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Epicatechin and brain health: current evidence with perspectives for integrated multi-omic analytical approaches

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Abstract

Epicatechin, a dietary flavan-3-ol abundant in cocoa and in a variety of fruits and beverages, has attracted increasing attention for its potential role in maintaining brain health. Human studies suggest that epicatechin is highly bioavailable following ingestion, primarily in the form of structurally related phase II and gut microbiota-derived metabolites. Epidemiological evidence suggests positive associations between consumption of epicatechin-rich foods and cognitive performance, while randomized controlled trials provide more robust, although sometimes inconsistent, evidence for benefits on cognitive function. The inconsistencies in results suggest potential interindividual variability in responsiveness, likely driven by differences in metabolism of epicatechin, gut microbiota composition, genetic polymorphism, or health status. Experimental in vivo studies also suggested that epicatechin exerts neuroprotective effects, including neuroinflammation, oxidative stress, or neurodegeneration, with implicated mechanisms involving Nrf2, AMPK, AKT/CREB, and autophagy-related signaling pathways. Emerging evidence further directs that epicatechin could support brain health by preserving neurovascular function and blood-brain barrier integrity. Recent advances using untargeted transcriptomic and proteomic approaches, as well as integrated multi-omic and bioinformatic analyses, have revealed complex regulatory mechanisms involving both coding and non-coding RNAs, and have identified key pathways related to endothelial function, inflammation, synaptic integrity, and cellular adhesion. This review synthesizes current human and experimental evidence on epicatechin and brain health, the importance of interindividual variability, and highlights the important role of multi-omics technologies in elucidating underlying molecular mechanisms of action. Such integrative approaches are needed for advancing precision nutrition strategies and for evaluating the therapeutic potential of epicatechin in brain health and neurodegenerative disease prevention.

Keywords: *epicatechin; brain health; cognitive function; polyphenols; multi-omics; bioinformatics.*

INTRODUCTION

Despite unprecedented advances in biomedical sciences, biotechnology, and medicine, the human brain remains one of the least understood organs and continues to represent a major scientific challenge. Even the concept of *brain health* lacks a universally accepted definition. One influential definition describes brain health as "*the preservation of optimal brain integrity and mental and cognitive function at a given age in the absence of overt brain diseases that affect normal brain function*" [1]. A wide range of neurological disorders can compromise brain function, including: a) brain disorders with overt structural damage, such as cerebrovascular disease, brain tumors, traumatic brain injury, and meningitis, b) functional brain disorders, such as neurodegenerative diseases and mental disorders, and c) brain conditions without detectable structural or functional impairment, like migraine and sleep disorders [1], most of which are age-related. Interestingly, the blood-brain barrier (BBB), formed by a monolayer of endothelial cells linked together through cell-cell junctions, plays a major role in most (if not all) neurodegenerative disorders because an increase in BBB permeability, characteristic for BBB dysfunction, leads

to the passage of immune cells and immune mediators into the brain, which then contribute to the process of neuroinflammation and, consequently, neurodegeneration [2-4]. As the global population ages rapidly, preserving brain health has become an increasingly urgent challenge, requiring coordinated international research efforts to address major unmet needs in clinical medicine [5].

Cognitive impairment is a hallmark of several neurological diseases, including Alzheimer's disease, Huntington's disease, Parkinson's disease, vascular dementia, multiple sclerosis, and traumatic brain injury. Unfortunately, modern medicine still lacks effective pharmacological treatments for these patients [6]. Conventional pharmacological therapies, such as cholinesterase inhibitors, N-methyl-D-aspartate receptor agonists, and dopaminergic agents, provide symptomatic relief without altering the underlying disease pathology. On the other hand, emerging therapeutic strategies, including monoclonal antibodies targeting amyloid beta and tau, stem cell-based regenerative approaches, neurotrophic factor delivery, genetic modulation, and nanotechnology-based drug delivery systems, offer new prospects for slowing the progression of cognitive decline [7]. Nevertheless, these approaches remain largely experimental or limited in clinical applicability. In this context, lifestyle medicine has gained increasing recognition as an effective non-pharmacological strategy for preventing and mitigating neurocognitive decline. Evidence suggests that relatively simple interventions targeting the six core pillars of lifestyle medicine: a) whole food, plant-based nutrition, b) regular physical activity, c) stress management, d) avoidance of harmful substances, e) restorative sleep, and f) social connections, may prevent, delay, or improve cognitive impairment [8]. In particular, plant-based dietary patterns such as the Mediterranean diet, the Dietary Approaches to Stop Hypertension (DASH) diet, and the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet have been consistently associated with cognitive protection and reduced risk of neurodegenerative disorders [8].

Polyphenols are important constituents of plant-based diets and are widely associated with beneficial health effects in humans [9,10], including effects on cognitive performance and brain function [11]. Among polyphenols, flavanols represent one of the most extensively studied subclasses, with epicatechin being one of the best-characterized compounds in terms of biological activity. Accordingly, this review focuses on the role of epicatechin in brain health, summarizing evidence from human and experimental studies and highlighting the potential of integrated multi-omics approaches to elucidate its molecular mechanisms of action in preserving brain health.

HUMAN STUDIES ON THE ROLE OF EPICATECHIN-RICH DIETARY SOURCES IN BRAIN HEALTH

Epicatechin is present in a wide variety of foods and beverages, including dark chocolate, broad beans, blackberries, peaches, green tea infusions, strawberries, apples, black grapes, and red raspberries [12]. Among these sources, cocoa exhibits by far the highest epicatechin content, making it the primary dietary source of this flavanol (Phenol-Explorer, http://phenol-explorer.eu; accessed on 07.01.2026) [13]. A human study employing radiolabeled (–)-epicatechin demonstrated a high bioavailability, which is essentially the result of the presence of its metabolites in the circulation [14]. Following ingestion, approximately 20% of epicatechin is absorbed in the small intestine and appears in the systemic circulation as a range of its structurally related metabolites, which are present at sub-micromolar concentrations. The major plasma structurally related epicatechin metabolites are the following: (–)-epicatechin-3′-*O*-glucuronide, 3′-*O*-methyl-(–)-epicatechin-5-sulfate, and (–)-epicatechin-3′-sulfate. These metabolites reach peak plasma concentrations approximately one hour after ingestion and are ultimately excreted in the urine. The fraction of epicatechin that is not absorbed in the small intestine progresses through the gastrointestinal tract and reaches the colon. Approximately 70% of ingested epicatechin enters the circulation following colonic metabolism and absorption. In the colon, the gut microbiota catalyzes the biotransformation of epicatechin into 5-carbon side chain ring fission metabolites, which subsequently undergo phase II metabolism (in the colon and/or the liver), and appear in the circulation at sub-micromolar concentrations. The major gut microbiota-derived epicatechin metabolites are the following: 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-sulfate and 5-(4′-hydroxyphenyl)-γ-valerolactone-3′-*O*-glucuronide. These metabolites reach peak plasma concentrations approximately six hours after ingestion and are ultimately excreted in the urine. Additional epicatechin-derived metabolites detected in urine, but not assessed in plasma, include: hippuric acid, 3′-hydroxyhippuric acid, and 3-(3′-hydroxyphenyl)hydracrylic acid [14].

A substantial body of epidemiological evidence suggests a positive association between the consumption of epicatechin-rich foods or beverages and brain health, particularly cognitive performance. Several observational studies have reported better cognitive function among individuals with higher intakes of chocolate, tea, or other epicatechin-rich foods or beverages [15-18]. However, these findings should be interpreted with caution, as they may be influenced by confounding factors such as overall diet quality, lifestyle habits, socioeconomic status, and the presence of other bioactive compounds in these foods, which can

have synergistic or additive effects [18]. More robust evidence regarding the brain health-promoting properties of epicatechin-rich dietary sources has been obtained from randomized controlled trials (RCTs). Consumption of an epicatechin-rich cocoa beverage has been demonstrated to improve cognitive performance under conditions of high cognitive demand in healthy adults [19]. In addition, a high-flavanol intervention (900 mg of cocoa flavanols, including 138 mg of (–)-epicatechin) has been shown to enhance dentate gyrus function and improve cognitive performance in older adults [20]. Furthermore, regular intake of cocoa flavanols has been shown to attenuate certain aspects of age-related cognitive decline, potentially mediated through improvements in insulin sensitivity and overall metabolic profile [21]. This finding is particularly important as it supports the close interrelationship between metabolic health and cognitive function and highlights the broader health-promoting properties of flavanols.

Nevertheless, not all RCTs have demonstrated beneficial effects of epicatechin-rich dietary sources on cognitive outcomes [22,23]. In addition, evidence from large-scale trials indicates that potential benefits may be restricted to specific subpopulations, such as individuals with poorer baseline diet quality, as observed in the COSMOS trial clinic subcohort [24]. These findings indicate interindividual variability in cognitive responses to epicatechin-rich dietary sources, as it has been reported generally for polyphenols and their health properties. In addition, this brief overview demonstrates that existing human studies have focused on the brain health-promoting effects of epicatechin-rich dietary sources rather than epicatechin as an isolated compound, thereby limiting the understanding of epicatechin's specific effects on brain health.

Regarding interindividual variability in the health effects of polyphenols in general, multiple determinants have been identified, including health status, habitual diet, sex, age, gut microbiota composition, and genetic background [25]. Among these, genetic factors represent a major challenge and opportunity for nutrition science [26,27]. Genetic variations may influence the health-promoting effects of phytochemicals at two distinct levels: a) absorption and metabolism, and b) downstream biological effects in target tissues. While the absorption, metabolism, and bioavailability of epicatechin have been relatively well characterized [28], its molecular mechanisms of action in the context of brain health remain incompletely understood. A deeper understanding of these mechanisms, as well as the identification of specific cellular and molecular targets, will facilitate elucidation of the genetic determinants of interindividual variability in the brain health-promoting effects of epicatechin. Addressing these gaps requires well-designed in-depth mechanistic studies of epicatechin as an isolated compound, alongside carefully controlled human intervention trials.

EXPERIMENTAL STUDIES ON THE ROLE OF EPICATECHIN IN BRAIN HEALTH

Experimental *in vivo* studies offer a key advantage in that they allow evaluation of the biological effects of epicatechin as a pure compound within the context of the whole organism, particularly when administered *via* oral route. Several animal studies have demonstrated beneficial effects of epicatechin on neurocognitive function across various models of brain pathology, while also identifying some of the associated molecular mechanisms of action. Epicatechin has been shown to antagonize lead-induced cognitive impairment in mice, an effect associated with activation of the Nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway, suggesting a role for enhanced antioxidant defense and cellular stress responses as potential mediators of neuroprotection [29]. In a mouse model of lipopolysaccharide-induced sepsis, epicatechin ameliorated cognitive impairment by suppressing neuroinflammation, improving mitochondrial function, enhancing synaptic plasticity, and partially preventing neuronal loss. Activation of the AMP-activated protein kinase (AMPK) signaling pathway was identified as one of the mechanisms involved [30]. Similarly, intraperitoneal administration of epicatechin exerted neuroprotective effects in a rat model of traumatic brain injury, where modulation of the AKT-p53/CREB signaling axis was implicated in improved neurological outcomes [31]. Epicatechin has also been shown to exert brain health-protective effects in a rat model of amyloid beta-induced hippocampal toxicity, which is relevant to the pathophysiology of Alzheimer's disease. These effects included significant improvements in memory performance, accompanied by reductions in lipid peroxidation and reactive oxygen species levels [32], decreased expression of heat shock proteins in the CA1 region of the hippocampus and attenuated neuronal death [33].

Further support in elucidating the molecular mechanisms of the neuroprotective role of epicatechin comes from a recent systematic review and meta-analysis of 12 rodent studies, demonstrating that epicatechin's therapeutic potential in preventing or mitigating oxidative stress-related cognitive dysfunction is mediated, at least in part, by its role in enhancing antioxidant defense and modulating neuroinflammation [34].

Beyond pathological conditions, brain health-protective properties of epicatechin have also been demonstrated under normal physiological conditions. Oral treatment with epicatechin was shown to stimulate frontal cortex neurogenesis and to improve frontal cortical region-dependent short-term memory in mice [35].

Unlike animal studies, evidence from *in vitro* studies examining the brain health-promoting effects of epicatechin remains limited, as the majority of available studies have employed supraphysiological concentra-

tions that are unlikely to be achieved *in vivo*, thereby limiting their translational relevance [28].

It is important to note that most experimental studies investigating the role of epicatechin in brain health have relied on targeted analytical approaches, focusing on several predefined genes or proteins associated with cognitive improvement at the transcriptomic or proteomic level. While such approaches offer valuable mechanistic insights, they do not provide a comprehensive view of the molecular networks underlying epicatechin's effects. One potential strategy to overcome this limitation is conducting integrative bioinformatic molecular meta-analyses, as exemplified by studies examining the effects of polyphenols on cardiometabolic health [36,37]. However, to the best of our knowledge, such an integrative bioinformatic molecular meta-analysis focusing specifically on the brain health-promoting properties of epicatechin has not yet been conducted.

THE USE OF MULTI-OMIC TECHNOLOGIES AND INTEGRATIVE BIOINFORMATICS TO ELUCIDATE THE MECHANISMS OF ACTION OF EPICATECHIN IN BRAIN HEALTH

In contrast to classical targeted approaches for gene expression analysis, the application of modern *omic* technologies, particularly transcriptomics and proteomics, offers substantial potential for identifying novel and previously unrecognized molecular mechanisms underlying the biological effects of epicatechin. An illustrative example is the use of an unbiased proteomic approach to investigate the mechanisms of action of epicatechin in a mouse model of tauopathies. In this model, epicatechin was shown to ameliorate cognitive deficits, reverse synaptic dysfunction and neuronal loss, attenuate neuroinflammation, and reduce the accumulation of pathological tau protein through stimulation of autophagy. Bioinformatic analysis of the proteomic data identified the mTOR signaling pathway as a candidate mechanism mediating epicatechin-induced autophagy, and subsequent biochemical experiments confirmed an inhibitory effect of epicatechin on mTOR signaling [38].

Integrated multi-genomic approaches provide even greater power to elucidate molecular mechanisms of action as well as cellular and molecular targets [26]. Such an approach has been applied to elucidate the molecular mechanisms of epicatechin's effects on cognitive and behavioral disturbances in an animal model of high-fat diet (HFD)-induced obesity. Epicatechin supplementation was shown to prevent short-term recognition memory impairment in HFD-induced obese mice, accompanied by mitigation of metabolic endotoxemia and attenuation of hippocampal neuroinflammation [39]. Furthermore, epicatechin supplementation dose-dependently alleviated anxiety-related behavior in HFD-induced obese mice, which was accompanied by increased hippocampal brain-derived neurotrophic factor, as well as partial or complete restoration of glucocorticoid receptor, mineralocorticoid receptor, and 11β-hydroxysteroid dehydrogenase type 1 expression [40]. The identification of affected molecular pathways and key regulatory factors was enabled through an integrated multi-genomic analysis coupled with bioinformatics, which evaluated changes at the level of the global transcriptome, including both protein-coding genes (mRNAs) and non-coding RNAs (miRNAs and lncRNAs) [41]. These analyses demonstrated that epicatechin has the capacity to induce complex genomic modifications in the hippocampus that counteract HFD-driven alterations. The modulated genes were involved in the regulation of multiple biological processes, including neuronal function, inflammation, endothelial function, cell-cell adhesion, and intracellular signaling.

In recent years, increasing attention has been paid to the importance of the functional neurovasculome in maintaining brain health. The neurovasculome comprises extracranial, intracranial, and meningeal blood vessels, as well as lymphatic vessels and their associated cellular components. Dysregulation of the neurovasculome has been strongly associated with the development of cognitive dysfunction in both neurovascular and neurodegenerative diseases [42]. One of the key functional aspects of the neurovasculome is neurovascular coupling, a dynamic process that ensures adequate cerebral blood flow in response to local neuronal activity. Neurovascular coupling is impaired during aging and is closely associated with cognitive decline, including in Alzheimer's disease, with astrocytic dysfunction and endothelial impairment playing central roles [43]. The neurovasculome also includes the BBB, which consists of a monolayer of specialized brain endothelial cells connected by tight junctions and functionally coordinated with perivascular brain cells, such as pericytes, astrocytes, microglia, and oligodendrocytes. This multicellular unit regulates the transport of cells and molecules between the systemic circulation and the central nervous system. BBB dysfunction is a hallmark of neuroinflammation-driven neurodegeneration and contributes to disease progression by amplifying inflammatory responses within the brain [44]. In this context, *in vitro* studies using human brain microvascular endothelial cells (HBMECs) are of particular importance, as they provide a relevant experimental model for investigating bioactive compounds with potential brain health-promoting effects.

Numerous previous studies have demonstrated that catechins exert beneficial effects on vascular function, in part by stimulating endothelial nitric oxide synthase activity and increasing nitric oxide bioavailability [45]. However, brain endothelial cells exhibit distinct phenotypic and functional characteristics compared

with peripheral endothelial cells, necessitating dedicated experimental studies specifically using HBMECs. Importantly, *in vitro* studies must apply physiologically relevant concentrations and exposure times of metabolites relevant to the bioactive compound of interest.

Aiming to elucidate the molecular mechanisms underlying the brain vascular health-promoting effects of epicatechin and using an integrated multi-omics approach at both the proteomic and transcriptomic (coding and non-coding RNAs) levels, one study identified multiple cellular pathways modulated by gut microbiome-derived epicatechin metabolites in a model of inflammation-impaired neurovascular endothelial function. These pathways included cell adhesion, cytoskeletal organization, focal adhesion, intracellular signaling, regulation of endothelial permeability, and interactions with immune cells, major pathways involved in the regulation of endothelial cell-cell junctions and therefore BBB permeability [46].

Even more detailed mechanistic insights were obtained using an *in vitro* model of lipotoxicity, in which HBMECs were treated with two distinct mixtures of epicatechin metabolites: structurally related phase II metabolites and gut microbiota-derived metabolites. Comprehensive integrated bioinformatic analyses of multi-omic data and subsequent computational modeling demonstrated that the protective effects of epicatechin metabolites on BBB integrity are primarily mediated through modulation of the vascular endothelial growth factor (VEGF) signaling pathway. Moreover, these effects were shown to involve additional pathways closely interconnected with VEGF signaling, including focal adhesion, Rap1 and Ras signaling, and regulation of the actin cytoskeleton. These pathways are critical for controlling cellular architecture, stress fiber formation, and intercellular adhesion, all of which are central determinants of endothelial permeability [47]. Collectively, these findings reveal the capacity of epicatechin metabolites to decrease permeability of brain vascular endothelial cells and also illustrate the strength of integrated multi-omics approaches combined with advanced bioinformatic analyses in elucidating the molecular mechanisms underlying the beneficial effects of epicatechin metabolites on neurovascular function and brain health.

CONCLUSIONS

Numerous human and experimental studies have demonstrated that epicatechin may have beneficial effects on cognitive function and brain health. These findings provide evidence suggesting that epicatechin, as a major polyphenol of cocoa and a constituent of other foods and beverages, may contribute to the preservation of brain health in the general population through appropriate dietary recommendations. We believe that the inconsistencies observed in some human studies should not be interpreted as evidence against the brain health-promoting properties of epicatechin but should rather serve as a driving force for further research aimed at identifying interindividual variability in responsiveness and underlying determinants of efficacy. At the same time, experimental evidence suggests potential for future pharmacological applications, although this field remains at an early, predominantly preclinical stage.

In this context, the application of integrated multi-omics technologies and advanced bioinformatic approaches will be crucial for further elucidating the molecular mechanisms of action of epicatechin related to its brain health-promoting properties, and for paving the way toward personalized nutrition and, potentially, personalized therapeutic strategies.

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Epikatehin i zdravlje mozga: trenutni dokazi i perspektive za integrisane multi-omika analitičke pristupe

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Kratak sadržaj

Epikatehin, prehrambeni flavan-3-ol prisutan u velikim količinama u kakau, kao i u raznovrsnom voću i pićima, privlači sve veću pažnju zbog svoje potencijalne uloge u očuvanju zdravlja mozga. Humane studije ukazuju na to da epikatehin ima visoku bioraspoloživost nakon unosa hrane, primarno u formi strukturno srodnih metabolita faze II i metabolita koje proizvodi crevna mikrobiota. Epidemiološki dokazi ukazuju na pozitivnu asocijaciju između konzumacije epikatehinom bogate hrane i kognitivnih performansi, dok randomizovana kontrolisana ispitivanja pružaju snažnije, mada ponekad nekonzistentne, dokaze o povoljnim efektima na kognitivne funkcije. Nedoslednost rezultata sugeriše na potencijalnu interindividualnu varijabilnost u odgovoru, koja je verovatno uslovljena razlikama u metabolizmu epikatehina, sastavu crevne mikrobiote, genskim polimorfizmima ili zdravstvenim statusom. Eksperimentalne in vivo studije takođe ukazuju na to da epikatehin ispoljava neuroprotektivne efekte, uključujući neuroinflamaciju, oksidativni stres ili neurodegeneraciju, pri čemu su uključeni mehanizmi povezani sa signalnim putevima Nrf2, AMPK, AKT/CREB i autofagije. Sve veći broj dokaza dodatno ukazuju da epikatehin može doprineti zdravlju mozga kroz očuvanje neurovaskularne funkcije i integriteta krvno-moždane barijere. Netargetirani transkriptomika i proteomika, kao i integrisane multi-omika i bioinformatičke analize nedavno su doprineli otkrivanju složenih regulatornih mehanizama, koji uključuju kako kodirajuće, tako i nekodirajuće RNK, i identifikovali su ključne signalne puteve povezane sa endotelskom funkcijom, inflamacijom, sinaptičkim integritetom i ćelijskom adhezijom. Ovaj pregledni rad sumira postojeće dokaze iz studija na ljudima i eksperimentalnih studija o epikatehinu i zdravlju mozga, naglašava značaj interindividualne varijabilnosti i ističe važnu ulogu multi-omika tehnologije u razjašnjavanju molekulskih mehanizama koji su u osnovi ovih procesa. Ovakvi integrativni pristupi su neophodni za unapređivanje strategija precizne ishrane i za procenu terapeutskog potencijala epikatehina u očuvanju zdravlja mozga i prevenciji neurodegenerativnih bolesti.

Ključne reči: *epikatehin; zdravlje mozga; kognitivne funkcije; polifenoli; multi-omika; bioinformatika.*