal (GI) tract of humans is home to a vast and varied microbial community comprising about 100 trillion microbes. The gut microbiota is made up of a variety of microorganism species, such as viruses, yeast, and bacteria. Firmicutes and Bacteroidetes comprise 90% of the gut microbiota, while *Verrucomicrobia*, *Proteobacteria*, *Fusobacteria*, and *Actinobacteria*, are the other major microbial groups (Dutta et al 2024). In the context of a healthy gut microbiota, the variance itself is seen as physiological, factors such as dietary preferences, age, and lifestyle. The intestinal and extraintestinal complications such as neurological disorders are greatly impacted by these physiological differences in gut microbiota. The makeup of the resident commensal communities differs from the typical state during gut microbiota dysbiosis. Research has demonstrated that gut dysbiosis contributes to the onset and progression of several conditions such as autoimmune, GI, respiratory, psychiatric, and viral conditions (Long et al 2020). Additionally, individuals with neurological and metabolic diseases have microbiota dysbiosis. Furthermore, extent data suggests that disruption of the number and composition of gut bacteria impacts synaptic plasticity and cognitive processes (Long et al 2020).

The GI microbiome primarily communicates with the central nervous system (CNS) through immune-related, neuronal, endocrine, and metabolic signalling pathways because the microbiome-gut-brain axis (MGBA) involves many interactions through multiple mechanisms. Communication between the brain and the gut's resident microbes occurs through neurotransmitters like γ-aminobutyric acid (GABA), serotonin, dopamine, or 5-hydroxytryptamine (5-HT), neuropeptides, hormones (like corticotrophin-releasing hormone secreted in the hypothalamic-pituitary-adrenal [HPA] axis), and short-chain fatty acids (SCFAs). In healthy conditions, the microbiota and immune system work together to produce the right immunological responses. On the other hand, immune response failure lies based on conditions like inflammatory and autoimmune diseases.

LPS and amyloids, two components of the GI microbiota, have also been demonstrated to have a significant role in some signalling pathways and proinflammatory cytokines linked to neurodegenerative inflammation. Therefore, "leaky gut syndrome" and dysbiosis of GI bacteria in AD patients might be viewed as key pathophysiological linkages in the transfer of neurotoxic chemicals derived from the microbiome over the BBB, which causes AD to proceed (Camilleri 2019).

Phytoconstituents responsible for enhancing cognition targeting the gut-brain axis

Phytoconstituents have been traditionally used for medical purposes, and standardized research on these substances is now underway. Several

phytoconstituents operate through various mechanisms, including those involving the GBA. Apigenin, an important plant flavonoid, has been shown to increase cognition (Hakimi et al 2020). Apigenin improved memory retention and learning impairments in mice with AD by restoring the ERK/CREB/BDNF pathway, reducing oxidative stress, and reducing the quantity of Aβ plaques. Apigenin plays a vital function in preserving brain health via the gut because of its capacity to correct imbalances in the gut flora and connect with the neurological system of the stomach and to that of the brain.

Table 1: Modulation of brain components and functions by common microbiota in the gut.

Gut Microorganism	Underlying MOA of gut microbiota	Behavioural changes	References
Bacteroides fragilis	↓4-Ethylphenylsulfate (4-EPS)	↑Communication ↓Repetitive behaviour ↓Anxiety-like behaviour	(Osadchiy et al 2019)
Lactobacillus reuteri	↑Oxytocin	↑Social behaviour Regulates neuronal plasticity	(Felger et al 2015)
Bifidobacterium longum	↑BDNF	↓Anxiety-like and depressive behaviour ↓Excitability ENS neurons	(Van et al 2021)
Lactobacillus sp., Ligilactobacillus sp., Ruminococcuss sp.	↑SCFA	↓depressive-like behaviour ↓Stress ↓Anxiety	(Van et al 2021; Kohler et al 2016)
Lactobacillus rhamnosus	↑GABA	↑Vagal mesenteric nerve firing ↑Stress responsiveness ↓Anxiety and depressive-like behaviour	(Gupta et al 2001)

By acting on the gut-brain axis, flavan-3-ols improve cognition via the following processes: gut bacteria metabolise flavan-3-ols to produce derivatives of arylvaleric acid and aryl-γ-valerolactone, which provide protection against AD. Aβ oligomers are specifically removed by valerolactones and their metabolites, preventing memory loss in AD mice models (Hakimi et al 2020). Isoorientin alters the gut microbiota in mice with AD, reducing the build-up of Aβ plaque and modifying the quantities of inflammatory markers including COX-2, iNOS, TNF-α, and IL-6. Promoting the expansion of certain bacteria in the intestinal and faecal microbiomes of AD mice, it improves cognitive performance. Isoorientin enhances cognition by protecting pre- and postsynaptic proteins, managing the p-PI3K/p-Akt/p-GSK3β pathway, and preventing hyperphosphorylation of tau protein, which halts apoptosis and neurodegeneration (Bedel et al 2018).

Curcumin interacts with the gut microbiota to produce metabolites that may address abnormalities in the gut microbiome, these metabolites are more pharmacologically active than curcumin. Different bacterial strains affect the gut-brain axis and cognitive function by producing different curcumin metabolites through metabolic pathways. Tetrahydrocurcumin (ThC), curcumin's active metabolite, enhances cognitive function and promotes neuronal regeneration in the hippocampus by activating the BDNF/TrkB-dependent pathway. This suggests that ThC has a role in altering signaling pathways that are essential for cognition. After traumatic brain injury, ThC decreased oxidative stress, increased autophagy-associated proteins, and mitigated apoptosis, highlighting its neuroprotective effects (Chang et al 2016). An investigation shows that resveratrol restores Wld S obstruction Nevertheless, exposure to WD suggested that SIRT2 regulation was dependable; this finding is surprising considering that resveratrol does not activate SIRT2 in vitro (Mishra et al 2024).

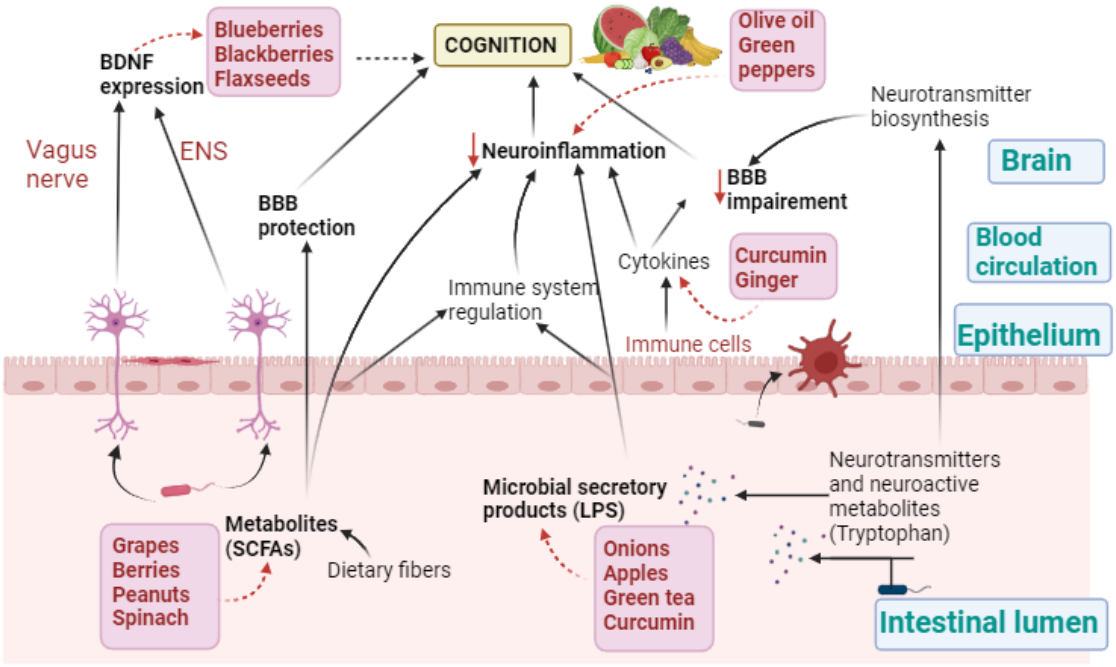

Fig. 1: Phytoconstituents influencing the gut-brain axis and its impact on cognition. (This figure illustrates the intricate relationship between diet, gut microbiota, and brain health through the gut-brain axis. It highlights how phytoconstituents found in different sources such as blueberries, blackberries, and flaxseeds can enhance cognition by promoting BDNF expression, SCFA synthesis, and protection against neuroinflammation. Key components like the vagus nerve and the ENS are shown to mediate these neurological effects. Additionally, the diagram emphasizes the role of dietary fibers from grapes, berries, and other foods in supporting the production of SCFA synthesis and other neurotransmitter biosynthesis, while compounds like curcumin and ginger help to regulate the immune response and maintain BBB integrity. BDNF expression is upregulated by the phytoconstituents available in blueberries, blackberries, and flaxseed. Olive oil and green pepper plays a major role in the reduction of neuroinflammation. These phytoconstituents play a significant role in the regulation of gut-brain axis associated cognition as depicted via various pathways and mechanisms. BDNF- Brain Derived Neurotrophic Factor; SCFAs- Short Chain Fatty Acids; ENS- Enteric Nervous System; BBB- Blood Brain Barrier)

The regulation of gut microbial diversity using the GLP-1, controlling gut and brain balance route, and improving gut-brain function balance via the resveratrol, 5-hydroxytryptamine (5-HT) syste affects the gut-brain axis. In the lamina propria of the small intestine, resveratrol reduces the expression of proinflammatory cytokines, balances Th1/Th2 towards Th2 polarisation, shifts the balance of T reg/Th17 towards T reg, and attenuates the increased permeability of the vascular and epithelial layers of the small intestine caused by cerebral ischemia. Resveratrol reduces the risk of BBB disruption following a stroke, which reduces neurological impairments and the size of cerebral infarcts. Its ability to reduce inflammation plays a part in its ability to improve cognitive function (Manolova et al 2014).

Phytoconstituents derived from plants found in Himalayan regions of India

Plants having medicinal constituents are utilized extensively to treat a wide range of illnesses and conditions including cognitive impairment. For the treatment of a variety of illnesses, rural and tribal tribes in India count on the Indian System of Medicines along with other recognized traditional

methods. One of the world's areas with the most biodiversity is the Himalayas.

Table 2: Phytoconstituents of many classes that control cognition by acting on the gut-brain axis

S.No.	Class	Name of phytoconstituents	Action	References
1.	Terpenoids	Linalool	Enhances gut microbiota balance and cognitive functions, and also enhances defence system of the neurological system against inflammation, oxidative stress, and neuronal death by targeting 5-HT, mucosal immunity, inflammatory markers	(Marques et al 2018)
		Ginkgolides B	Increment in 5-HT and BNDF producing gut microbiome; lowering anxiety and depression and also enhances mental capacity	(Temel et al 2020)
2.	Phenols	Eugenol	Neuroprotection by microbes from oxidative stress, toxicity, and stress brought on by IBS (Irritable Bowel Syndrome)	(Kosari et al 2018)
		Carvacrol	Depression is prevented by neuroprotection provided by enhancement of 5-HT levels and BDNF	(Kosari et al 2018)
		Ellagic acid	Offers neuroprotection against oxidative stress	(Moore et al 2018)
		Curcumin	Enhancement of BDNF, 5-HT, and kynurenine; all support neuroprotection against oxidative stress, depression, and apoptosis	(Marques et al 2018)
3.	Flavanoids	Anthocyanins	Focusing on increase levels of BNDF, 5-HT, and the healthy gut microbiome results in antidepressant, anti-inflammatory, and brain-aging prevention	(Moore et al 2018)
		Chrysin	Neuroprotection and gut defence against inflammation, apoptosis, and oxidative stress	(Dutta et al 2005)
		Hesperidin	Controls gastrointestinal motility and offers neuroprotection against inflammatory responses, toxicity, and depression.	(Moore et al 2018, Dutta et al 2005)
4.	Polyphenols	Resveratrol	Increases the 5-HT, prevents the reuptake of 5-HT, and offers neuroprotection against toxicity, oxidative damage, and effects similar to IBS.	(Sun et al 2020)

In the Indian Himalayan Region, there are approximately 3000 plant species that have been identified. These include medical plants, wild foods, fodder, medicinal and aromatic plants that provide essential oils, and sacred plants. As a vast series of mountains dividing China (Tibet) from India, the Himalayas are described as "strict," including latitudes of 26°20′ and 35°40′ North, and longitudes of 74°50′ and 95°40′ East. Jammu and Kashmir, Uttarakhand, Meghalaya, Arunachal Pradesh, Tripura, Himachal Pradesh, Sikkim, Manipur, Nagaland, Mizoram, and the hilly provinces of West Bengal and Assam are among the ten states that make up the Indian Himalayan region (Novelle et al 2015). As shown in table 3, The *Viccinium* genus (blueberries) shows in-vivo neuroprotective effects by protecting microglial cells and reducing neuroinflammation found in the Western Himalayas (Jammu and Kashmir, Uttarakhand). *Bauhinia coccinea* exhibits significant in-vitro anti-acetylcholinesterase, anti-amyloid-β, and antioxidant activities found in the Eastern Himalayas (Uttarakhand). In the Himalayan foothills (Doon valleys), *Bacopa floribunda* suppresses oxidative stress and neuroinflammation through in vivo mechanisms. *Calotropis gigantea* (stigmasterol)

lowers apoptosis induction by suppressing ROS production in-vitro in Uttarakhand and Sikkim. Finally, *Rhodiola rosea* shows anti-inflammatory, anti-apoptotic, and antioxidant effects in vivo in high-altitude regions of Ladakh, Himachal Pradesh, and Jammu and Kashmir (Lansky et al 2023).

Table 3: Medicinal plants found in different regions of Himalaya of India and their effects on brain

Plant	Type of study	Effects	Habitat	Reference
Viccinium genus (blueberries)	In-vivo	Protected microglia cells and reduces neuroinflammation	Western Himalayas (Jammu and Kashmir, Uttrakhand)	(Debnath et al 2020)
Bauhinia coccinea	In-vitro	Anti-AchE, anti-amyloid-β, and Antioxidant	Eastern Himalayas (Uttranchal Pradesh)	(Debnath et al 2020)
Bacopa floribunda	In-vivo	Suppression of oxidative stress, neuroinflammation	Himalayan foothills (Doon valleys)	(Kim et al 2021)
Calotropis gigantean (Stigmasterol)	In-vitro	Apoptosis induction is lowered by suppressing ROS production	Lower hilly areas Uttrakhand and Sikkim	(Pratiwi et al 2021)
Rhodiola rosea	In-vivo (Wistar rats)	Anti-inflammatory, anti-apoptotic and antioxidant	Ladakh, Himanchal Pradesh and Jammu and Kashmir	(Kim et al 2021; Pratiwi et al 2021)

Conclusion

The gut-brain axis is crucial for cognitive function, enabling communication between the gut microbiota and the brain via signalling molecules such as neurotransmitters, hormones, and cytokines. Disruptions in this communication, like gut dysbiosis, are linked to cognitive decline and neurodegenerative diseases such as Alzheimer's. Poor diet and obesity further contribute to cognitive impairment by causing gut barrier dysfunction and chronic inflammation. Phytoconstituents like apigenin, flavan-3-ols, and curcumin have shown potential to improve cognition by promoting gut microbiota balance, reducing inflammation, and activating neuroprotective pathways. These compounds, along with probiotics, enhance gut-brain interactions, reduce neuroinflammation, and support brain health. Research on these natural agents opens new possibilities for treating cognitive decline and neurological disorders by targeting the GBA.

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