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A review on green tea catechins in Alzheimer's disease of efficacy mechanism and future direction

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Abstract

Alzheimer's disease (AD) is a complex neurodegenerative disorder with limited treatment options. Green tea rich in catechins has been investigated for its potential neuroprotective and cognitive – enhancing effect. Oxidative stress is a component of the pathological mechanisms underlying AD. It is caused by a disruption of the balance between reactive oxygen species and antioxidant molecules. This imbalance also causes neuroinflammation. Catechins, which are bioactive components of tea, have antioxidative and anti-inflammatory effects. Moreover, other potential properties related to AD prevention and modification have been reported in in vitro and in vivo studies. Several clinical studies have also been conducted to date. The current review summarizes recent updates and perspectives of the effects of catechins on AD based on the molecular mechanisms and related clinical studies. This review examine the current evidence on green tea efficacy, mechanism and future direction in AD management.

Keywords: Alzheimer's disease; Catechin; Molecular Mechanisms; Clinical Study; Neuroprotection; Cognitive Enhancement

1. Introduction

Over 100 years ago, the first case of Alzheimer's disease (AD) was reported by Dr. Alois Alzheimer, in a German woman, Auguste Deter. It was subsequently named "Alzheimer's disease" by Dr. Emil Kraepelin and colleagues [1,2,3,4]. The number of individuals with AD is gradually increasing due to worldwide aging. The Alzheimer's Association estimated the prevalence of AD in the U.S. In 2016 to be 5.3 million cases, and another study indicated that there were over 45 million individuals living with AD worldwide [5,6]. Two types of medications have been developd to treat AD symptoms: (1) acetylcholinesterase (AChE) inhibitors (donepezil, rivastigmine, and galantamine), and (2) an N-methyl-d-aspartate (NMDA) receptor antagonist (memantine). However, there is currently no cure [4]. In addition, the strategy for AD drug development has recently shifted toward disease prevention rather than treatment. As such, a combination of pharmaceutical and nonpharmaceutical approaches is important [4].

Green tea catechins, particularly epigallocatechin-3-gallate (EGCG), have garnered considerable attention for their potential therapeutic benefits in neurodegenerative diseases, including Alzheimer's disease (AD). Alzheimer's is characterized by the accumulation of amyloid-beta plaques, tau protein tangles, oxidative stress, and chronic neuroinflammation, all of which contribute to cognitive decline. Due to their potent antioxidant, anti-inflammatory, and neuroprotective properties, green tea catechins are being investigated for their ability to counteract these pathological processes. This review explores the efficacy, underlying mechanisms, and future perspectives of green tea catechins as

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a potential therapeutic option for Alzheimer's disease, highlighting their role in reducing amyloid-beta toxicity, preventing tau aggregation, and mitigating oxidative damage in the brain [37,38].

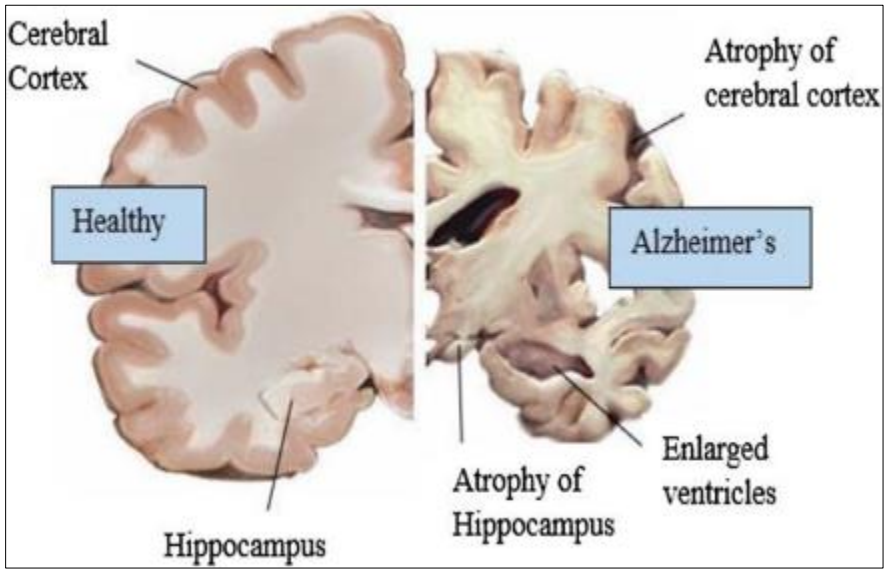

Figure 1 Difference of Healthy Alzheimer's Brain

2. Classification of Alzheimer's Disease

Alzheimer's disease (AD) can be classified based on its onset, pathology, and progression. The common classifications as,

2.1. Based on Onset

2.1.1. Early-Onset Alzheimer's Disease (EOAD)

This form appears before the age of 65 and constitutes about 5-10% of all cases. It's more likely to be linked to genetic mutations (familial AD) [41,42,44].

2.1.2. Let – onset of Alzheimer's Disease (LOAD):

Occurs after age 65 and is the most common form of AD. It has a more complex etiology, influenced by A combination of genetic, lifestyle, and environmental factors [44].

2.2. Based on Stages of Alzheimer's Disease:

2.2.1. Preclinical Alzheimer's Disease

No symptoms are noticeable yet, but changes in the brain (e.g., amyloid plaques) have already started.This stage can last for years before any symptoms appear [38].

2.2.2. Mild Cognitive Impairment (MCI) Due to Alzheimer's Disease

Individuals experience noticeable memory lapses but can still carry out daily tasks [42,43].

2.2.3. Mild Alzheimer's Disease

- Memory loss becomes more pronounced.
- Symptoms include confusion, trouble handling Money, poor judgment, mood changes, and increased anxiety [40].

2.2.4. Moderate Alzheimer's Disease

- Memory and cognitive deficits worsen, and the Patient requires more help with daily activities.

- Symptoms include difficulty recognizing loved ones, problems with language, disorientation, and changes in behavior (e.g., wandering, agitation).

2.2.5. Severe Alzheimer's Disease

Patients lose the ability to communicate coherently, need help with personal care, and experience a significant decline in physical abilities (e.g., walking, sitting) In this final stage, patients may become bedridden and are vulnerable to infections like pneumonia [18,44].

2.2.6. Pathophysiology of AD

Its pathophysiology involves complex interactions between genetic, molecular, and environmental factors, leading to the characteristic features of amyloid plaques, neurofibrillary tangles, and widespread neuronal loss [1].

Amyloid Plaques

One of the hallmark features of Alzheimer's disease is the accumulation of extracellular amyloid-beta (Aβ) plaques in the brain. These plaques are formed from the abnormal processing of the amyloid precursor protein (APP), which is normally cleaved by enzymes (alpha, beta, and gamma secretases) to produce smaller peptide fragments. In Alzheimer's, beta and gamma secretase activity predominates, leading to the production of insoluble Aβ42, which aggregates into plaques. The accumulation of Aβ42 is toxic to neurons, contributing to synaptic dysfunction, oxidative stress, and neuroinflammation. [26,27].

Neurofibrillary Tangles

Another key feature of AD is the formation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein. Tau is a microtubule-associated protein that normally helps stabilize the structure of microtubules, essential for intracellular transport in neurons. In Alzheimer's, tau becomes hyperphosphorylated, which disrupts its normal function and causes it to aggregate into insoluble tangles. These tangles impair axonal transport, leading to neuronal dysfunction and cell death. The spread of tau pathology correlates with diseases progression and cognitive decline [1,26].

Neuroinflammation

Chronic neuroinflammation plays a significant role in Alzheimer's disease progression. Microglia, the brain's resident immune cells, are activated in response to amyloid plaques and other pathological stimuli. While microglial activation is initially protective, prolonged activation leads to the release of pro-inflammatory cytokines and chemokines, which exacerbate neuronal injury. The dysregulated immune response contributes to the loss of synapses and neurons, worsening cognitive impairment [26,27].

Synaptic Dysfunction and Neuronal Loss

Both amyloid plaques and tau tangles contribute to synaptic dysfunction, a core feature of AD. Synapse loss, particularly in regions like the hippocampus and cortex, correlates with cognitive decline. The toxic effects of amyloid-beta and tau, combined with oxidative stress and inflammation, lead to widespread neuronal death. As neurons degenerate, there is a decrease in acetylcholine, a neurotransmitter critical for memory and learning, which is particularly affected in AD [1,27].

Genetic Factors

There are both sporadic and familial forms of Alzheimer's disease. The majority of cases are sporadic and associated with aging, while early-onset familial AD is linked to mutations in specific genes. Mutations in the APP gene, PSEN1, and PSEN2 (presenilin genes) are associated with increased production of Aβ42, leading to early plaque formation and disease onset. The apolipoprotein E (APOE) gene is also a major genetics Risk factor, with the APOE ε4 allele increasing the risk of late-onset AD by influencing Aβ deposition and clearance [27].

Mitochondrial Dysfunction and Oxidative Stress

Oxidative stress is a critical component of AD pathogenesis. Mitochondrial dysfunction in neurons leads to increased production of reactive oxygen species (ROS), which damage proteins, lipids, and DNA. Oxidative damage, coupled with impaired mitochondrial function, further exacerbates neuronal death. Aβ and tau aggregation also contribute to Oxidative stress, creating a vicious cycle of neuronal injury [26,27].

Vascular Contributions

Cerebrovascular dysfunction is increasingly recognized as a contributor to Alzheimer's disease. Reduced cerebral blood flow, blood-brain barrier (BBB) breakdown, and vascular pathology (e.g., amyloid angiopathy) may exacerbate neuronal damage. Vascular risk factors like hypertension, diabetes, and atherosclerosis are associated with a higher risk of developing Alzheimer's, highlighting the interaction between vascular and neurodegenerative process [1,26,27].

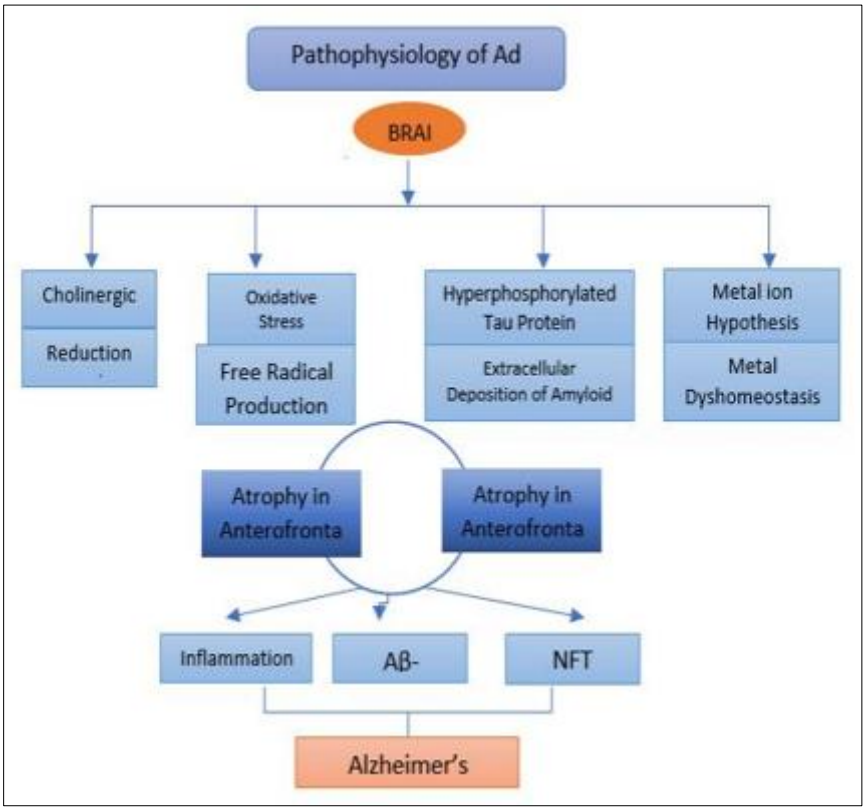

Figure 2 Pathophysiology of AD

Symptoms of Alzheimer's Disease

- memory loss
- difficulty in problem solving and planning.
- confusion with time and place
- difficulty in completing familiar task
- challenges in understanding visual and spatial relationship [33,34].

2.3. Causes of Alzheimer's disease

The exact cause of Alzheimer's is not fully understood, but a combination of genetic, environmental, and lifestyle factors plays a role.

- Amyloid Plaques
- Neurofibrillary Tangles
- Genetic Factors
- Age
- Lifestyle and Heart Health:
- Head Injury
- 7.Brain Inflammation [21,22,30].

2.4. Risk factors in AD

While there is no cure for Alzheimer's, early detection and interventions like medications, cognitive therapies, and lifestyle changes can help slow its progression and improve quality of life.

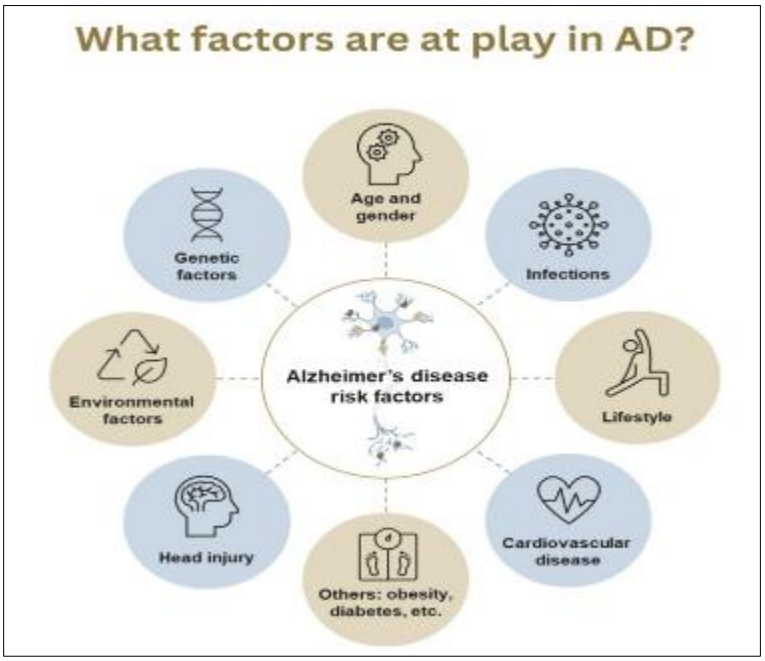

Figure 3 Risk Factors of AD

2.5. Green tea catechins in the treatment of AD

Green tea catechins, particularly epigallocatechin gallate (EGCG), have been researched for their potential role in preventing or slowing the progression of Alzheimer's disease (AD). Catechins are natural antioxidants found in green tea that may offer neuroprotective benefits [37,38] .

- Antioxidant effect
- Anti amyloid property
- Anti-inflammatory effect
- Chelation of metal ions
- Neuroprotective signalling
- Improvement in cognitive function [37,38].

Figure 4 Green Tea

2.6. Drugs used in treatment of AD

- Donepezil
- Rivastigmine

- Galantamine [8].

Molecular Mechanisms Underlying the Effects of Catechins in AD :

- Inhibition of Amyloid-Beta (Aβ) Aggregation
- Reduction of Tau Protein Hyperphosphorylation
- Antioxidant Effects
- Anti-inflammatory Action
- Metal Chelation
- Mitochondrial Protection
- Enhancement of Synaptic Plasticity.
- Inhibition of Acetylcholinesterase[5,28,29]

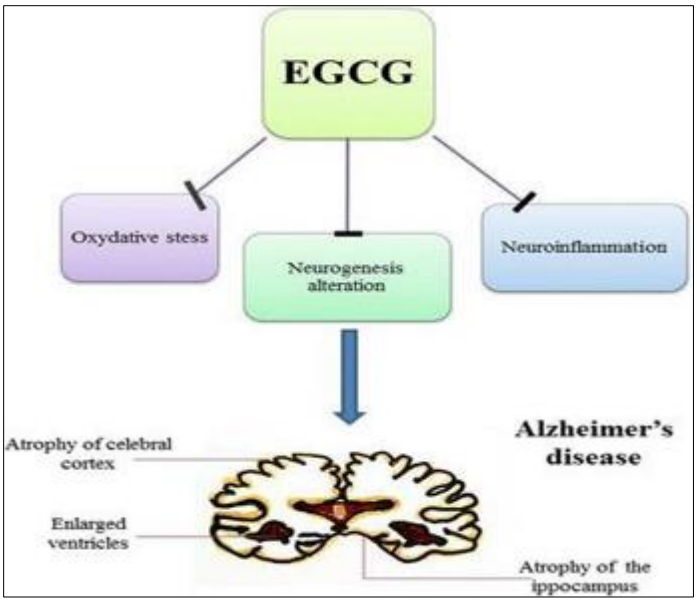

Figure 5 Mechanism of Catechins

2.7. Several Uses of green tea

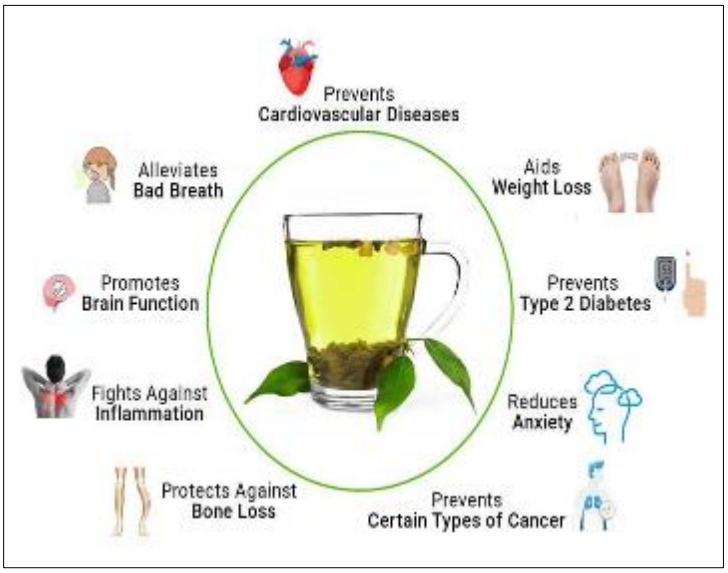

Figure 6 Uses of Green Tea

3. Conclusion

The review on the efficacy, mechanism, and future direction of green tea catechins (GTCs) in Alzheimer's Disease (AD) suggests that GTCs, particularly epigallocatechin gallate (EGCG), have shown promising neuroprotective effects. These effects are attributed to the antioxidant, anti-inflammatory, and anti-amyloidogenic properties of catechins. They inhibit amyloid-beta (Aβ) aggregation, promote Aβ clearance, and protect neurons from oxidative stress and inflammation, which are hallmarks of AD.

While preclinical studies (in vitro and animal models) strongly support the potential of GTCs in alleviating AD pathology, clinical trials have yielded mixed results. Factors such as bioavailability, dosage, and treatment duration may influence the therapeutic efficacy in humans.

Future Directions

- Improvement in Bioavailability: Since EGCG has low bioavailability, research is needed to improve delivery methods or develop GTC analogs that can cross the blood-brain barrier more effectively.
- Combination Therapies: Exploring the combination of GTCs with other therapeutic agents could enhance their efficacy in AD treatment.
- Long-term Human Trials: More extensive and well-designed human clinical trials are necessary to confirm the protective effects observed in preclinical studies and to establish effective therapeutic protocols.
- Molecular Targeting: Investigating the precise molecular pathways through which GTCs exert neuroprotective effects may open new therapeutic avenues.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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