

Therapeutic Effects of Catechins

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Catechins are polyphenolic flavonoids derived from catechu, which is the tannic juice or boiled extract of *Acacia catechu* L. Green tea, one of the most consumed beverages worldwide, obtained from the buds and leaves of the plant *Camellia sinensis*, is a well-known source of catechins. Moreover, catechins are found in a variety of foods and herbs including wine, apples, persimmons, cocoa, grapes, berries, and cocoa-based products. Due to numerous hydroxyl groups, catechins have powerful antioxidant and metal-chelating properties, which have been confirmed in in-vitro and clinical studies.

catechins

epigallocatechin-3-gallate

antioxidant

neurodegenerative disorders

neurological disorders

multiple sclerosis

fetal alcohol spectrum disorders

Down syndrome

age-related cognitive decline

1. Overview

In recent years, neurological and neurodegenerative disorders research has focused on altered molecular mechanisms in search of potential pharmacological targets, e.g., imbalances in mechanisms of response to oxidative stress, inflammation, apoptosis, autophagy, proliferation, differentiation, migration, and neuronal plasticity, which occur in less common neurological and neurodegenerative pathologies (Huntington disease, multiple sclerosis, fetal alcohol spectrum disorders, and Down syndrome). Here, we assess the effects of different catechins (particularly of epigallocatechin-3-gallate, EGCG) on these disorders, as well as their use in attenuating age-related cognitive decline in healthy individuals. Antioxidant and free radical scavenging properties of EGCG - due to their phenolic hydroxyl groups-, as well as its immunomodulatory, neuritogenic, and autophagic characteristics, makes this catechin a promising tool against neuroinflammation and microglia activation, common in these pathologies. Although EGCG promotes the inhibition of protein aggregation in experimental Huntington disease studies and improves the clinical severity in multiple sclerosis in animal models, its efficacy in humans remains controversial. EGCG may normalize DYRK1A (involved in neural plasticity) overproduction in Down syndrome, improving behavioral and neural phenotypes. In neurological pathologies caused by environmental agents, such as FASD, EGCG enhances antioxidant defense and regulates placental angiogenesis and neurodevelopmental processes. As demonstrated in animal models, catechins attenuate age-related cognitive decline, which results in improvements in long-term outcomes and working memory, reduction of hippocampal neuroinflammation, and enhancement of neuronal plasticity; however, further studies are needed. Catechins are valuable compounds for treating and preventing certain neurodegenerative and neurological diseases of genetic

and environmental origin. However, the use of different doses of green tea extracts and EGCG makes it difficult to reach consistent conclusions for different populations.

2. Catechins

Catechins are polyphenolic flavonoids derived from catechu, which is the tannic juice or boiled extract of *Acacia catechu* L. Green tea, one of the most consumed beverages worldwide, obtained from the buds and leaves of the plant *Camellia sinensis*, is a well-known source of catechins. Moreover, catechins are found in a variety of foods and herbs including wine, apples, persimmons, cocoa, grapes, berries, and cocoa-based products. Due to numerous hydroxyl groups, catechins have powerful antioxidant and metal-chelating properties, which have been confirmed in in-vitro and clinical studies [1][2][3].

In recent years, (-)-epigallocatechin-3-gallate (EGCG) and (-)-epicatechin-3-gallate (ECG) have been the subject of multiple studies due to their anti-cancer, anti-obesity, anti-diabetic, anti-cardiovascular, anti-infectious, or hepatoprotective effects [4]. Some works have focused on the use of catechins on neurodegenerative disorders, e.g., Alzheimer's disease and Parkinson's disease [5][6][7][8]. The present review is centered on the potential application of these antioxidants as therapeutic compounds in less-common neurological disorders, neurodegenerative disorders, and age-related cognitive decline.

Recently, catechins have attracted attention in the field of neurodegenerative disorders like Huntington disease (HD) (estimated prevalence of 2.7–5.7/100,000) and multiple sclerosis (MS), the most frequent cause of permanent non-traumatic disability in young adults, with high-risk areas in Europe, Canada, United States, New Zealand, and Australia (prevalence > 60/100,000) [9][10][11][12]. We further review the effect of catechins on Down syndrome (DS) and Fetal Alcohol Spectrum Disorders (FASD). DS is the most common chromosome abnormality among newborns (trisomy 21), with an estimated prevalence of 23/10,000 births [13][14], while FASD is caused by the toxic and teratogenic effects of prenatal alcohol consumption, with global and European prevalence of 7.7/1000 and 19.8/1000, respectively [15][16]. Recent evidence shows a common cellular and molecular origin disrupted by trisomy and alcohol intake, leading to craniofacial and neurocognitive phenotypes of DS and FASD [17].

3. Conclusions

Interest in catechin use has been growing in recent years. Their natural origin and multiple mechanisms of action make them a feasible option for the management of different neurological diseases. Although flavan-3-ols or catechins comprise a high number of bioactive compounds, this study focused mainly on EGCG. It has potent antioxidant activity compared to other catechins, positive effects on brain function, and ability to cross the blood-brain barrier, making it a promising tool for the treatment of neurodegenerative disorders. Modulation of microglia activation, reduction of inflammatory mediators [18][19][20], iron-chelating properties [8], neuritogenic activity [21], autophagic flow restoration, and reduced apoptosis [22][23], are some examples of how EGCG can act on brain function. The use of EGCG in less common neurodegenerative diseases, such as HD, is supported by the ability of

EGCG to inhibit protein aggregation [24][25][26]. Preliminary results from clinical trials assessing changes in cognitive performance are promising [27], but further clinical trials are required in humans to validate them. Neuroinflammation is characterized by microglial activation, which contributes to HD progression; thus, this flavan-3-ol may be used to reinforce regular treatments to help decrease inflammatory and apoptotic mediators in microglia and exert a neuroprotective effect. The immunomodulatory effects of EGCG also play a critical role in MS, characterized by focal lymphocytic (T-cells) infiltration, demyelination, and axonal and neuronal damage. EGCG diminishes immune cell infiltration, modulates T-cell balance [28][29], and reduces inflammatory cytokines [29], attenuating the symptoms of the disease. Furthermore, EGCG interferes in the modulation of neuronal transcription factors -important in remyelination processes [30][31]- and reduces oxidative stress [32]. Although catechins show no effect on the development of new hyperintense lesions on MRI [33] or brain atrophy, their use has demonstrated improvement of muscle metabolism during exercise [34] and amelioration of neurodegeneration, as judged by the increase of brain N-acetyl aspartate levels in MS individuals [35].

Catechins, particularly EGCG and ECG, exert their neuroprotective effects through an antioxidant action via free radical scavenging and regulation of oxidative stress response [36][37]. EGCG has a greater ability to donate electrons in comparison to other flavan-3-ols due to its eight hydroxyl groups, notably in the 3', 4', and 5' positions, and its antioxidant potential mainly comes from these functional groups. Moreover, its phenolic groups (particularly in the B-ring) can chelate metals, increasing its antioxidant capacity. EGCG can also reduce certain metals, such as iron and copper, related to the Fenton reaction, an advanced oxidation process in which highly reactive hydroxyl radicals (OH-) are produced [38].

EGCG's antioxidant properties are key for early interventions aiming to prevent secondary FASD disabilities, since one of the main pathophysiological mechanisms of alcohol-related disorders is oxidative stress. EGCG modulates antioxidant defense and oxidative stress balance in FASD-like rodent models [39][40][41], resulting in the reduction of neuronal loss and recovery of maturation delay, and prevents early astrocyte differentiation and disturbances in neuronal plasticity produced by maternal drinking [41]. Moreover, EGCG prevents neuronal apoptosis and ameliorates inflammatory response secondary to PAE [40], and regulates the expression of genes and proteins involved in brain development and neural differentiation [39] associated with improvements in memory and learning abilities [40]. Understanding the effect EGCG has on ethanol-induced epigenetic alterations, as well as the modulatory effect of EGCG on DYRK1A may clarify the beneficial outcomes of catechins on FASD neurodevelopment. Regarding fetal growth, EGCG promotes the correct development by regulating placental angiogenic processes [39][41]. Studies in children are necessary, such as neuro-SAF, to evaluate the effect of EGCG on cognitive performance and translate the promising results found in animals to human populations [42].

As FASD and DS show common molecular and cellular origins during fetal development, EGCG treatment has been proposed to reverse disabilities related to both syndromes by improving neurogenesis, neuronal differentiation, cell death, and synaptic plasticity processes by regulating Dyrk1A overexpression [43]. Recent literature demonstrates a rescue of behavioral and cognitive outcomes in DS animal models treated with EGCG supplements. EGCG inhibits DYRK1A overexpression, a gene involved in a range of routes associated to neural progenitor cell growth, and the primary gene candidate to explain DS phenotype [44]; treatment with EGCG may

normalize its overproduction improving behavioral and neural phenotypes in this condition. EGCG acts on hippocampal neurogenesis, responsible of cognitive disabilities [45]; thus, treatments aiming to restore neurogenesis alterations may be effective in DS individuals [46]. Moreover, recent studies highlight that EGCG modulates epigenetic changes, restoring epigenetic balance [47] and promotes mitochondrial biogenesis [48]. The potential effect of EGCG in modulating plasticity alterations in DS seems to be more beneficial if the treatment is started during the first years of life [47].

Furthermore, the combination of cognitive training with EGCG may synergistically improve the effects of such therapy in FASD and DS [49].

Finally, the antioxidant properties of catechins and other flavanols on healthy populations may help prevent many chronic diseases related with lifestyle as judged by significant increase in alpha, beta and theta electroencephalogram activity in the midline frontal and central regions [50]. Observational studies have shown that regular diets rich in catechins improve different cognitive functions [51][52]. Thus, some authors have developed randomized, placebo-controlled studies to assess the use of EGCG or green tea extracts. Their findings suggest that catechins may promote improvement in cognitive function of healthy populations [50][53], but further investigation is needed to confirm the results and establish the molecular and cognitive pathways of these potential benefits. The reduction in hippocampal neuroinflammation or the increased expression of genes involved in long-term changes in neuronal circuits and plasticity synapses may be the mechanisms associated to the beneficial effects exerted by EGCG on age-related cognitive decline [54][55]. To date, there are no studies in humans reproducing the encouraging results obtained with the use of EGCG in animal models. Human research has been carried out with different types of green tea extracts at different proportions of many catechins, and mild improvements have been seen in certain areas of cognition or population subgroups [5][56][57]. Thus, prevention or improvement of cognitive decline remains uncertain, requiring more evidence to determine which populations and areas can be improved with catechin supplementation.

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