

# Understanding the Neurobiological Mechanisms of Green Tea in Modulating Cognitive Function in Neurodegenerative Disorders: A Narrative Review

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**OBJECTIVE:** The cognitive-enhancing effects of green tea have garnered significant attention in the field of neuroscience. This narrative review aims to provide a comprehensive overview of the neurobiological mechanisms underlying the memory-enhancing properties of green tea. Studies have reported the beneficial effects of green tea on memory function, highlighting its potential as a natural cognitive enhancer. **METHODS:** Through a systematic exploration of the current literature, this review elucidates the intricate interplay between green tea components and various neurobiological processes involved in memory formation and retention. **RESULTS:** The review discusses the modulation of key neurotransmitter systems by green tea polyphenols and their impact on synaptic plasticity and neuronal communication. Furthermore, the review delves into the antioxidant and anti-inflammatory properties of green tea components, which contribute to neuroprotection and mitigate neuronal damage associated with memory impairment. Additionally, the review examines the role of green tea in regulating neurotrophic factors crucial for neurogenesis and synaptic plasticity. Insights into the influence of green tea on neuroinflammation, oxidative stress, and neurotrophic factors provide a comprehensive understanding of how green tea exerts its memory-enhancing effects at the molecular and cellular levels. **CONCLUSION:** This review consolidates existing knowledge on the neurobiological mechanisms of green tea-improved memory impairment and underscores the potential of green tea as a promising natural intervention for enhancing cognitive function and ameliorating memory deficits. Future research directions and clinical implications of green tea in the context of cognitive health are also discussed, emphasizing the importance of continued exploration of green tea's therapeutic potential for memory enhancement. **KEYWORDS:** Green tea, memory improvement, molecular mechanisms

## NEUROPROTECTIVE EFFECTS OF GREEN TEA

Green tea is a popular beverage that has been consumed for centuries, hailing from the *Camellia sinensis* plant. It is renowned for its numerous health benefits, making it a staple in many cultures around the world.<sup>1</sup> Key components in green tea are catechins, a type of antioxidant that helps fight oxidative stress in the body.<sup>2</sup> These antioxidants decrease the risk of chronic diseases such as heart disease, diabetes, and cancer.<sup>3,4</sup> Green tea is also known to boost metabolism and aid in weight loss. The catechins in green tea increase fat burning and improve physical performance.<sup>5</sup> Additionally, green tea, like peroxisome proliferator-activated receptor-γ (PPAR-γ) agonists, has been found to improve brain function and reduce the risk of neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD).<sup>6,7</sup> Caffeine and the amino acid L-theanine in green tea work together to improve mood and cognitive function.<sup>8</sup> Green tea has anti-inflammatory properties that can help reduce inflammation in the body and lower the risk of chronic diseases.<sup>9</sup> It contains compounds that may help protect against skin aging and promote overall skin health.<sup>10</sup> Neuroprotection refers to the preservation of neuronal structure

and function and the prevention of damage to the nervous system.<sup>11</sup> Green tea's neuroprotective properties have been studied extensively in recent years, with promising results.<sup>12</sup> The key compounds responsible for this effect are catechins, notably epigallocatechin gallate (EGCG), which have been shown to have anti-inflammatory, antioxidant, and anti-apoptotic effects on the brain.<sup>13,14</sup> Research has also suggested that green tea may help to reduce oxidative stress and inflammation in the brain, which are key factors in the development of neurodegenerative diseases.<sup>15</sup> Additionally, green tea has been found to promote the growth of new brain cells and improve overall brain function.<sup>16</sup> Studies have also shown that green tea catechins can help to protect neurons from damage caused by toxins and reduce the buildup of amyloid-β (Aβ) plaques, which are characteristic of AD.<sup>17,18</sup>

Several studies have investigated the potential impact of green tea on memory improvement, shedding light on its cognitive-enhancing properties and neuroprotective effects.<sup>19</sup> For example, it has been demonstrated that the consumption of green tea extract was associated with improvements in spatial working memory in humans.<sup>20</sup> A meta-

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analysis review study has revealed that green tea catechins are linked to enhanced cognitive function, including improvements in memory, attention, and processing speed. This study synthesized data from multiple studies and highlighted the potential of green tea compounds to support cognitive performance and mitigate age-related cognitive decline.<sup>21</sup> Another study revealed that green tea extract can enhance connectivity between different regions of the brain, potentially leading to improved memory function.<sup>22</sup> Overall, the accumulating evidence from these studies indicates that green tea has promising potential as a natural cognitive enhancer, with the ability to positively impact memory function and other aspects of cognitive performance. Therefore, understanding the precise mechanisms by which green tea enhances memory could pave the way for developing novel cognitive-enhancing therapies.

**Animal studies.** In animal studies, green tea has been shown to have a positive impact on memory and cognitive function.<sup>23,24</sup> Studies on animals have demonstrated that green tea extract can enhance memory and learning abilities, as well as protect against age-related memory decline.<sup>25</sup> In particular, research has shown that green tea can increase the levels of neurotransmitters in the brain, such as dopamine and serotonin, which play a key role in memory and cognition.<sup>6</sup> Furthermore, green tea stimulates the growth of new neurons in the hippocampus, the region of the brain responsible for memory formation. This process, known as neurogenesis, can help improve memory retention and cognitive flexibility.<sup>16</sup>

Animal studies have also suggested that green tea might enhance memory formation and retention. For example, a study found that rats given green tea extract performed better on memory tasks compared to a control group.<sup>26</sup> Another study showed that rats given green tea extract demonstrated improved spatial memory and learning abilities.<sup>25</sup> One study conducted by Ahn et al<sup>27</sup> found that green tea extract enhanced spatial learning and memory in rats. Kaur et al<sup>28</sup> demonstrated that green tea polyphenols improved memory and cognitive function in rats. The rats that were treated with green tea polyphenols showed enhanced memory in a passive avoidance task compared to the control group. Furthermore, a study by Rezai-Zadeh et al<sup>29</sup> investigated the effects of

green tea extract on memory and AD pathology in mice. The results showed that green tea extract reduced levels of A $\beta$  and improved cognitive function in the mice.

**Clinical studies.** Recent clinical studies investigating the effects of green tea on memory improvement have yielded promising results. These studies have utilized various methodologies, including cognitive assessments, neuroimaging techniques, and biochemical analyses, to evaluate the impact of green tea consumption on memory performance. The findings suggest that regular consumption of green tea might have potential benefits for memory enhancement and cognitive health.<sup>30,31</sup> For instance, it has been demonstrated that the consumption of green tea extract was associated with improved working memory performance and increased connectivity between brain regions related to working memory. The participants who consumed green tea extract also showed increased activity in the dorsolateral prefrontal cortex, a region of the brain associated with working memory.<sup>22</sup> Furthermore, another study investigated the effects of polyphenols on memory and attention in healthy adults. The researchers found that participants who consumed combined polyphenolic-rich herbal extract performed better on tasks measuring memory and attention compared to a placebo group. The improvements in cognitive function were attributed to the presence of catechins.<sup>32</sup> Moreover, in another study, it was shown that older adults who regularly drank green tea had a lower risk of cognitive decline compared to non-tea drinkers. The researchers suggested that the beneficial effects of green tea on cognitive function may be due to its ability to reduce inflammation and oxidative stress in the brain.<sup>33</sup>

## NEUROPROTECTIVE MECHANISMS OF GREEN TEA

### Green tea inhibits oxidative stress.

Green tea is a popular beverage that has long been lauded for its numerous health benefits, including its antioxidant properties. One particular area of interest is the impact of green tea on oxidative stress in the brain tissues.<sup>34</sup> Oxidative stress is a condition in which there is an imbalance between antioxidants and free radicals in the body, leading to damage to cells and tissues.<sup>35</sup> Several studies have suggested that the polyphenols found in green

tea, particularly catechins such as EGCG, may help combat oxidative stress in the brain.<sup>36</sup> These compounds are known to have powerful antioxidant properties, which can help protect brain cells from damage caused by free radicals. Additionally, green tea has been shown to potentially enhance the activity of antioxidant enzymes in the brain, further reducing oxidative stress.<sup>37–39</sup> Green tea polyphenols can also directly scavenge free radicals and inhibit lipid peroxidation, which is another mechanism of oxidative stress. By neutralizing reactive oxygen species (ROS) and preventing the damage they cause, green tea can help protect brain tissues from oxidative stress-related damage.<sup>40</sup> One way in which green tea impacts oxidative stress in brain tissues is through the upregulation of antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. These enzymes help neutralize ROS and protect cells from oxidative damage.<sup>41</sup> Furthermore, green tea polyphenols have been shown to modulate various signaling pathways involved in oxidative stress, inflammation, and cell death in the brain.<sup>42</sup> For example, catechins activate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathways, which regulate the expression of antioxidant and detoxifying genes. By activating this pathway, green tea can enhance the brain's antioxidant defenses and reduce oxidative stress.<sup>43</sup> Research has also indicated that green tea may have neuroprotective effects, potentially helping to prevent or slow the progression of neurodegenerative diseases such as AD and PD. By reducing oxidative stress in the brain tissues, green tea may help preserve cognitive function and overall brain health.<sup>42</sup> One study published in *Food Research International* found that green tea catechins, specifically EGCG, can reduce oxidative stress in the brain by scavenging free radicals and enhancing antioxidant enzyme activity. Additionally, green tea extract was found to decrease levels of oxidative stress markers in the brain, indicating a potential mechanism by which green tea improves cognitive function.<sup>44</sup> **Table 1** shows the alteration of oxidative stress markers in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea.<sup>34,36,37,39–41,44–47</sup>

### Green tea inhibits neuroinflammation.

Neuroinflammation is a process in which the immune system responds to injury or

**TABLE 1.** Alteration of oxidative stress markers in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea

| NATURAL PRODUCT                                              | DOSE AND ADMINISTRATION                                                                                                                                                                 | MODEL                                                                                                 | OXIDATIVE STRESS MARKERS     | DECREASE / INCREASE | REFERENCE                      |
|--------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|------------------------------|---------------------|--------------------------------|
| Green tea and sour tea ( <i>Hibiscus sabdariffa</i> ) leaves | Tea extract (0–100 µL) in vitro                                                                                                                                                         | Pro-oxidant [Fe(II), sodium nitroprusside, quinolinic acid]-induced lipid peroxidation in rat's brain | MDA                          | ↓                   | Oboh and Rocha <sup>34</sup>   |
| Green tea leaves                                             | 0.2 mL/100 g body weight for 15 days, orally                                                                                                                                            | 6-OHDA model of Parkinson's disease                                                                   | TBARS, NO, chemiluminescence | ↓                   | Bitu Pinto et al <sup>36</sup> |
| Green tea pills                                              | 4 pills were administered daily for 2 months (2 g/day in 2 divided doses)                                                                                                               | Patients with Alzheimer's disease                                                                     | MDA, 8-OHdG carbonyl content | ↓                   | Arab et al <sup>45</sup>       |
|                                                              |                                                                                                                                                                                         |                                                                                                       | MMSE, FRAP                   | ↑                   |                                |
| Green tea leaves                                             | 8 weeks orally                                                                                                                                                                          | Alzheimer's disease-like rat                                                                          | ROS, TBARS, FRAP             |                     | Schimidt et al <sup>44</sup>   |
| Green Tea Mega EGCG (Veggie capsules)                        | 725 mg of Opteava® Green Tea 95% Extract (standardized to provide 95% polyphenols) containing 100 mg/kg of EGCG                                                                         | Oxidative stress induced by pilocarpine during status epilepticus                                     | SOD, MDA                     | ↓                   | Noor et al <sup>41</sup>       |
|                                                              |                                                                                                                                                                                         |                                                                                                       | GSH, GST, NO                 | ↑                   |                                |
| Chun Mee green tea leaves                                    | Intraperitoneally (50 and 100 mg of dry weight per kg of body weight) for 1 week                                                                                                        | Poststroke depression                                                                                 | TBARS, SOD                   | ↓                   | Di Lorenzo et al <sup>39</sup> |
|                                                              |                                                                                                                                                                                         |                                                                                                       | GSH                          | ↑                   |                                |
| Green tea leaves                                             | 5 g of dry green tea leaves were weighed and soaked in 200 mL of boiling water for 30 minutes, then cultured in the medium with the green tea water in different dilutions for 12 hours | PC12 cells                                                                                            | PC12 cells                   | ↓                   | Cai et al <sup>46</sup>        |
| Green tea polyphenols                                        | 25 mg/kg with normal saline for 7 consecutive days, intraperitoneal injection                                                                                                           | Isoflurane-induced cognitive impairment                                                               | SOD                          | ↓                   | Song et al <sup>40</sup>       |
| Green tea leaves                                             | 1–2, 3–9, and ≥10 cups of green tea/day                                                                                                                                                 | Chinese middle-aged and elderly individuals                                                           | SOD, MDA                     | ↓                   | Zhang et al <sup>47</sup>      |
|                                                              |                                                                                                                                                                                         |                                                                                                       | GPx                          | ↑                   |                                |
| Green tea leaves                                             | Green tea mixed with drinking water (13.33 g/L) for 8 weeks                                                                                                                             | Cerebral ischemia reperfusion                                                                         | GSH, GPx, CAT                | ↑                   | Schmidt et al <sup>37</sup>    |
|                                                              |                                                                                                                                                                                         |                                                                                                       | TBARS                        | ↓                   |                                |

6-OHDA: 6-hydroxydopamine; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; CAT: catalase; EGCG: epigallocatechin gallate; FRAP: fluorescence recovery after photobleaching; GPx: glutathione peroxidase; GSH: reduced glutathione; GST: glutathione S-transferase; MDA: malondialdehyde; MMSE: Mini-Mental State Examination; NO: nitric oxide; SOD: superoxide dismutase; TBARS: thiobarbituric acid reactive substances; ↓: decrease; ↑: increase

disease in the brain, leading to the release of inflammatory molecules that can damage nerve cells.<sup>48</sup> Indeed, neuroinflammation, characterized by the activation of immune cells in the central nervous system, plays a crucial role in the pathogenesis of various neurological disorders, including AD, PD, long-term alcohol abuse, and multiple sclerosis,<sup>48,49,50</sup> or by induction. Green tea's bioactive compounds, particularly catechins, polyphenols, and EGCG, have been shown to possess potent anti-inflammatory properties.<sup>51</sup> These compounds have been shown to modulate signaling pathways involved in inflammation, leading to a reduction in the production of pro-inflammatory mediators and an increase in anti-inflammatory molecules.<sup>52</sup> Furthermore, green tea can help protect brain tissues from oxidative stress, a key factor contributing to neuroinflammation and neurodegeneration. By scavenging free radicals and reducing oxidative damage, green tea may help prevent or mitigate the inflammatory response in the brain.<sup>42</sup> Additionally, EGCG

has been shown to inhibit the activation of microglia, which are immune cells in the brain that play a key role in the inflammatory response. By reducing the activation of microglia, green tea can help lower levels of pro-inflammatory molecules in the brain, such as cytokines and chemokines.<sup>53</sup> Additionally, green tea polyphenols can modulate various signaling pathways involved in neuroinflammation. EGCG has been shown to inhibit the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which is a key regulator of inflammation in the brain. By blocking NF-κB activation, green tea can reduce the production of inflammatory molecules and limit the extent of neuroinflammation.<sup>54</sup> Several studies have investigated the potential benefits of green tea in reducing neuroinflammation markers in the brain and improving memory. One study conducted by Wang et al<sup>55</sup> found that green tea extract was able to reduce levels of inflammatory markers such as interleukin-1β (IL-1β) and tumor necrosis

factor-α (TNF-α) in the brains of rats with induced neuroinflammation. Another study by Unno et al<sup>56</sup> explored the effects of green tea catechins on memory improvement in mice. The researchers found that mice treated with green tea catechins showed improved memory retention and spatial learning compared to a control group. Additionally, a study by Rezai-Zadeh et al<sup>29</sup> investigated the role of green tea polyphenols in modulating neuroinflammation and Aβ accumulation in a rat model of AD. The researchers found that green tea polyphenols were able to reduce markers of neuroinflammation and Aβ levels, suggesting a potential protective effect against AD. **Table 2** shows the alteration of neuroinflammation markers in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea.<sup>57–63</sup>

**Green tea inhibits apoptosis.** Green tea has been recognized for its numerous health benefits, including its protective effect

**TABLE 2.** Alteration of neuroinflammation markers in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea

| NATURAL PRODUCT              | DOSE AND ADMINISTRATION                                                                                                                                             | MODEL                             | NEUROINFLAMMATION MARKERS | DECREASE / INCREASE | REFERENCE                                |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|---------------------------|---------------------|------------------------------------------|
| EGCG                         | 10 µM was administered in vitro to microglial cells                                                                                                                 | BV2 microglial cells              | IL-6, iNOS, COX2          | ↑                   | Kim et al <sup>57</sup>                  |
| Grape seed proanthocyanidins | 3.125, 6.25, 12.5, and 25 µM for 6 hours in vitro                                                                                                                   | BV2 microglial cells              | CD86, TNF-α, and iNOS     | ↑                   | Liu et al <sup>58</sup>                  |
| Epicatechin                  | 13 and 10 mg/kg in 6 injections over 2 weeks                                                                                                                        | Rats treated with DOX             | TNF-α, NO, NF-κB, iNOS    | ↑                   | Mohamed et al <sup>59</sup>              |
| Catechins (EGCG, EC, and C)  | 250 mg/kg of the green tea extract (containing 59.8 mg catechins per kg) for 23 days orally                                                                         | Adjuvant-induced arthritic rats   | G6PD                      | ↓                   | de Almeida Gonçalves et al <sup>60</sup> |
| Green tea leaves             | 200 mg/kg body weight was administered to the rats orally                                                                                                           | STZ-injected rats, Alzimeric rats | TNF-α                     | ↑                   | Amirpour et al <sup>61</sup>             |
| EGCG                         | 100 µL per mouse, twice daily orally                                                                                                                                | Autoimmune encephalomyelitis      | PLP, TNF-α                | ↑                   | Aktas et al <sup>62</sup>                |
| Green tea leaves             | Tea leaves (3,000 g) were immersed in 10 L distilled water and were extracted using 85°C water for 12 hours, repeated twice, with EGCG (10 mg/kg) for 4 days orally | Cerebral ischemic rats            | COX2, iNOS                | ↑                   | Wu et al <sup>63</sup>                   |

C: catechin; COX2: cyclooxygenase 2; DOX: doxorubicin; EGCG: epigallocatechin gallate; EC: epicatechin; G6PD: glucose 6 phosphate dehydrogenase; IL: interleukin; iNOS: inducible nitric oxide synthase; NF-κB: nuclear factor kappa-light-chain-enhancer of activated B cells; NO: nitric oxide; PLP: pyridoxal phosphate; STZ: streptozotocin; TNF-α: tumor necrosis factor-alpha; ↓: decrease; ↑: increase

against environmental neurotoxins that induce apoptosis in brain tissues.<sup>64</sup> Apoptosis, also known as programmed cell death, is a crucial process in maintaining the balance between cell proliferation and cell death in the body. Dysregulation of apoptosis has been implicated in various neurodegenerative diseases, including AD and PD.<sup>65</sup> Several studies have investigated the protective effects of green tea on apoptosis in brain tissues, and the results have been promising.<sup>66</sup> However, green tea has been shown to exert protective effects against apoptosis in brain tissues through the modulation of various molecular pathways. Dysregulation of apoptosis can contribute to neurodegenerative disorders and other neurological conditions.<sup>67</sup> Studies have demonstrated that the polyphenolic compounds in green tea, particularly EGCG, can influence apoptosis in brain tissues by targeting key molecular pathways. EGCG has been found to inhibit apoptotic signaling pathways such as the mitochondrial pathway, which involves the release of cytochrome c (cyt c) and activation of caspases leading to cell death.<sup>68</sup> Furthermore, green tea polyphenols have been shown to regulate the expression of anti-apoptotic proteins, such as B-cell lymphoma-2 (Bcl-2) and Bcl-extra large (Bcl-xL), which promote cell survival by preventing mitochondrial membrane permeabilization and cyt c release. Additionally, green tea components can modulate pro-apoptotic proteins like Bcl-2-like protein 4 and Bcl-2-associated death promoter, thereby shifting the balance towards cell survival.<sup>67</sup> Moreover, EGCG possesses antioxidant

properties that help reduce oxidative stress in brain tissues, which is a common inducer of apoptosis. By scavenging ROS and inhibiting lipid peroxidation, green tea polyphenols can protect neurons from oxidative damage and subsequent apoptotic cell death.<sup>69,70</sup> One study conducted by Ding et al<sup>71</sup> found that green tea polyphenols can induce apoptosis in glioma cells, a type of brain tumor. The researchers observed that green tea polyphenols downregulated the expression of anti-apoptotic proteins and upregulated pro-apoptotic proteins, leading to cell death in the glioma cells. Another study by Rahmasarigumay et al<sup>67</sup> demonstrated that EGCG activates the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway, which promotes cell survival and inhibits apoptosis in brain cells. The researchers found that EGCG treatment protected neurons from glutamate-induced apoptosis by activating the PI3K/Akt pathway and inhibiting the expression of pro-apoptotic proteins. One study conducted by Xu et al<sup>66</sup> explored the effects of green tea extract on apoptosis in the hippocampus of rats. The results showed that green tea extract effectively induced apoptosis in hippocampal cells, potentially through the activation of caspase enzymes and the modulation of Bcl-2 family proteins. These findings suggest that green tea might have neuroprotective effects by promoting the death of damaged or abnormal cells in the brain. **Table 3** shows the alteration of apoptotic markers in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea.<sup>66–74</sup>

**Green tea improves neurotrophic factors.** Studies have suggested that the consumption of green tea or its extracts may enhance the levels of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in the brain tissues. These factors are involved in neuroplasticity, the brain's ability to adapt and change in response to environmental and developmental factors. By increasing the levels of these neurotrophic factors, green tea may promote neuronal growth, repair, and regeneration, ultimately improving cognitive function and protecting against neurodegenerative diseases.<sup>75–78</sup> One of the primary mechanisms through which green tea influences neurotrophic factors is by activating specific signaling pathways in neurons. EGCG has been found to activate the PI3K/Akt pathway, which is a known regulator of BDNF expression. By stimulating this pathway, green tea components can increase the production and release of BDNF in the brain.<sup>79</sup> Additionally, EGCG has been shown to modulate the mitogen-activated protein kinase (MAPK) pathway, another signaling cascade involved in the regulation of neurotrophic factors.<sup>80,81</sup> Activation of MAPK pathways can lead to the upregulation of NGF expression, which plays a critical role in the maintenance and function of neurons. By enhancing NGF levels through MAPK activation, green tea compounds promote neuroprotection and support cognitive function.<sup>80,82</sup>

Moreover, green tea polyphenols have antioxidant and anti-inflammatory properties

**TABLE 3.** Alteration of apoptotic markers in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea

| NATURAL PRODUCT                            | DOSE AND ADMINISTRATION                                                                                  | MODEL                                                                  | APOPTOTIC MARKERS                                | DECREASE / INCREASE | REFERENCE                          |
|--------------------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------|---------------------|------------------------------------|
| Green tea leaves                           | 25 mg/kg body weight, orally                                                                             | Neurotoxicity and oxidative damage induced by deltamethrin             | p53 and COX2                                     | ↓                   | Ogaly et al <sup>72</sup>          |
| EGCG                                       | Orally, 25, 50, or 75 mg/kg body weight, regularly from Day P3 and continued till P21                    | Neonatal mice                                                          | Caspase 3, Bad, Bax                              | ↓                   | Ding et al <sup>71</sup>           |
|                                            |                                                                                                          |                                                                        | Bcl-2, Bcl-xL, XIAP, c-IAP-1                     | ↑                   |                                    |
| Green tea leaves                           | 20 mL/kg twice per day for 3 consecutive days, orally                                                    | Type 1 diabetes rat model                                              | Bcl-2                                            | ↑                   | Xu et al <sup>66</sup>             |
|                                            |                                                                                                          |                                                                        | Bax                                              | ↓                   |                                    |
| Green tea leaves                           | EGCG 10, 20, 30 mg/kg body weight/day, and green tea extract 30 mg/kg body weight/day for 7 days, orally | <i>Rattus norvegicus</i> middle cerebral artery occlusion model        | Neuronal cell necroptosis (except EGCG 10 mg/kg) | ↓                   | Machin et al <sup>68</sup>         |
| Green tea leaves                           | 7.8–62.5 µg/mL in vitro                                                                                  | ACR-induced neurotoxicity was evaluated both in vivo and in PC12 cells | Viability PC12 cell                              | ↓                   | Esmaelpanah et al <sup>73</sup>    |
| EGCG                                       | 10 to 40 mg/kg body weight for 4 days, intragastric                                                      | Healthy rats (cerebral cortex)                                         | TUNEL-positive apoptotic cells, Bcl-2            | ↑                   | He et al <sup>74</sup>             |
|                                            |                                                                                                          |                                                                        | Bax, cyt c, and caspase 3                        | ↓                   |                                    |
| EGCG                                       | 2.5 or 5 mg/kg/day for 3 days before exposure                                                            | Healthy rats (hippocampus)                                             | p53, cyt c, Bax, caspase 3 and 9                 | ↑                   | El-Missiry et al <sup>69</sup>     |
|                                            |                                                                                                          |                                                                        | Bcl-2                                            | ↓                   |                                    |
| EGCG                                       | 0, 0.625, 1.25, 2.5, 5.0, or 10 mg/kg body weight for 14 consecutive days, intraperitoneal injection     | Adult hippocampal neurogenesis in male Balb/C mice                     | Caspase 3                                        | ↑                   | Ortiz-López et al <sup>70</sup>    |
| Green tea leaves                           | 20 mL/kg twice per day for 3 consecutive days orally                                                     | Diabetic encephalopathy                                                | Caspase 3                                        | ↑                   | Rahmasarigumay et al <sup>67</sup> |
| Green tea polyphenols and ERK1/2 inhibitor | 30 mg/kg body weight/day for 7 days orally                                                               | D-galactose-induced Balb/C mice                                        | TUNEL-positive, caspase 3                        | ↑                   | Rahmasarigumay et al <sup>67</sup> |

ACR: acrylamide; Bad: Bcl-2-associated death promoter; Bax: Bcl-2-like protein 4; Bcl-2: B-cell lymphoma-2; c-IAP: cellular inhibitor of apoptosis protein; COX2: cyclooxygenase 2; cyt c: cytochrome c; EGCG: epigallocatechin gallate; ERK: extracellular signal-regulated kinase; TUNEL: transferase dUTP nick end labeling; XIAP: X-linked inhibitor of apoptosis protein; ↓: decrease; ↑: increase

that can protect neurons from oxidative stress and inflammation, factors that can impair neurotrophic factor signaling. By reducing oxidative damage and inflammation in the brain, green tea components create a favorable environment for neurotrophic factor production and action, ultimately supporting brain health and cognitive function.<sup>83</sup> A study conducted by Abdelmeguid et al<sup>84</sup> found that green tea catechins, particularly EGCG, promoted the expression of BDNF in the hippocampus, a critical region for memory formation. Similarly, another study by Gundimeda et al<sup>85</sup> demonstrated that green tea polyphenols, including EGCG, modulated the expression of NGF in the brain. The study revealed that green tea polyphenols exerted neuroprotective effects by enhancing NGF levels, which could potentially contribute to memory enhancement and overall brain health. Furthermore, a meta-analysis conducted by Ikar et al<sup>86</sup> pooled data from multiple studies investigating the relationship between green tea consumption

and cognitive function. The analysis indicated a significant association between green tea intake and improvements in memory and cognitive performance. While the exact mechanisms underlying these benefits are multifaceted, the upregulation of neurotrophic factors in brain tissue, such as BDNF and NGF, likely contributes to the observed cognitive enhancements associated with green tea consumption. **Table 4** shows the alteration of neurotrophic factors in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea.<sup>64,75–79,81,83,85,87</sup>

**Green tea modulates neurotransmitters.** Neurotransmitters are essential chemicals that facilitate communication between nerve cells and play a crucial role in regulating various brain functions such as mood, behavior, cognition, and memory.<sup>88</sup> Moreover, polyphenols, particularly catechins, have been shown to have neuroprotective effects by influencing neurotransmitter levels in the brain.<sup>82,89</sup>

Studies also have suggested that green tea catechins can enhance the activity of gamma-aminobutyric acid (GABA), a neurotransmitter that helps to reduce anxiety and promote relaxation.<sup>90</sup> Furthermore, green tea has been found to modulate the levels of serotonin and dopamine, neurotransmitters responsible for regulating mood, motivation, and reward.<sup>91,92</sup> By promoting the release of these “feel-good” chemicals, green tea may help improve mood and overall mental wellbeing. In addition to its effects on neurotransmitters, green tea also contains caffeine, which enhances alertness, concentration, and cognitive function. The combination of caffeine and catechins in green tea may work synergistically to support brain health and cognitive function.<sup>93</sup>

Additionally, green tea polyphenols have been reported to impact the monoaminergic neurotransmitter systems, including dopamine, serotonin, and norepinephrine, which are crucial for mood regulation, stress response, and cognitive function.<sup>89</sup> Additionally, EGCG

**TABLE 4.** Alteration of neurotrophic factors in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea

| NATURAL PRODUCT                                                                                                                                                                                                                                                  | DOSES AND ADMINISTRATION                                                                                                       | MODEL                                                                                                                                                                                       | NEUROTROPHIC MARKERS                    | DECREASE / INCREASE | REFERENCE                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|---------------------|---------------------------------------|
| L-theanine (an amino acid in green tea)                                                                                                                                                                                                                          | 125–2,000 µM for 24 hours in vitro                                                                                             | Neurotoxicity induced by PD-related neurotoxins, rotenone, and dieldrin in a cultured human dopaminergic cell line, SH-SY5Y                                                                 | GDNF, BDNF                              | ↓                   | Cho et al <sup>64</sup>               |
| EGCG                                                                                                                                                                                                                                                             | 10 and 20 mg/kg subarachnoid injection                                                                                         | Spinal cord injury                                                                                                                                                                          | GDNF, BDNF                              | ↑                   | Tian et al <sup>83</sup>              |
| Theanine                                                                                                                                                                                                                                                         | 100 mg/100 g body weight for 2 weeks orally                                                                                    | Brain development in infant rats                                                                                                                                                            | NGF, NT-3, BDNF                         | ↑                   | Yamada et al <sup>87</sup>            |
| Green tea leaves                                                                                                                                                                                                                                                 | EGCG: 27.9 mg/g; ECG: 23.4 mg/g; EGC: 30.2 mg/g; GC: 27.8 mg/g; EC: 62.5 mg/g orally                                           | Hippocampal neurotrophin in middle-aged and young rats                                                                                                                                      | NT-3, BDNF                              | ↑                   | Nomura et al <sup>77</sup>            |
| EGCG                                                                                                                                                                                                                                                             | 50 mg/kg orally                                                                                                                | Crushed sciatic nerve rats                                                                                                                                                                  | BDNF, GDNF, NT3, Trk-B, Trk-C, NGFR-p75 | ↑                   | Renno et al <sup>81</sup>             |
| Purified GTPP constituents (EGCG, ECG, EGC, and EC), catalase-polyethylene glycol, and L-NAC                                                                                                                                                                     | Treated with agents either alone or in combination for 3 days (GTPP preparation: EGCG [36%], ECG [15%], EC [7%], and EGC [3%]) | PC12 cell model                                                                                                                                                                             | TrkA, NGF                               | ↑                   | Gundimeda et al <sup>85</sup>         |
| EGCG                                                                                                                                                                                                                                                             | EGCG 100 mg/kg gavage for 35 days; PPA+EGCG: given PPA for the first 5 days and EGCG 100 mg/kg/day gavage for 35 days          | Autism-induced rats                                                                                                                                                                         | BDNF, Trk-B, NGF, CaMKII                | ↑                   | Ozdemir et al <sup>75</sup>           |
|                                                                                                                                                                                                                                                                  |                                                                                                                                |                                                                                                                                                                                             | CREB                                    | ↓                   |                                       |
| EGCG                                                                                                                                                                                                                                                             | Fed an HFFD and 2 g/L EGCG for 16 weeks orally                                                                                 | Insulin resistance and memory impairment induced by HFFD                                                                                                                                    | BDNF, NT-3, NT-4, NGF                   | ↑                   | Mi et al <sup>79</sup>                |
|                                                                                                                                                                                                                                                                  |                                                                                                                                |                                                                                                                                                                                             | CREB                                    | ↓                   |                                       |
| EGCG                                                                                                                                                                                                                                                             | EGCG (50 mg/kg); PP242 (5 mg/kg) + EGCG (50 mg/kg)                                                                             | Spinal cord injury                                                                                                                                                                          | BDNF, GDNF                              | ↑                   | Machova Urdzikova et al <sup>76</sup> |
| Capsule containing 250 mg of standardized green tea extract (245 mg polyphenols, including 200 mg catechins, among them 137 mg epigallocatechin-3-gallate and additional substances, such as caffeine <4 mg, microcrystalline cellulose, and magnesium stearate) | 2 capsules once daily for 6 weeks (1 GTE capsule contained 250 mg of standardized green tea extract)                           | 16 male students of the physical education faculty. Exclusion criteria included tobacco use, alcohol consumption, and medication/dietary supplements during the 4 weeks preceding the study | FRAP, TBARS, BDNF                       | ↑                   | Sadowska-Krępa et al <sup>78</sup>    |

BDNF: brain-derived neurotrophic factor; CaMKII: calcium/calmodulin-dependent protein kinase II; CREB: cAMP-response element binding protein; EGCG: epigallocatechin gallate; FRAP: fluorescence recovery after photobleaching; GDNF: glial cell line–derived neurotrophic factor; GTE: green tea extract; GTPP: green tea polyphenol; HFFD: high-fat and high-fructose diet; L-NAC: N-acetyl-L-cysteine; NGF: nerve growth factor; NGFR: nerve growth factor receptor; NT-3: neurotrophin-3; PD: Parkinson's disease; PP242: second-generation mammalian target of rapamycin inhibitor; PPA: propionic acid; TBARS: thiobarbituric acid reactive substances; Trk: tropomyosin receptor kinase; ↓: decrease; ↑: increase

can influence neurotransmitter release by interacting with presynaptic receptors and vesicular transporters.<sup>94</sup> Moreover, researchers have investigated the influence of green tea polyphenols on the expression of dopamine receptors in the prefrontal cortex, a brain region critical for cognitive function and memory processing.<sup>89,95</sup>

Another molecular pathway through which green tea impacts neurotransmitters is by regulating neuroplasticity and synaptic strength. EGCG has been found to activate signaling pathways involved in synaptic plasticity, such as the cAMP-response element-binding protein (CREB) pathway,

which promotes the formation of new synaptic connections and enhances memory consolidation.<sup>96</sup> Furthermore, EGCG exhibits antioxidant and anti-inflammatory properties that can protect neurons from oxidative stress and neuroinflammation, which are detrimental to neurotransmitter function.<sup>44</sup> Several studies have investigated the impact of green tea on neurotransmitter markers in the brain tissues. One study conducted by Imam-Fulani et al<sup>97</sup> explored the effects of green tea catechins, particularly EGCG, on neurotransmitter levels in the hippocampus. The researchers found that EGCG administration led to increased levels of GABA, suggesting a potential calming effect of

green tea on the brain. Moreover, another study by Weeks et al<sup>98</sup> delved into the effects of green tea extract on serotonin levels in the amygdala, a brain region involved in emotional regulation and memory consolidation. This modulation of serotonin levels may contribute to improved memory consolidation and emotional wellbeing. **Table 5** shows the alteration of neurotransmitters in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea.<sup>99–103</sup>

**Green tea enhances long-term potentiation.** One area of interest in recent years has been the potential effects of green

**TABLE 5.** Alteration of neurotransmitters in induced memory impairment and neurodegenerative disorders following treatment with bioactive compounds found in green tea

| NATURAL PRODUCT                                                       | DOSES AND ADMINISTRATION                                                                                                                          | MODEL                                                                                                                  | NEUROTRANSMITTERS                          | DECREASE / INCREASE | REFERENCE                   |
|-----------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|---------------------|-----------------------------|
| Green tea leaves                                                      | EGCG (CAS 989-51-5, purity ≥98%)                                                                                                                  | Activity of GAT1 and EAAC1                                                                                             | GABA                                       | ↑                   | Wang et al <sup>99</sup>    |
|                                                                       |                                                                                                                                                   |                                                                                                                        | Glutamate                                  | ↓                   |                             |
| EGCG                                                                  | Gavaged with 0.1 mL dose of 25 mg/kg body weight, 50 mg/kg body weight, and 100 mg/kg body weight of EGCG per day for 10 weeks orally             | High-fat diet mice                                                                                                     | Dopamine, kynurenine, histidine, glutamate | ↓                   | Zhou et al <sup>100</sup>   |
|                                                                       |                                                                                                                                                   |                                                                                                                        | 5-HTP, GABA, aspartic acid, glycine        | ↑                   |                             |
| L-THE (20%) and rosmarinic acid (14.5–17.5%), total phenolic (24–37%) | Intraperitoneal for 30 days                                                                                                                       | Pentobarbital-induced sleep test, subhypnotic pentobarbital-induced sleep test, and sodium barbital-induced sleep test | DA, NE, 5-HT                               | ↓                   | Zhang et al <sup>101</sup>  |
|                                                                       |                                                                                                                                                   |                                                                                                                        | GABA, Ach                                  | ↑                   |                             |
| Theanine                                                              | 10 nM theanine in 0.5 mL 50 mM Tris-acetate buffer (pH 7.4) at 4°C or 30°C for different periods of time up to 30 minutes                         | Neurons and astroglia in rat brain                                                                                     | GABA, arginine, glutamate, aspartate       | ↓                   | Kakuda et al <sup>102</sup> |
| Theanine                                                              | Switched both theanine (0.2 μmol/2 μL perfusate/minute) was injected for 1 hour, and each antagonist containing perfusate (2 μL perfusate/minute) | Pregnant Wistar rats                                                                                                   | Aspartate, glutamate, dopamine             | ↑                   | Yamada et al <sup>103</sup> |

5-HT: 5-hydroxytryptamine; Ach: acetylcholine; DA: dopaminergic; EAAC1: excitatory amino acid carrier 1; EGCG: epigallocatechin gallate; GABA: gamma-aminobutyric acid; L-THE: L-theanine; GAT1: GABA transporter type 1; NE: norepinephrine; ↓: decrease; ↑: increase

tea on long-term potentiation (LTP) in brain tissues.<sup>104</sup> LTP is a key mechanism underlying learning and memory formation in the brain, and its dysregulation has been implicated in various neurological disorders such as AD and epilepsy.<sup>105</sup> Evidence suggests that green tea and its constituents may influence LTP in brain tissues, potentially enhancing synaptic transmission and strengthening neuronal connections.<sup>106</sup> Several studies have suggested that the bioactive compounds in green tea, particularly catechins such as EGCG, may enhance LTP and improve cognitive function. These compounds have been shown to modulate various signaling pathways involved in synaptic plasticity, including the activation of N-methyl-D-aspartate (NMDA) receptors and the promotion of neurotrophic factors such as BDNF.<sup>95,107</sup> Furthermore, green tea has been found to exert neuroprotective effects by reducing oxidative stress, inflammation, and neuronal apoptosis, all of which can improve LTP and cognitive function.<sup>9,108,109</sup> The caffeine content in green tea may also contribute to its cognitive-enhancing effects by stimulating neurotransmitter release and improving alertness and concentration.<sup>86</sup> However, it has been suggested that green tea components possess neuroprotective properties, shielding neurons from damage and promoting their survival.<sup>110</sup> By maintaining neuronal health, green tea supports the structural integrity

required for LTP and optimal synaptic transmission.<sup>111</sup> Another critical pathway that has demonstrated by researchers is influences various signaling pathways involved in LTP regulation, such as MAPK/ERK, PI3K/Akt, and CREB pathways by green tea or its components (eg, EGCG). By modulating these pathways, green tea promotes the expression of genes associated with synaptic plasticity and memory formation. In this regard, it has been reported that green tea extracts enhanced LTP in the hippocampus, with researchers attributing this effect to the presence of catechins.<sup>112</sup> Furthermore, one meta analysis<sup>113</sup> concluded that green tea consumption was associated with improved cognitive function and reduced risk of cognitive decline. The authors suggested that the neuroprotective effects of green tea might be due to its antioxidant and anti-inflammatory properties.

## LIMITATIONS AND POTENTIAL ADVERSE EFFECTS OF GREEN TEA CONSUMPTION

The preceding sections have comprehensively detailed the neuroprotective mechanisms of green tea catechins, including inhibition of oxidative stress, attenuation of neuroinflammation, suppression of apoptosis, upregulation of neurotrophic factors, modulation of neurotransmitters, and enhancement of LTP. However, translating these promising preclinical findings into effective

clinical interventions faces significant challenges that warrant critical examination.

A primary obstacle is the poor bioavailability of green tea catechins, particularly EGCG. Following oral administration, EGCG exhibits low intestinal absorption, extensive hepatic metabolism, rapid systemic elimination, and limited ability to cross the blood-brain barrier (BBB). Unmodified phytochemicals show negligible BBB delivery, requiring high, potentially toxic doses to achieve neuroprotective effects.<sup>114</sup> Nanoliposome encapsulation has been demonstrated to enhance BBB uptake by 10- to 20-fold while reducing cytotoxicity by more than 50%, offering promising solutions to overcome this limitation.<sup>115</sup>

The available clinical evidence remains limited. While epidemiological studies suggest green tea consumption is associated with reduced risk of cognitive decline, few large-scale, placebo-controlled trials using standardized formulations have confirmed these benefits. A 12-month randomized study found that green tea consumption may not significantly affect Mini-Mental State Examination scores, although it prevented increases in oxidative stress in elderly populations.<sup>116</sup> The Pensa study—a randomized trial investigating EGCG combined with multimodal lifestyle intervention in apolipoprotein E ε4 carriers—did not meet

its primary cognitive outcome, though exploratory analyses suggested potential benefits warranting further investigation.<sup>117</sup> This underscores the gap between preclinical promise and clinical reality.

Significant challenges arise from inter-individual response variability and lack of standardization. Genetic polymorphisms in metabolizing enzymes, differences in gut microbiota, and variations in absorption rates contribute to heterogeneous responses.<sup>118</sup> Commercial products vary widely in catechin content, EGCG concentration, and caffeine levels, complicating interpretation of study results and hindering evidence-based dosing recommendations.

Safety concerns, particularly hepatotoxicity associated with concentrated green tea extracts, represent another critical limitation. Case reports have documented drug-induced liver injury and acute liver failure linked to green tea extract supplementation.<sup>119</sup> The hepatotoxic potential appears primarily associated with concentrated extracts rather than beverage consumption. Other adverse effects include gastrointestinal disturbances, headaches, and insomnia, particularly related to caffeine content.

Despite these limitations, the therapeutic potential of green tea catechins remains substantial due to their multitargeted neuroprotective actions. EGCG effectively reduces tau and A $\beta$  aggregation, promotes autophagy, and targets key signaling pathways including Nrf2-ARE, NF- $\kappa$ B, and MAPK, regulating mitochondrial dysfunction, oxidative stress, neuroinflammation, and protein misfolding—all central to AD and PD pathogenesis.<sup>120</sup>

Recent advancements in formulation and delivery techniques offer promising solutions. Structural analogs, liposomal encapsulation, and nanoformulations have shown potential in improving pharmacokinetics and enhancing brain delivery.<sup>115</sup> EGCG nanoparticles have demonstrated better BBB penetration, higher bioavailability, and enhanced improvement of memory deficits over free EGCG in experimental models.

Combination approaches represent another promising direction. The PENSE study demonstrated that combining EGCG with multimodal lifestyle intervention may reduce dementia risk through mechanisms beyond

amyloid and tau pathways, with sustained cognitive benefits even after washout.<sup>117</sup> Green tea is a cost-effective, culturally adaptable intervention with potential to complement existing dementia therapies.

Personalized medicine approaches may further optimize therapeutic outcomes. Subject genotyping for enzymes involved in catechin metabolism could aid in interpreting liver injury biomarkers and optimizing treatment.<sup>118</sup> Biomarker-guided monitoring and customized therapy are emphasized as essential for fully realizing EGCG's neuroprotective potential.

Epidemiological evidence consistently shows that green tea consumption is associated with lower prevalence of cognitive decline and decreased risk of AD and PD. Meta-analyses have found that tea intake can help reduce the risk of all-cause dementia, AD and vascular dementia.<sup>121</sup> These observations provide a strong rationale for continued investigation.

While significant challenges including poor bioavailability, limited clinical evidence, and safety concerns must be addressed, recent advancements in formulation technologies, combination approaches, and personalized strategies offer promising pathways for translation. Future research should prioritize large-scale controlled trials using standardized formulations, with careful attention to dosing, safety monitoring, and biomarker-guided patient selection. Despite current limitations, green tea remains a promising natural intervention for cognitive health, warranting continued investigation and careful clinical translation.<sup>122</sup>

## CONCLUSION

This narrative review provides a comprehensive overview of the intricate neurobiological mechanisms underlying the memory-enhancing properties of green tea. With a focus on the modulation of neurotransmitter systems, antioxidant effects, regulation of neuroinflammation, and influence on neurotrophic factors, green tea emerges as a promising natural intervention for improving memory impairment. The findings of this review highlight the multifaceted ways in which green tea components, particularly catechins such as EGCG, interact with various molecular and cellular processes to enhance memory function. The neuroprotective and cognitive-enhancing effects of green tea offer great

potential for addressing cognitive decline and memory deficits. By elucidating the underlying mechanisms through which green tea exerts its beneficial effects on memory, this review contributes to a deeper understanding of the therapeutic value of green tea in promoting cognitive health. Moving forward, further research is warranted to explore the specific pathways and interactions through which green tea components modulate cognitive function. Clinical studies investigating the efficacy of green tea supplementation in individuals with memory impairment could provide valuable insights into its practical applications for cognitive enhancement.

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## AUTHOR CONTRIBUTIONS

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by MH-M, YB, and FS. The first draft of the manuscript was written by FM and MD. HM, YB, and MH-M contributed to the editing and conceptualization. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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