Supplemental Material S1

Search methodology

Section 3.1. Search: ((("catechin"[MeSH Terms] OR "catechin"[All Fields] OR "catechins"[All Fields] OR "catechine"[All Fields] OR "catechines"[All Fields]) NOT ("polyphenol s"[All Fields] OR "polyphenoles"[All Fields] OR "polyphenolic"[All Fields] OR "polyphenolics"[All Fields] OR "polyphenols"[MeSH Terms] OR "polyphenols"[All Fields] OR "polyphenol"[All Fields])) AND ("antioxidant s"[All Fields] OR "antioxidants"[Pharmacological Action] OR "antioxidants"[MeSH Terms] OR "antioxidants"[All Fields] OR "antioxidant"[All Fields] OR "antioxidating"[All Fields] OR "antioxidation"[All Fields] OR "antioxidative"[All Fields] OR "antioxidatively"[All Fields] OR "antioxidatives"[All Fields] OR "antioxidizing"[All Fields] OR ("anti inflammatory agents"[Pharmacological Action] OR "anti inflammatory agents"[MeSH Terms] OR ("anti inflammatory"[All Fields] AND "agents"[All Fields]) OR "anti inflammatory agents"[All Fields] OR "antiinflammatories"[All Fields] OR "antiinflammatory"[All Fields])) AND ("neurodegenerative"[All Fields] OR "neurodegeneratives"[All Fields])) AND (2010:2021[pdat]). Filters: Article types: classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article, multicenter study, observational study, randomized con-trolled trial. Publication dates: 2010-2021(included); Species: humans, mouse, rat; Languages: English.

Search: ("autophagies"[All Fields] OR "autophagy"[MeSH Terms] OR "autophagy"[All Fields] OR "autophagy s"[All Fields]) AND ("catechin"[MeSH Terms] OR "catechin"[All Fields] OR "catechins"[All Fields] OR "catechine"[All Fields] OR "catechines"[All Fields]) AND ("neuron s"[All Fields] OR "neuronal"[All Fields] OR "neuronally"[All Fields] OR "neuronals"[All Fields] OR "neurone s"[All Fields] OR "neurones"[All Fields] OR "neuronic"[All Fields] OR "neurons"[MeSH Terms] OR "neurons"[All Fields] OR "neuron"[All Fields] OR "neurone"[All Fields] OR ("neurodegenerative"[All Fields] OR "neurodegeneratives"[All Fields])). Filters: Article types: classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article, multicenter study, observational study, randomized con-trolled trial. Publication dates: 2010-2021(included); Species: humans, mouse, rat; Languages: English.

Search: ("autophagies"[All Fields] OR "autophagy"[MeSH Terms] OR "autophagy"[All Fields] OR "autophagy s"[All Fields]) AND ("catechin"[MeSH Terms] OR "catechin"[All Fields] OR "catechins"[All Fields] OR "catechine"[All Fields] OR "catechines"[All Fields]) AND ("neuron s"[All Fields] OR "neuronal"[All Fields] OR "neuronally"[All Fields] OR "neuronals"[All Fields] OR "neurone s"[All Fields] OR "neurones"[All Fields] OR "neuronic"[All Fields] OR "neurons"[MeSH Terms] OR "neurons"[All Fields] OR "neuron"[All Fields] OR "neurone"[All Fields] OR ("neurodegenerative"[All Fields] OR "neurodegeneratives"[All Fields])). Filters: Article types: classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article, multicenter study, observational study, randomized con-trolled trial. Publication dates: 2010-2021(included); Species: humans, mouse, rat; Languages: English.

Search: ("catechin"[MeSH Terms] OR "catechin"[All Fields] OR "catechins"[All Fields] OR "catechine"[All Fields] OR "catechines"[All Fields]) AND "DYRK1A"[All Fields]. Filters: Article types: classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article, multicenter study, observational study, randomized con-trolled trial. Publication dates: 2010-2021(included); Species: humans, mouse, rat; Languages: English.

Section 3.2. Search: ("epigallocatechin gallate"[Supplementary Concept] OR "epigallocatechin gallate"[All Fields] OR ("tea"[MeSH Terms] OR "tea"[All Fields] OR ("green"[All Fields] AND "tea"[All Fields]) OR "green tea"[All Fields])) AND ("huntington disease"[MeSH Terms] OR ("huntington"[All Fields] AND "disease"[All Fields]) OR "huntington disease"[All Fields]). Filters: Article types: classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article, multicenter study, observational study, randomized con-trolled trial. Publication dates: 2010-2021(included); Species: humans, mouse, rat; Languages: English.

Search: ("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]); (catechin: "catechin"[MeSH Terms] OR "catechin"[All Fields] OR "catechins"[All Fields] OR "catechine"[All Fields] OR "catechines"[All Fields]). Filters: Article types: classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article, multicenter study, observational study, randomized controlled trial; Publication dates: 2010-2021(included); Species: humans, mouse, rat; Languages: English.

Section 3.3. Search: ("Fetal Alcohol Spectrum Disorders"[Mesh]) AND "Catechin"[Mesh]: 1 result (((("Fetal Alcohol Spectrum Disorders"[Mesh]) OR "Alcohol-Related Disorders"[Mesh]) OR "Alcohol-Induced Disorders"[Mesh]) AND ("Catechin"[Mesh]). ("Fetal Alcohol Spectrum Disorders"[Mesh]) AND "epigallocatechin gallate" [Supplementary Concept]. Filters: Article types: classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article, multicenter study, observational study, randomized controlled trial; Publication dates: 2010-2021(included); Species: humans, mice, rat; Languages: English.

Section 3.4. (("epigallocatechin gallate"[Supplementary Concept] OR "epigallocatechin gallate"[All Fields] OR ("tea"[MeSH Terms] OR "tea"[All Fields] OR ("green"[All Fields] AND "tea"[All Fields]) OR "green tea"[All Fields])) AND ("down syndrome"[MeSH Terms] OR ("down"[All Fields] AND "syndrome"[All Fields]) OR "down syndrome"[All Fields])) AND (2010:2021[pdat]). Filters: Article types: classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article, multicenter study, observational study, randomized con-trolled trial. Publication dates: 2010-2021(included); Species: humans, mouse, rat; Languages: English.

Section 3.5. Search: ("health"[MeSH Terms] OR "health"[All Fields] OR "health's"[All Fields] OR "healthful"[All Fields] OR "healthfulness"[All Fields] OR "healths"[All Fields]); ("healthies"[All Fields] OR "healthy"[All Fields]); ("catechin"[MeSH Terms] OR "catechin"[All Fields] OR "catechins"[All Fields] OR "catechine"[All Fields] OR "catechines"[All Fields]). ("neurology"[MeSH Terms] OR "neurology"[All Fields] OR "neurology's"[All Fields]); ("mental"[All Fields] OR "mentalities"[All Fields] OR "mentality"[All Fields] OR "mentalization"[MeSH Terms] OR "mentalization"[All Fields] OR "mentalizing"[All Fields] OR "mentalize"[All Fields] OR "mentalized"[All Fields] OR "mentally"[All Fields]); ("cognition"[MeSH Terms] OR "cognition"[All Fields] OR "cognitions"[All Fields] OR "cognitive"[All Fields] OR "cognitively"[All Fields] OR "cognitives"[All Fields]). Filters: Article types: classical article, clinical study, clinical trial, comparative study, controlled clinical trial, journal article, multicenter study, observational study, randomized con-trolled trial. Publication dates: 2010-2021(included); Species: humans; Languages: English.

Supplementary tables

Table S1. Summary of the Grading of Recommendation, Assessment, Development, and Evaluation approach (GRADE) evidence profile for neurodegenerative diseases.

Quality Assessment						No. of Subjects		Effect		Quality	Importance
No. of Studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**No. of Patients**	**Control**	**Relative (95% CI)**	**Absolute**		
Huntington disease											
Beasley et al., 2019 [1]**, Varga et al., 2018** [2]**, Ehrnhoefer et al., 2006** [3]**: Ability of EGCG to modify htt aggregation (no follow-up)**											
3	Experimental	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	In vitro or Drosophila models		EGCG acted as a potent inhibitor of fibril formation ($p < 0.05$)		Low ++	Important
Multiple sclerosis											
Mähler et al., 2015 [94]: Metabolic response to EGCG in MS (12 weeks of follow-up)											
1	DBPC crossover	No serious risk of bias	No serious inconsistency	Indirectness (subrogated variables)	Serious imprecision (low sample size)	18	18	Working efficiency: placebo: 20 +/−3 EGCG: 25 +/−6 (p = 0.004) Postprandial FAOx: placebo: 8.3 +/−4.3 EGCG: 8.6 +/−5.0 (sex differences)		Low ++	Important
Mossakowski et al., 2015 [93]: Tracking sources of oxidative stress during chronic neuroinflammation (no follow-up)											
1	RDBPC	No serious risk of bias	No serious inconsistency	Indirectness (subrogated variables)	Serious imprecision	n = 6 RRMS + EGCG + GA	n = 6 RRMS + GA 6 RRMS 6 CIS 6 controls 6 SPMS	NOX activity. on CD11b+: Control 3.4 ± 0.6%. RRMS untreated: 18.3 ± 2.5%, RRMS + GA: 10.8 ± 2.8%, RRMS + GA+ EGCG: 6.4 ± 1.2%		Low ++	Less important
Lovera et al., 2012 [96]: Safety and futileness of Polyphenon in MS (Ph1 and Ph2) (six months of follow-up)											
1	Ph1: single group Ph2: RDBPC	No serious	No serious inconsistency	No serious indirectness	Serious imprecision	Ph1: 10 Ph2: 8	Ph2: 5	NAA adjusted for creatinine: 10% [3.4%,16.2%]		Moderate +++	Important

		risk of bias						Ph2 was stopped before because 5/7 participants had elevated liver enzymes			
Bellmann–Strobl et al., 2021 [4], **Rust et al., 2021** [5]**: Efficacy and safety of EGCG treatment in MS (36 months follow-up)**											
2	RDBPC	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	92	91	No differences on efficacy. No differences on adverse events.		High ++++	Important

Abbreviations: EGCG: epigallocatechin-3-gallate; DBPC: Double blind placebo controlled study; Rt-PA: recombinant tissue plasminogen activator; NIHSS: National Institutes of Health stroke scale; OTT: onset-to-treatment time; GA: glatiramer acetate; FAOx: fat oxidation; RDBPC: Randomized double blind placebo controlled study; RRMS: relapsing-remitting multiple sclerosis; CIS: clinically isolated syndrome; SPMS: secondary progressive multiple sclerosis; NOX: nicotinamide adenine dinucleotide phosphate (NADPH) oxidases; EAE: experimental autoimmune encephalomyelitis; PhI: Phase I; PhII: Phase II; NAA: N-acetyl aspartate; MS: multiple sclerosis; HD: Huntington disease; HTT: huntingtin. Quality of evidence grades: high (++++), moderate (+++), low (++).

Table S2. Summary of GRADE evidence profile for fetal alcohol spectrum disorders.

Quality Assessment						**No. of Patients**		**Effect**		**Quality**	**Importance**
Nº of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Cases**	**Control**	**Relative (95%CI)**	**Absolute**		
Long (2010) [6], **Almeida (2021)** [7]**: EGCG and growth restriction prevention (no follow-up)**											
2	Experimental C57BL/6 mouse models of FASD.	No serious risk of bias	Serious inconsistency (assessment of different measures)	No serious indirectness	No serious imprecision	48	18	Fetal growth improvement ($p < 0.05$)		Very low +	Important
Long (2010) [6], **Tiwari (2010)** [8], **Almeida (2021)** [7]**: EGCG effect on oxidative stress (follow-up of variable period)**											
3	Experimental rodent models of FASD.	No serious risk of bias	No serious inconsistency	Serious indirectness (different comparisons)	No serious imprecision	76	25	Oxidative stress improvement ($p < 0.05$)		Very low +	Important
Tiwari (2010) [8]**: EGCG and apoptosis prevention (28 days follow-up)**											
1	Experimental Wistar rat model of FASD.	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	28	7	Apoptosis reduction ($p < 0.05$)		Low ++	Important

Long (2010) [6], Almeida (2021) [7]: EGCG and growth restriction prevention (no follow-up)										
2	Experimental C57BL/6 mouse models of FASD.	No serious risk of bias	No serious inconsistency	Serious indirectness (different comparisons)	No serious imprecision	48	18	Improvement in neural maturation and differentiation ($p < 0.05$)	Very low +	Important
Tiwari (2010) [8]: EGCG prevention on cognitive impairment (28 days follow-up)										
1	Experimental Wistar rat model of FASD.	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	28	7	Cognitive improvement ($p < 0.05$)	Low ++	Important

Abbreviations. EGCG: epigallocatechin-3-gallate. FASD: fetal alcohol spectrum disorders. Quality of evidence grades: low (++), very low (+).

Table S3. Summary of GRADE evidence profile for Down syndrome.

Quality Assessment						No. of Patients		Effect		Quality	Importance
Nº of studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Cases**	**Control**	**Relative (95%CI)**	**Absolute**		
Gu et al., 2020 [9], **Catuara–Solarz et al., 2016** [10], **Valenti et al., 2016** [11], **Valenti et al., 2013** [12], **Souchet et al., 2015** [13], **De Toma et al., 2019** [14], **De Toma et al., 2020** [15], **Catuara et al., 2015** [16], **Stagni et al., 2016** [17]**: Ability of EGCG to restore intellectual disability (no follow-up)**											
9	Experimental Ts65Dn or overexpress DYRK1A mouse models of DS or cell cultures	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision			EGCG treatment derived cognitive improvements linked to neuromodulatory effects at the hippocampus ($p < 0.05$)	-	Low ++	Important
Goodlett et al., 2020 [18], **Stringer et al., 2015** [19], **Stringer et al., 2017** [20]**: Ability of EGCG to restore intellectual disability (no follow-up)**											
3	Experimental Ts65Dn mouse models of DS	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision			EGCG was not found to produce beneficial therapeutic effects on behavior, learning, and memory ($p < 0.05$)	-	Low ++	Important
de La Torre et al., 2014 [21], **de La Torre et al., 2016** [22]**: Ability of EGCG to restore intellectual disability (12 + six months of follow-up)**											
2	RDBPC	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	43 DS	41 controls	Participants treated with EGCG and cognitive training had significantly higher scores in memory, learning, and behavior subdomains ($p < 0.05$)	-	High ++++	Critical
Starbuck et al., 2021 [23]**: Therapeutic potential of EGCG for ameliorating facial dysmorphologies associated with DS (follow-up of variable periods)**											
1	Case control study	Risk of bias for small n treated	No serious inconsistency	No serious indirectness	No serious imprecision	63 DS, four mosaics, 13 treated with EGCG	207 euploids	EGCG modulates facial development with dose-dependent effects ($p < 0.05$)	-	Moderate +++	Important

with EGCG

Abbreviations. EGCG: epigallocatechin,-3-gallate. DS: Down syndrome. RDBPC: randomized, double blind, placebo-controlled study. Quality of evidence grades: high (++++), moderate (+++), low (++).

Table S4. Summary of GRADE evidence profile on the neurologic effects of catechins in healthy populations.

Quality Assessment						**No. of Patients**		**Effect**		**Quality**	**Importance**
Nº of Studies	**Design**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**		**Control**	**Relative (95% CI)**	**Absolute**		
Kesse–Guyot et al., 2012 [24], **Biasibetti et al., 2013** [25]**: Association between polyphenol intake and cognitive function (13 years of follow-up)**											
2	Observational,	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	3382	-	Associations between quartiles of catechin intakes and language and verbal memory: Q1: 48.1 +/−0.7, Q2: 49.3 +/−0.7, Q3: 49.4 +/−0.7, Q4: 50.1 +/−0.7 *p* = 0.001; executive function: Q1: 51.3 +/−0.7, Q2: 51.0 +/−0.7, Q3: 50.1 +/−0.7, Q4: 49.9 +/−0.7, *p* = 0.01; cognitive status: Q4 vs. Q1: OR = 0.24, 95% CI: 0.08, 0.72	-	Low ++	Important
Mohamed S, et al., (2013) [26]**: Cognitive effects of OPLE (two months follow up)**											
1	RDBPC	No serious	No serious inconsistency	Serious indirectness	Serious imprecision	15	15	Short-term memory (*p* <	-	Low ++	Important

		risk of bias		(subrogated variables, selected population)	(low sample size)			0.001), spatial visualization ability and processing speed ($p < 0.05$) improved after of OPLE.			
Scholey A, et al., (2012)[27]**; Emma L, et al., (2012)** [28]**, Dietz C, et al.,(2017)**[29]**, Liu Y, et al., (2018)** [30]**: Effect of EGCG, green tea extract or matcha tea on brain and mood**											
4	RSBPC crossover trial	No serious	No Serious inconsistency	Serious indirectness (subrogated variables)	No serious imprecision	105	105	No differences on mood. Reduction in oxy-Hb only with 135 mg of EGCG ($p < 0.001$). EEG: increase in alpha, beta and theta activity with EGCG. Matcha: improvement in basic attention and psychomotor speed response. Decaffeinated GTE improved reading span only in older women ($p = 0.04$)	-	Moderate +++	Important
Ide et al., (2016) [31]**, Sakurai et al., (2020)** [32]**, Baba et al., (2020)** [33]**: Green tea intake on cognitive dysfunction (one year of follow-up)**											
3	RDBPC	No serious	No serious inconsistency	No serious indirectness	No serious imprecision	71	68	Global cognitive and memory	-	High ++++	Important

risk of bias	function tests: no significant differences.

Abbreviations: Q: quartile, OPLE: alcoholic oil palm leaves extract, EGCG: epigallocatechin-gallate, EEG: electroencephalogram, GTE: green tea extract, RDBPC: randomized, double blind, placebo-controlled study, RSBPC: randomized, single blind, placebo-controlled study. Quality of evidence grades: high (++++), moderate (+++), low (++).

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