Therapeutic Effects of Catechins

Subjects: Nutrition & Dietetics
Contributor: Giorgia Sebastiani

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.

Keywords: 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 epigalocatechin-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 beneficious if the treatment if 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.

References

1. Sutherland, B.A.; Rahman, R.M.; Appleton, I. Mechanisms of action of green tea catechins, with a focus on ischemia-induced neurodegeneration. J. Nutr. Biochem. 2006, 17, 291–306.
2. Cardoso, R.R.; Neto, R.O.; D'Almeida, C.T.D.S.; Nascimento, T.P.D.; Pressete, C.G.; Azevedo, L.; Martino, H.S.D.; Cameron, L.C.; Ferreira, M.S.L.; de Barros, F.A.R. Kombuchas from green and black teas have different phenolic profile, which impacts their antioxidant capacities, antibacterial and antiproliferative activities. Food Res. Int. 2020, 128, 108782.
3. Bernatoniene, J.; Kopustinskiene, D.M. The Role of Catechins in Cellular Responses to Oxidative Stress. Molecules 2018, 23, 965.
4. Reygaert, W.C. Green Tea Catechins: Their Use in Treating and Preventing Infectious Diseases. BioMed Res. Int. 2018, 2018, 1–9.
5. Ide, K.; Yamada, H.; Takuma, N.; Kawasaki, Y.; Harada, S.; Nakase, J.; Ukawa, Y.; Sagesaka, Y.M. Effects of green tea consumption on cognitive dysfunction in an elderly population: A randomized placebo-controlled study. Nutr. J. 2015, 15, 1–9.
6. Lim, H.J.; Shim, S.B.; Jee, S.W.; Lee, S.H.; Lim, C.J.; Hong, J.T.; Sheen, Y.Y.; Hwang, D.Y. Green tea catechin leads to global improvement among Alzheimer's disease-related phenotypes in NSE/hAPP-C105 Tg mice. J. Nutr. Biochem. 2013, 24, 1302–1313.
7. Pervin, M.; Unno, K.; Ohishi, T.; Tanabe, H.; Miyoshi, N.; Nakamura, Y. Beneficial Effects of Green Tea Catechins on Neurodegenerative Diseases. Molecules 2018, 23, 1297.
8. Mandel, S.A.; Avramovich-Tirosh, Y.; Reznichenko, L.; Zheng, H.; Weinreb, O.; Amit, T.; Youdim, M.B.H. Multifunctional activities of green tea catechins in neuroprotection: Modulation of cell survival genes, iron-dependent oxidative stress and PKC signaling pathway. NeuroSignals 2005, 14, 46–60.
9. Pringsheim, T.; Wiltshire, K.; Day, L.; Dykeman, J.; Steeves, T.; Jette, N. The incidence and prevalence of Huntington's disease: A systematic review and meta-analysis. Mov. Disord. 2012, 27, 1083–1091.
10. Ramagopalan, S.V.; Sadovnick, A.D. Epidemiology of Multiple Sclerosis. Neurol. Clin. 2011, 29, 207–217.
11. Glaser, A.; Stahmann, A.; Meissner, T.; Flachenecker, P.; Horáková, D.; Zaratin, P.; Brichetto, G.; Pugliatti, M.; Rienhoff, O.; Vukusic, S.; et al. Multiple sclerosis registries in Europe—An updated mapping survey. Mult. Scler. Relat. Disord. 2019, 27, 171–178.
12. Wallin, M.T.; Culpepper, W.J.; Nichols, E.; Bhutta, Z.A.; Gebrehiwot, T.T.; Hay, S.I.; Khalil, I.A.; Krohn, K.J.; Liang, X.; Naghavi, M.; et al. Global, regional, and national burden of multiple sclerosis 1990–2016: A systematic analysis for the

Global Burden of Disease Study 2016. Lancet Neurol. 2019, 18, 269–285.

13. Lanzoni, M.; Kinsner-Ovaskainen, A.; Morris, J. Socio-Economic Regional Microscope Series EUROCAT-Surveillance of Congenital Anomalies in Europe: Epidemiology of Down syndrome 1990–2014. Available online: (accessed on 22 March 2021).
14. Lanzillotta, C.; Di Domenico, F. Stress Responses in Down Syndrome Neurodegeneration: State of the Art and Therapeutic Molecules. Biomolecules 2021, 11, 266.
15. Kobor, M.S.; Weinberg, J. Focus on: Epigenetics and Fetal Alcohol Spectrum Disorders. Alcohol Res. Health J. Natl. Inst. Alcohol Abus. Alcohol. 2011, 34, 29–37.
16. Brocardo, P.S.; Gil-Mohapel, J.; Christie, B.R. The role of oxidative stress in fetal alcohol spectrum disorders. Brain Res. Rev. 2011, 67, 209–225.
17. Solzak, J.P.; Liang, Y.; Zhou, F.C.; Roper, R.J. Commonality in Down and fetal alcohol syndromes. Birth Defects Res. Part A Clin. Mol. Teratol. 2013, 97, 187–197.
18. Degan, D.; Ornello, R.; Tiseo, C.; Carolei, A.; Sacco, S.; Pistoia, F. The Role of Inflammation in Neurological Disorders. Curr. Pharm. Des. 2018, 24, 1485–1501.
19. Marinovic, M.; Morandi, A.; Otton, R. Green tea catechins alone or in combination alter functional parameters of human neutrophils via suppressing the activation of TLR-4/NFκB p65 signal pathway. Toxicol. Vitr. 2015, 29, 1766–1778.
20. Bao, J.; Liu, W.; Zhou, H.-Y.; Gui, Y.-R.; Yang, Y.-H.; Wu, M.-J.; Xiao, Y.-F.; Shang, J.-T.; Long, G.-F.; Shu, X.-J. Epigallocatechin-3-gallate Alleviates Cognitive Deficits in APP/PS1 Mice. Curr. Med. Sci. 2020, 40, 18–27.
21. Unno, K.; Pervin, M.; Nakagawa, A.; Iguchi, K.; Hara, A.; Takagaki, A.; Nanjo, F.; Minami, A.; Nakamura, Y. Blood–Brain Barrier Permeability of Green Tea Catechin Metabolites and their Neuritogenic Activity in Human Neuroblastoma SH-SY5Y Cells. Mol. Nutr. Food Res. 2017, 61.
22. Gu, H.-F.; Nie, Y.-X.; Tong, Q.-Z.; Tang, Y.-L.; Zeng, Y.; Jing, K.-Q.; Zheng, X.-L.; Liao, D.-F. Epigallocatechin-3-Gallate Attenuates Impairment of Learning and Memory in Chronic Unpredictable Mild Stress-Treated Rats by Restoring Hippocampal Autophagic Flux. PLoS ONE 2014, 9, e112683.
23. Mandel, S.A.; Amit, T.; Weinreb, O.; Reznichenko, L.; Youdim, M.B.H. Simultaneous Manipulation of Multiple Brain Targets by Green Tea Catechins: A Potential Neuroprotective Strategy for Alzheimer and Parkinson Diseases. CNS Neurosci. Ther. 2008, 14, 352–365.
24. Beasley, M.; Stonebraker, A.; Hasan, I.; Kapp, K.L.; Liang, B.J.; Agarwal, G.; Groover, S.; Sedighi, F.; Legleiter, J. Lipid Membranes Influence the Ability of Small Molecules to Inhibit Huntingtin Fibrillization. Biochemistry 2019, 58, 4361–4373.
25. Ehrnhoefer, D.E.; Duennwald, M.; Markovic, P.; Wacker, J.L.; Engemann, S.; Roark, M.; Legleiter, J.; Marsh, J.L.; Thompson, L.M.; Lindquist, S.; et al. Green tea (−)-epigallocatechin-gallate modulates early events in huntingtin misfolding and reduces toxicity in Huntington's disease models. Hum. Mol. Genet. 2006, 15, 2743–2751.
26. Varga, J.; Dér, N.P.; Zsindely, N.; Bodai, L. Green tea infusion alleviates neurodegeneration induced by mutant Huntingtin in Drosophila. Nutr. Neurosci. 2018, 23, 183–189.
27. Priller, J. Effects of EGCG (Epigallocatechin Gallate) in Huntington's Disease The ETON-Study—A Randomized, Double-blind, Stratified, Placebo-controlled Prospective Investigator Initiated Multicenter Trial-Charite University, Berlin, Germany ClinicalTrials.gov Identifier: NCT01357681. Available online: (accessed on 29 April 2021).
28. Wang, J.; Ren, Z.; Xu, Y.; Xiao, S.; Meydani, S.N.; Wu, D. Epigallocatechin-3-Gallate Ameliorates Experimental Autoimmune Encephalomyelitis by Altering Balance among CD4+ T-Cell Subsets. Am. J. Pathol. 2012, 180, 221–234.
29. Sun, Q.; Zheng, Y.; Zhang, X.; Hu, X.; Wang, Y.; Zhang, S.; Zhang, N.; Nie, H. Novel immunoregulatory properties of EGCG on reducing inflammation in EAE. Front. Biosci. 2013, 18, 332–342.
30. Mohammad-Reza, S.; Farhad, M.; Mahnaz, A.; Salehi, Z. Effects of Green Tea Epigallocatechin-3-Gallate (EGCG) On Proteolipid Protein (PLP) and Oligodendrocyte Transcription Factor 1 (Olig1) Expression in the Cerebral Cortex of Cuprizone Induced Multiple Sclerosis Mice; A Western Blot Study. Casp. J. Neurol. Sci. 2016, 1, 1–9.
31. Semnani, M.; Mashayekhi, F.; Azarnia, M.; Salehi, Z. Effects of green tea epigallocatechin-3-gallate on the proteolipid protein and oligodendrocyte transcription factor 1 messenger RNA gene expression in a mouse model of multiple sclerosis. Folia Neuropathol. 2017, 3, 199–205.
32. Mossakowski, A.A.; Pohlan, J.; Bremer, D.; Lindquist, R.; Millward, J.M.; Bock, M.; Pollok, K.; Mothes, R.; Viohl, L.; Radbruch, M.; et al. Tracking CNS and systemic sources of oxidative stress during the course of chronic neuroinflammation. Acta Neuropathol. 2015, 130, 799–814.

33. Bellmann-Strobl, J.; Paul, F.; Wuerfel, J.; Dörr, J.; Infante-Duarte, C.; Heidrich, E.; Körtgen, B.; Brandt, A.; Pfüller, C.; Radbruch, H.; et al. Epigallocatechin Gallate in Relapsing-Remitting Multiple Sclerosis. Neurol. Neuroimmunol. Neuroinflamm. 2021, 8, e981.

34. Mähler, A.; Steiniger, J.; Bock, M.; Klug, L.; Parreidt, N.; Lorenz, M.; Zimmermann, B.F.; Krannich, A.; Paul, F.; Boschmann, M. Metabolic response to epigallocatechin-3-gallate in relapsing-remitting multiple sclerosis: A randomized clinical trial. Am. J. Clin. Nutr. 2015, 101, 487–495.

35. Lovera, J.; Ramos, A.; Devier, D.; Garrison, V.; Kovner, B.; Reza, T.; Koop, D.; Rooney, W.; Foundas, A.; Bourdette, D. Polyphenon E, Non-futile at Neuroprotection in Multiple Sclerosis but Unpredictably Hepatotoxic: Phase I Double-blind Group and Phase II Randomized Placebo-Controlled Studies. J. Neurol. Sci. 2015, 358, 46–52.

36. Fang, E.F.; Hou, Y.; Palikaras, K.; Adriaanse, B.A.; Kerr, J.S.; Yang, B.; Lautrup, S.; Hasan-Olive, M.; Caponio, D.; Dan, X.; et al. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat. Neurosci. 2019, 22, 401–412.

37. Romeo, L.; Intrieri, M.; D'Agata, V.; Mangano, N.G.; Oriani, G.; Ontario, M.L.; Scapagnini, G. The major green tea polyphenol, (-)-epigallocatechin-3-gallate, induces heme oxygenase in rat neurons and acts as an effective neuroprotective agent against oxidative stress. J. Am. Coll. Nutr. 2009, 28, 492S–499S.

38. Zhong, Y.; Ma, C.-M.; Shahidi, F. Antioxidant and antiviral activities of lipophilic epigallocatechin gallate (EGCG) derivatives. J. Funct. Foods 2012, 4, 87–93.

39. Long, L.; Li, Y.; Wang, Y.D.; He, Q.Y.; Li, M.; Cai, X.D.; Peng, K.; Li, X.P.; Xie, D.; Wen, Y.L.; et al. The Preventive Effect of Oral EGCG in a Fetal Alcohol Spectrum Disorder Mouse Model. Alcohol. Clin. Exp. Res. 2010, 34, 1929–1936.

40. Tiwari, V.; Kuhad, A.; Chopra, K. Epigallocatechin-3-gallate ameliorates alcohol-induced cognitive dysfunctions and apoptotic neurodegeneration in the developing rat brain. Int. J. Neuropsychopharmacol. 2010, 13, 1053–1066.

41. Almeida-Toledano, L.; Andreu-Fernández, V.; Aras-López, R.; García-Algar, Ó.; Martínez, L.; Gómez-Roig, M.D. Epigallocatechin Gallate Ameliorates the Effects of Prenatal Alcohol Exposure in a Fetal Alcohol Spectrum Disorder-Like Mouse Model. Int. J. Mol. Sci. 2021, 22, 715.

42. Algar, O.G.; de Salut Mar, P. Epigallocatechin Gallate (EGCG) to Improve Cognitive Performance in Foetal Alcohol Syndrome (FAS) Children (Neuro-SAF) Full Text View ClinicalTrials.gov. Available online: (accessed on 8 April 2021).

43. Tejedor, F.J.; Hämmerle, B. MNB/DYRK1A as a multiple regulator of neuronal development. FEBS J. 2010, 278, 223–235.

44. Dierssen, M.; De Lagrán, M.M. DYRK1A (Dual-Specificity Tyrosine-Phosphorylated and -Regulated Kinase 1A): A Gene with Dosage Effect During Development and Neurogenesis. Sci. World J. 2006, 6, 1911–1922.

45. Cué, C.M.; Dierssen, M. Plasticity as a therapeutic target for improving cognition and behavior in Down syndrome. Chang. Brains Appl. Brain Plast. Adv. Recover Hum. Abil. 2020, 251, 269–302.

46. Valenti, D.; de Bari, L.; de Rasmo, D.; Signorile, A.; Henrion-Caude, A.; Contestabile, A.; Vacca, R.A. The polyphenols resveratrol and epigallocatechin-3-gallate restore the severe impairment of mitochondria in hippocampal progenitor cells from a Down syndrome mouse model. Biochim. Biophys. Acta Mol. Basis Dis. 2016, 1862, 1093–1104.

47. De Toma, I.; Ortega, M.; Catuara-Solarz, S.; Sierra, C.; Sabidó, E.; Dierssen, M. Re-establishment of the epigenetic state and rescue of kinome deregulation in Ts65Dn mice upon treatment with green tea extract and environmental enrichment. Sci. Rep. 2020, 10, 1–18.

48. Valenti, D.; De Rasmo, D.; Signorile, A.; Rossi, L.; de Bari, L.; Scala, I.; Granese, B.; Papa, S.; Vacca, R.A. Epigallocatechin-3-gallate prevents oxidative phosphorylation deficit and promotes mitochondrial biogenesis in human cells from subjects with Down's syndrome. Biochim. Biophys. Acta Mol. Basis Dis. 2013, 1832, 542–552.

49. Catuara-Solarz, S.; Espinosa-Carrasco, J.; Erb, I.; Langohr, K.; Gonzalez, J.R.; Notredame, C.; Dierssen, M. Combined Treatment With Environmental Enrichment and (–)-Epigallocatechin-3-Gallate Ameliorates Learning Deficits and Hippocampal Alterations in a Mouse Model of Down Syndrome. eNeuro 2016, 3.

50. Scholey, A.; Downey, L.A.; Ciorciari, J.; Pipingas, A.; Nolidin, K.; Finn, M.; Wines, M.; Catchlove, S.; Terrens, A.; Barlow, E.; et al. Acute neurocognitive effects of epigallocatechin gallate (EGCG). Appetite 2012, 58, 767–770.

51. Kesse-Guyot, E.; Fézeu, L.; Andreeva, V.A.; Touvier, M.; Scalbert, A.; Hercberg, S.; Galan, P. Total and Specific Polyphenol Intakes in Midlife Are Associated with Cognitive Function Measured 13 Years Later. J. Nutr. 2011, 142, 76–83.

52. Biasibetti, R.; Tramontina, A.C.; Costa, A.P.; Dutra, M.F.; Quincozes-Santos, A.; Nardin, P.; Bernardi, C.L.; Wartchow, K.M.; Lunardi, P.S.; Gonçalves, C.-A. Green tea (−)epigallocatechin-3-gallate reverses oxidative stress and reduces acetylcholinesterase activity in a streptozotocin-induced model of dementia. Behav. Brain Res. 2013, 236, 186–193.

53. Wightman, E.L.; Haskell, C.F.; Forster, J.S.; Veasey, R.C.; Kennedy, D.O. Epigallocatechin gallate, cerebral blood flow parameters, cognitive performance and mood in healthy humans: A double-blind, placebo-controlled, crossover investigation. Hum. Psychopharmacol. Clin. Exp. 2012, 27, 177–186.
54. Unno, K.; Pervin, M.; Taguchi, K.; Konishi, T.; Nakamura, Y. Green Tea Catechins Trigger Immediate-Early Genes in the Hippocampus and Prevent Cognitive Decline and Lifespan Shortening. Molecules 2020, 25, 1484.
55. Ramis, M.R.; Sarubbo, F.; Tejada, S.; Jiménez, M.; Esteban, S.; Miralles, A.; Moranta, D. Chronic Polyphenon-60 or Catechin Treatments Increase Brain Monoamines Syntheses and Hippocampal SIRT1 LEVELS Improving Cognition in Aged Rats. Nutrients 2020, 12, 326.
56. Baba, Y.; Inagaki, S.; Nakagawa, S.; Kaneko, T.; Kobayashi, M.; Takihara, T. Effect of Daily Intake of Green Tea Catechins on Cognitive Function in Middle-Aged and Older Subjects: A Randomized, Placebo-Controlled Study. Molecules 2020, 25, 4265.
57. Sakurai, K.; Shen, C.; Ezaki, Y.; Inamura, N.; Fukushima, Y.; Masuoka, N.; Hisatsune, T. Effects of Matcha Green Tea Powder on Cognitive Functions of Community-Dwelling Elderly Individuals. Nutrients 2020, 12, 3639.