Chapter 11
Neurocognitive Improvement Through Plant Food Bioactives: A Particular Approach to Alzheimer's Disease

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1 Introduction

Alzheimer's disease (AD) is currently one of the most prevalent neurodegenerative disorders, directly related to increasing rates of morbidity and autonomy impairment between worldwide citizens. Social and demographical changes are direct contributors; notwithstanding, modern lifestyle, oxidative stress and its related diseases, and, consequently, premature aging are also important triggering factors (Sun et al. 2008; Ngo and Li 2013).

Numerous drugs have been developed mainly to act as symptomatic agents, despite the serious side effects and increasing evidences of lack of effectiveness. Most of them were derived from plant-mimetic synthesis, but tenuous differences on their chemical structure and also the occurrence of synergisms in the pool of the whole plant phytochemicals are sufficient to provide considerable influences on the final biological potential (Ngo and Li 2013; Katalini et al. 2014; Ahmed et al. 2015). The use of medicinal plants, mainly through botanical preparations, is a millenary practice, which has been effectively used for a multitude of health conditions (Vanaclocha and Cañigueral 2003; Murray 2004; Murray and Pizzorno 2012). The interest for natural matrices is still increasing, not only to confirm its bioactive potential, but also to deepen knowledge on the modes of action, metabolism, bioavailability, bioefficacy, and active concentrations, aiming to develop upcoming and safer alternatives to the current ones. Among them, plant phytochemicals have shown to have promissory neurocognitive properties. In this sense, the present chapter aims to provide systematic information about the use of plant-food-derived bioactive molecules with evident in vitro and in vivo neuroprotective and neuroregenerative effects.

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2 Alzheimer's Disease: Current Perspective

Human life cycle is a complex process, and numerous aspects still remain a mystery. Apart from the birth, growth, and maturation phases, the aging process is also an important focus among medical community and scientists. Memory decline and cognitive functions comprise the most evident signals of brain changes and activity impairment (Alza et al. 2014).

In the last decades, an exponential increase of brain-related diseases, namely neurodegenerative diseases, has been observed. Taking into account social and demographic changes, in which older people assume the leadership, it is normally conceived that age-related diseases tends to increase progressively. Notwithstanding, and disturbingly, a double prevalence every 20 years has been counted, increasing nearly to 115 million by 2050 (Vauzour 2014). Among the neurodegenerative diseases, AD and Parkinson's (PD) diseases, also dementia, comprise the most representative and alarming causes of morbidity and autonomy impairment among worldwide population (Vauzour 2014; Ahmed et al. 2015; Sun et al. 2015). Genetic and human lifestyle has been pointed as the most pronounced triggering factors to the development of those complex medical conditions (Sun et al. 2008; Vauzour 2014; Ahmed et al. 2015). One of the first features in patients with AD is the presence of brain lesions, commonly known as senile plaques: deposits of β-amyloid (Aβ) protein between neurons (Kumar and Nisha 2014; Adewusi and Steenkamp 2015). Being a product from sequential proteolytic cleavage, Aβ is abnormally accumulated in older individuals due to a clearance impairment and/or its overproduction. In particular, to Aβ overproduction, genetic changes/mutations, namely from amyloid precursor protein (APP), are underlying, being related to early AD manifestation (Yoo and Park 2012). High doses of Aβ are highly toxic, due to its ability of self-aggregation, forming, respectively, fibrillary or monomeric and then oligomeric forms. Particularly, Aβ aggregated as oligomers is highly harmful once acting as oxidative stress enhancer. Thus, and in association with free radical overproduction, Aβ oligomeric forms largely determine the magnitude of cognitive damages, leading to synaptic dysfunctions, inflammation, and, consequently, organic dysfunctions (Yoo and Park 2012; Kumar and Nisha 2014). Aβ also induces neuronal death and activates downstream c-Jun N-terminal kinase signal and *N*-methyl-D-aspartate-type glutamate receptor (NMDAR), which leads to synaptic loss and improves neuronal dysfunction (Yoo and Park 2012). Several studies indicate that the main components present in amyloid plaques of AD individuals range from 40 and 42 amino acid sequences (Patil et al. 2010; Kumar and Nisha 2014). Acetylcholine shortage is also a triggering factor for neuronal decline and AD progression (Yoo and Park 2012). Despite all the pharmaceutical advances, acetylcholinesterase (AChE) inhibitors still remain the most popular prescribed drugs for symptomatic intervention, such as donepezil, galantamine, rivastigmine, and tacrine. Memantine is also used but acts as *N*-methyl-D-aspartic acid modulator (Ngo and Li 2013). Notwithstanding, those drugs possess

numerous side effects and evidence a weak ability to block and even to reverse AD, acting only on clinical symptoms, but not on causal factors or prevention.

Botanical preparations are a complex pool of phytochemicals, being their ethnopharmacological potential mainly conferred by secondary metabolites (Spencer et al. 2012). Particularly to AD, a multitude of studies have shown that they act as prominent brain health improvers, being useful not only to prevent but also to block and even avert neurological dysfunctions (Marco and Carreiras 2006; Essa et al. 2012; Smid et al. 2012; Spencer et al. 2012; Konrath et al. 2013; Ahmed et al. 2015). Furthermore, it is convenient to highlight that the majority of chemical drugs are plant-derived mimetic; notwithstanding, in the whole plant, different proportions of phytochemicals, their synergisms, antagonisms, and polyvalent reactions improve the bioactive potential and also block some harmful substances.

Apart from those aspects, a correct and active lifestyle, which includes physical and intellectual activity, and balanced diet are also well-established aspects that provide important benefits to preserve, improve, and even block memory and cognition impairment (van Praag 2009; Murray and Pizzorno 2012). Regarding dietary aspects, not only correct food choices, but also nutritional supplementation confers prominent influences. Functional foods and nutraceuticals have the ability to act as bioactives by simply enriching daily diet (Murray and Pizzorno 2005, 2012). Overall, the use of plant-derived preparations, as part of a healthy lifestyle, might have a great impact on life expectancy and health improvement.

3 Plant-Food-Based Formulations: An Integrative Approach

Natural matrices are an extremely rich source of bioactive molecules. Through photosynthesis, numerous organic compounds mainly derived from primary (lipids, proteins, carbohydrates, and chlorophyll) and secondary (such as, terpenes, steroids, alkaloids, and phenolic compounds) metabolites are daily produced by higher plants (Nelson and Cox 2000). They possess crucial biological functions, most of them related to their proper survival, optimum growth, nutrition, and protection against invaders (Nelson and Cox 2000). Notwithstanding, increasing evidences confirm phytochemical, human health benefits, when integrated as part of daily routine (Cowan 1999; Fernandez-Panchon et al. 2008; Kaushik et al. 2010; Goodman et al. 2011).

Several plant-derived preparations can be used according to the final biological potential and/or selected phytochemical(s). For example, berries (such as blueberry, cranberry, bilberry, grapes, barberry, and strawberry) have been related to antiaging benefits, mainly due to their richness in phenolic compounds, including anthocyanins (Larrosa et al. 2010; Tulipani et al. 2011; Hoggard et al. 2013; Norberto et al. 2013; McKay et al. 2015). They can be directly consumed as fresh fruits, or even through infusions/decoctions, capsules, drops, and extracts, among others.

Despite the health-improving effects, the abundance of bioactive compounds in those matrices is doubtless different, and therefore, the final phytopharmacological potential will considerably vary. Apart from this aspect, the bioavailability and related bioefficacy of plant phytochemical preparations will also differ (Holst and Williamson 2008; Rein et al. 2013; Velderrain-Rodríguez et al. 2014). It means that despite the promissory bioactive properties of numerous natural products, it is important to select the most adequate extraction solvent, binomial time/temperature, or type of formulation/preparation, according to each specific finality. All of the stated premises assume that those products are correctly controlled in order to possess the higher abundance in bioactive constituents.

Regarding plant-derived phytochemicals with documented in vitro and in vivo neuroprotective (Tables 1, 2, 3, 4, 5, 6 and 7) and neuroregenerative (Figs. 1, 2, 3, 4 and 5) effects, methanol (MeOH), water (H_2O), ethanol (EtOH), and mixtures of the previous (MeOH: H_2O; EtOH: H_2O) extraction solvents, in different proportions, are amongst to the most commonly used extraction solvents. Dichloromethane (DCM), ethyl acetate (EtOAc), *n*-butanol, chloroform, and DCM: MeOH have also been sporadically used, mainly for alkaloid, terpene, and saponin extraction.

It is convenient to highlight that the use of solvent mixtures, such as MeOH: H_2O, has been increasingly adopted. In fact, recent studies show that specific proportions of solvent mixtures improve the efficiency of extraction and consequently the richness on bioactive molecules in the final extract.

4 Plant Food Bioactive Molecules with Neuroprotective Activity

4.1 Bioactive Compounds with In Vitro Neuroprotective Activity

4.1.1 Commercial Molecules

Tables 1 and 2 show the major groups of compounds from commercial origin with reported in vitro neuroprotective effects.

Among phenolic compounds (Table 1), flavan-3-ols, flavones, flavonols, isoflavones, lignans, phenolic acids, and stilbenes comprise the most common classes. Quercetin (a flavonol), followed by myricetin (a flavonol) and kaempferol (a flavonol), and then apigenin (flavone), baicalein (flavone), catechin (flavan-3-ols), and EGCG (flavan-3-ols) are the most studied phenolic compounds. In particular, quercetin has shown several neuroprotective effects, being its ability to reduce and/or to prevent reactive oxygen species (ROS) overproduction amongst to the most prominent; its active concentrations varied significantly according to the model used, but interestingly, as described by Vepsäläinen et al. (2013), at 0.5, 2.5, and 10 μM a, pronounced reduction in ROS overproduction was observed in

Table 1 Phenolic compounds (from commercial origin) with reported in vitro neuroprotective effects

Bioactive molecule	Experimental models	Active concentration	Reference
Flavan-3-ols			
Catechin	Mouse cortical neuron cultures	30 μM[a]	Choi et al. (2014)
	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
EGCG	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
	Mouse cortical neuron cultures	30 μM[a]	Choi et al. (2014)
Epicatechin	Mouse cortical neuron cultures	30 μM[a]	Choi et al. (2014)
Flavones			
Apigenin	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
	Mouse cortical neuron cultures	30 μM[a]	Choi et al. (2014)
Baicalein	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
	Mouse cortical neuron cultures	30 μM[a]	Choi et al. (2014)
Luteolin	Mouse cortical neuron cultures	30 μM[a]	Choi et al. (2014)
Morin	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
Scutellarein	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
Flavonols			
Fisetin	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
Kaempferol	PC12 cells	3–30 μM	Roth et al. (1999)
	Human T47D breast cancer cells	3–30 μM	Roth et al. (1999)
	Mouse cortical neuron cultures	30 μM[a]	Choi et al. (2014)
Myricetin	Th-T assay	1.95 μM[b]	Xie et al. (2014)
	Human SH-SY5Y neuroblastoma cells, menadione-induced ROS production	0.5, 2, 5, 10, 20 μM	Vepsäläinen et al. (2013)
	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)

(continued)

Table 1 (continued)

Bioactive molecule	Experimental models	Active concentration	Reference
	Mouse cortical neuron cultures	30 μM[a]	Choi et al. (2014)
Quercetin	Mouse cortical neuron cultures	30 μM[a]	Choi et al. (2014)
	Primary cultures of astrocytes and microglial cells	8 μM[b,c]	Elmann et al. (2013)
	Primary cultures of astrocytes	10 μM	Elmann et al. (2014)
	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
	Human SH-SY5Y neuroblastoma cells, menadione-induced ROS production	0.5, 2, 5, 10 μM	Vepsäläinen et al. (2013)
	Bovine serum albumin, D-ribose-induced AGE formation	600 μM[b]	Ferchichi et al. (2012)
Isoflavones			
Genistein	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
Lignans			
NDGA	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
Phenolic acids			
3,5-di-*O*-Caffeoylquinic acid	Human neuroblastoma clonal SH-SY5Y $A\beta_{1-42}$-treated cells	20 μM	Han et al. (2010)
Caffeic acid	Th-T assay	118 μM[b]	Kurisu et al. (2013)
Chlorogenic acid	Bovine serum albumin, D-ribose-induced AGE formation	2000 μM[b]	Ferchichi et al. (2012)
Ferulic acid	Mutant human APP-overexpressing murine neuron-like cells	1.563–12.5 μM	Mori et al. (2013)
p-Coumaric acid	PC12 cells, $A\beta_{25-35}$-induced toxicity	5, 25, 50 μM	Yoon et al. (2014)
Rosmarinic acid	PC12 cells, $A\beta_{25-35}$-induced neurotoxicity	23.6 μM[d]	Na et al. (2010)
	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
Stilbenes			
Resveratrol	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)

[a]Tested concentration to measure the percentage of LDH release after 20 μM $A\beta_{25-35}$ exposure; [b]IC_{50} values; [c]varied according to the used assay; [d]ED_{50} value

EGCG Epigallocatechin gallate; *NDGA* nordihydroguaiaretic acid; *ROS* reactive oxygen species; *Th-T assay* Thioflavin-T assay; *AGEs* advanced glycation end-products

Table 2 Non-phenolic compounds (from commercial origin) with reported in vitro neuroprotective effects

Bioactive molecule	Experimental models	Active concentration	Reference
Glycosides			
Salidroside	SH-SY5Y human neuroblastoma cells, β-amyloid-induced oxidative stress	10, 50, 100 μM	Zhang et al. (2010)
Iridoid glycosides			
Geniposide	N2a cell formaldehyde-exposed	200 μM	Chen et al. (2014)
Phenylethanoids			
Acteoside-tetramethylether	Th-T assay	>200 μM[a]	Kurisu et al. (2013)
Hydroxytyrosol		96 μM[a]	
Oraposide-tetramethylether		>200 μM[a]	
Quinones			
1,4-Benzoquinone	Insulin as amyloid model	50 μM	Gong et al. (2014)
1,4-Naphthoquinone			
9,10-Anthraquinone			
9,10-Phenanthraquinone			
Aloe-emodin			
Chrysophanol			
Emodin			
Terpenes			
Asiatic acid	Primary Sprague–Dawley rat cortical neurons	10 μM	Patil et al. (2010)
Bilobalide	Th-T assay	14.84%[b]	Xie et al. (2014)
Carnosic acid	U373MG human astrocytoma cells	50 μM	Yoshida et al. (2014)
Ginkgolide A	Th-T assay	21.10%[b]	Xie et al. (2014)
Ginkgolide B	Th-T assay	13.56%[b]	Xie et al. (2014)
	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
Ginkgolide C	Th-T assay	13.92%[b]	Xie et al. (2014)
Hyperforin	Hippocampal neuron cultures-amyloid fibrils and Aβ oligomer-induced damage	1 μM	Dinamarca et al. (2006)

(continued)

Table 2 (continued)

Bioactive molecule	Experimental models	Active concentration	Reference
Ursolic acid	PC12 cells, $A\beta_{25-35}$-induced toxicity	1, 10, 20 μM	Yoon et al. (2014)
Withanolide A	Primary Sprague–Dawley rat cortical neurons	100 μM	Patil et al. (2010)
Others			
Purpurogallin trimethyl ether	Unilamellar vesicles, Aβ42-induced liposome permeabilization	50 μM	Gauci et al. (2011)
Rhein	Insulin as amyloid model	50 μM	Gong et al. (2014)

[a]IC_{50} values; [b]inhibition percentage of the tested compounds at the concentration of 100 μM
Th-T assay and Thioflavin-T assay

human SH-SY5Y neuroblastoma cells (with menadione as oxidative stress inducer). In the same line, myricetin also evidenced a similar potential, being together with quercetin the flavonols with the highest in vitro potential.

Two phenolic acids (ferulic acid and *p*-coumaric acid) and the flavonol (kaempferol) also showed interesting effects, directly related to their potent antioxidant activity. The active concentrations were 1.563–12.5 μM (ferulic acid), 5, 25, 50 μM (*p*-coumaric acid), and 3–30 μM (kaempferol). Other phenolic acids, such as rosmarinic (23.6 μM) and 3,5-di-caffeoylquinic (20 μM) acids, also evidenced significant effects, followed by the flavan-3-ols (catechin, EGCG, and epicatechin) and the flavones (apigenin, baicalein, and luteolin), which were effective at 30 μM. On the other hand, the flavones (morin and scutellarein), the flavonol fisetin, the isoflavone genistein, the lignan NDGA, and, lastly, the stilbene resveratrol were only effective at 50 μM. Finally, caffeic and chlorogenic acids proved to be the least effective, once the active concentrations were 118 μM and 2000 μM, respectively, which correspond to the IC_{50} values.

By comparing the in vitro neuroprotective effects of phenolic compounds with other bioactive non-phenolic compounds (Table 2), it is clearly evident that the first ones evidenced a greater effect, mainly the flavonols (quercetin and myricetin), being highly effective at lower doses. It is particularly convenient to highlight the effect of the following terpenes: hyperforin (1 μM), ursolic acid (1, 10, 20 μM), and asiatic acid (10 μM) which presented the most prominent activity at lower concentrations. Salidroside, a glycoside, several quinones (1,4-benzoquinone, 1,4-naphthoquinone, 9,10-anthraquinone, 9,10-phenanthraquinone, aloe-emodin, chrysophanol, and emodin), the terpenes (carnosic acid and ginkgolide B), and lastly purpurogallin trimethyl ether and rhein evidenced similar effects to those of phenolic compounds, which were effective at 50 μM.

Overall, the phenolic compounds seem to present more significant in vitro neuroprotective effects than non-phenolic molecules, which might be attributed to their

Table 3 Plant-origin phenolic compounds with reported in vitro neuroprotective effects

Origin	Plant part	Bioactive extract/molecule	Experimental models	Active concentration	Reference
Anthocyanins		*Anthocyanins*			
Ribes nigrum L.	Whole plant	Anthocyanin-rich extract	SH-SY5Y-APP751 cells, staurosporine-induced apoptosis	4–31 μg/mL	Vepsäläinen et al. (2013)
Chalcones					
Psoralea corylifolia L.	Seeds	4-Hydroxylonchocarpin	Murine microglial cell line (BV-2), LPS-induced oxidative stress	10.2 μg/mL[a]	Lee et al. (2005)
Pulicaria incisa (Lam.) DC.	Aerial parts	Pulichalconoid B	Primary cultures of astrocytes and microglial cells	20 μM[a,b]	Elmann et al. (2013)
Flavones					
Achillea fragrantissima (Forssk.) Sch.Bip.	Whole plant	3,5,4′-trihydroxy-6,7,3′-trimethoxyflavone	Primary cultures of astrocytes	8 μM	Elmann et al. (2014)
Calophyllum flavoramulum Hend. & Wyatt-Sm.	Leaves	Amentoflavone	Bovine serum albumin, D-ribose-induced AGE formation	0.05 mM[a]	Ferchichi et al. (2012)
Eragrostis ferruginea (Thunb.) P. Beauv.	Aerial parts	7-Demethylageconyflavone A	PC12 cells, $A\beta_{25\text{-}35}$-induced neurotoxicity	>100 μM[c]	Na et al. (2010)
		Tricin		20.3 μM[c]	
		Age-conyflavone A		58.7 μM[c]	
Rosmarinus officinalis L.	Whole plant	Luteolin	PC12 cells, corticosterone-induced neurotoxicity	30, 40, 50 μM	Sasaki et al. (2013)
Psoralea corylifolia L.	Seeds	chromenoflavanone [7,8-dihydro-8-(4-hydroxyphenyl)-2,2-dimethyl-2*H*,6*H*-benzo-(1,2-b:5,4-b′)dipyran-6-one]	Murine microglial cell line (BV-2), LPS-induced oxidative stress	11.4 μg/mL[a]	Lee et al. (2005)

(continued)

Table 3 (continued)

Origin	Plant part	Bioactive extract/molecule	Experimental models	Active concentration	Reference
Flavonols					
Calophyllum flavoramulum Hend. & Wyatt-Sm.	Leaves	Quercitrin	Bovine serum albumin, D-ribose-induced AGEs formation	0.50 mM[a]	Ferchichi et al. (2012)
Ginkgo biloba L.	Leaves	Quercetin 3-*O*-β-D-rutinoside	Th-T assay	33.02 μM[a]	Xie et al. (2014)
		Quercetin 3-*O*-α-L-(β-D-glucopyranosyl)-(1,2)-rhamnopyranoside		67.182 μM[a]	
		Quercetin 3-*O*-α-(6″-*p*-coumaroyl glucopyranosyl-β-1,2-rhamnopyranoside)		32.56 μM[a]	
		Kaempferol 3-*O*-β-D-rutinoside		30.89%[d]	
		Isorhamnetin 3-*O*-β-D-rutinoside		23.62%[d]	
		Kaempferol 3-*O*-α-L-(β-D-glucopyranosyl)-(1,2)-rhamnopyranoside		30.49%[d]	
		Kaempferol 3-*O*-α-(6‴-p-coumaroyl glucopyranosyl-β-1,2-rhamnopyranoside)		34.98%[d]	
Isoflavones					
Flemingia macrophylla L.	Aerial parts	Osajin	Neuronal cells Aβ-induced damage	5.01 μM[c]	Shiao et al. (2005)
		5,7,4′-Trihydroxy-6,8-diprenylisoflavone		11.25 μMc	
		5,7,4′-Trihydroxy-6,3′-diprenylisoflavone		4.47 μM[c]	
Lignans					
Eragrostis ferruginea (Thunb.) P. Beauv.	Aerial parts	Nectandrin B	PC12 cells, $A\beta_{25\text{-}35}$-induced neurotoxicity	44.1 μM[c]	Na et al. (2010)
		4-Ketopinoresinol		54.8 μM[c]	

(continued)

Table 3 (continued)

Origin	Plant part	Bioactive extract/molecule	Experimental models	Active concentration	Reference
Magnolia fargesii (Finet & Gagnep.) W. C.Cheng	Flower buds	(+)-Eudesmin	BV-2 cells	30 μM[a]	Kim et al. (2009)
		(+)-Magnolin		20.5 μM[a]	
		(+)-Yangambin		28.6 μM[a]	
		Epimagnolin B		10.9 μM[a]	
Valeriana amurensis P. Smirn. ex Kom.	Rhizomes and roots	Olivil-4′-O-β-D-glucopyranoside	$A\beta_{1-42}$-induced PC12 cell neurotoxicity	5, 12.5, 25 μM	Wang et al. (2014a)
		Lariciresinol-4,4′-di-*O*-β-D-glucopyranoside			
		Olivil-4-*O*-β-D-glucopyranoside			
		8-Hydroxylariciresinol-4'-*O*-β-D-glucopyranoside			
		Lariciresinol-4-*O*-β-D-glucopyranoside			
		Neoarctin A			
		Lariciresinol-4'-*O*-β-D-glucopyranoside			
		(−)-Massoniresinol 3a-*O*-β-D-glucopyranoside			
		(+) Pinoresinol-4,4'-di-*O*-β-D-glucopyranoside	$A\beta_{25-35}$-induced PC12 cell death	5, 12, 25 μM	Wang et al. (2012)
		(+) Pinoresinol-8-*O*-β-D-glucopyranoside			
		8-Hydroxypinoresinol- 4,4′-di-*O*-β-D-glucopyranoside			
Phenolic acids					
Calophyllum flavoramulum Hend. & Wyatt-Sm.	Leaves	3,4-dihydroxybenzoic acid	Bovine serum albumin, D-ribose-induced AGEs formation	0.50 mM[a]	Ferchichi et al. (2012)
Rosmarinus officinalis L.		Rosmarinic acid	PC12 cells, corticosterone-induced neurotoxicity	5, 15, 25 μM	Sasaki et al. (2013)
Salvia miltiorrhiza Bunge		Salvianolic acid B	PC12 cells, $A\beta_{25-35}$-induced cytotoxicity	10, 100, 200 μg/mL	Zhou et al. (2011)

(continued)

Table 3 (continued)

Origin	Plant part	Bioactive extract/molecule	Experimental models	Active concentration	Reference
Stilbenes					
Vitis vinifera L.	Skin and seeds	Resveratrol	PC12 rat pheochromocytoma cells, $A\beta_{25\text{-}35}$-induced apoptosis	10, 20 μM	Kim et al. (2007)
Tannins					
Paeonia suffruticosa Andr.	Whole plant	1,2,3,4,6-Penta-*O*-galloyl-β-D-glucopyranose	SK-N-SH cells	10 μM	Fujiwara et al. (2009)
Xanthones					
Calophyllum flavoramulum Hend. & Wyatt-Sm.	Leaves	3-Methoxy-2-hydroxyxanthone	Bovine serum albumin, D-ribose-induced AGE formation	0.06 mM[a]	Ferchichi et al. (2012)

[a]IC_{50} values; [b]varied according to the used assay; [c]ED_{50} values; [d]inhibition percentage of the tested compounds at the concentration of 100 μM
Th-T assay Thioflavin-T assay. *AGEs* advanced glycation end-products; *LPS* lipopolysaccharide

Table 4 Plant-origin non-phenolic compounds with reported in vitro neuroprotective effects

Origin	Plant part	Bioactive molecule	Experimental models	Active concentration	Reference
Alkaloids					
Crinum macowanii Baker	Bulbs	Hamayne	HeLa cells line	10 μg/mL[a]	Kwon et al. (2011)
		Lycorine		5 μg/mL[a]	
Coumarins					
Eleutherococcus senticosus (Rupr. et Maxim.) Maxim.	Rhizomes	Isofraxidin	Rat cortical neurons	1; 10 μM	Bai et al. (2011)
		Isofraxidin 7-*O*-glucoside			
Curcuminoids					
Curcuma longa L.	Whole plant	Calebin-A	PC12 cells from β-amyloid ($\beta_{25\text{-}35}$; $\beta_{1\text{-}42}$) insults	1; 2 μg/mL[b,c]	Park and Kim (2002)
		Curcumin		7; 10 μg/mL[b,c]	
		Demethoxycurcumin		4; 5 μg/mL[b,c]	
		Bisdemethoxycurcumin		2; 3.5 μg/mL[b,c]	
Iridoids					
Valeriana amurensis P. Smirn. ex Kom.	Rhizomes and roots	Xiecaoside E	$A\beta_{1\text{–}42}$-induced PC12 cell neurotoxicity	5, 12.5, 25 μM	Wang et al. (2014a)
Quinones					
Euclea crispa subsp. *Crispa*	Roots	Natalenone	HeLa cells	50 μg/mL[a]	Kwon et al. (2011)

(continued)

Table 4 (continued)

Origin	Plant part	Bioactive molecule	Experimental models	Active concentration	Reference
Saponins					
Eleutherococcus senticosus (Rupr. et Maxim.) Maxim.	Rhizomes	Stigmasterol 3-*O*-β-D-glucopyranoside	Rat cortical neurons	1; 10 μM	Bai et al. (2011)
		Eleutheroside E			
		Eleutheroside B			
Terpenes					
Croton yanhuii Y. T. Chang	Twigs	Crotonpene A	PC12 cells	15 μM	Sun et al. (2014)
		Crotonpene B			
Euclea crispa subsp. *Crispa*	Roots	3-oxo-oleanolic acid	HeLa cells	10 μg/mL[a]	Kwon et al. (2011)
Laurus nobilis L.	Leaves	Spirafolide	DA-induced apoptosis in human neuroblastoma SH-SY5Y cells	5.7 μM[b]	Ham et al. (2010)
Rosmarinus officinalis L.	Whole plant	Carnosic acid	PC12 cells, corticosterone-induced neurotoxicity	10, 20, 30 μM	Sasaki et al. (2013)
Tussilago fárfara L.	Flower buds	Tussilagone	Murine microglial cells	8.67 μg/mL (NO)[a] 14.1 μg/mL (PGE_2)a	Lim et al. (2008)
Valeriana amurensis P. Smirn. ex Kom.	Rhizomes and roots	Heishuixiecaoline A	$A\beta_{25-35}$-induced PC12 cells death	5, 12, 25 μM	Wang et al. (2012)
		Heishuixiecaoline B			
		Heishuixiecaoline C			
		Volvalerenal C			

[a]IC_{50} values; [b]ED_{50} values; [c]obtained results to anti-βA(25–35) and anti-βA(1–42) activities, respectively

Table 5 Ecdysterones, phenylethanoid glycosides, and other plant-derived bioactive compounds with in vitro neuroprotective effects

Origin	Plant part	Bioactive molecule	Experimental models	Active concentration	Reference
Ecdysterones					
Klaseopsis chinensis (S.Moore) L. Martins	Roots	2-*O*-Acetyl-20-hydroxyecdysone	SH-SY5Y neuroblastoma cells, $A\beta_{42}$-induced cytotoxicity	50 μM	Yang et al. (2010)
		3-*O*-Acetyl-20-hydroxyecdysone			
		25,26-Didehydroponasterone A			
		Stachysterone C			
		Carthamosterone			
Phenylethanoid glycosides					
Orobanche minor J. E. Smith.	Whole plant	Acteoside	Th-T assay	8.9 μM[a]	Kurisu et al. (2013)
		Oraposide		3.6 μM[a]	
Others					
Curcuma comosa Roxb.		(*3R*) 1,7-Diphenyl-(4E,6E)-4,6-heptadien-3-ol	LPS-treated microglia	0.1, 0.5, 1 μM	Thampithak et al. (2009)
Curcuma longa L.		1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,4,6-heptatrien-3-one	PC12 cells from β-amyloid ($\beta_{25\text{-}35}$; $\beta_{1\text{-}42}$) insults	>50 μg/mL[b,c]	Park and Kim (2002)
		1-Hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-6-heptene-3,5-dione		30.7; 44.3 μg/mL[b,c]	
		1,7-Bis(4-hydroxyphenyl)-1-hep- tene-3,5-dione		0.5; 1.0 μg/mL[b,c]	
		1,7-Bis(4-hydroxyphenyl)-1,4,6-heptatrien-3-one		>50 μg/mL[b,c]	
		1,5-Bis(4-hydroxy-3-methoxyphenyl)-1,4-pentadien-3-one		>50 μg/mL[b,c]	

(continued)

Table 5 (continued)

Origin	Plant part	Bioactive molecule	Experimental models	Active concentration	Reference
Cynanchum paniculatum (Bunge) Kitag.	Roots	2,3-dihydroxy-4-methoxyacetophenone	HT22 cells, glutamate-induced neurotoxicity	10.94 μM[b]	(Weon et al. 2013)
Dendrobium nobile Lindley		3-[[(6-Methoxy-10-methyl-1H,3H- benzo[h]furo [4,3,2-de]-2-benzopyran-1-yl)oxy]methyl]-5-methylnaphtho[2,3-b]furan-4,9-dione	PC12 cells, H_2O_2-induced cell death	5, 10 μg/mL	Yoon et al. (2011)
Eleutherococcus senticosus (Rupr. et Maxim.) Maxim.	Rhizomes	β-Sitosterol 3-*O*-β-D-glucopyranoside	Rat cortical neurons	1; 10 μM	Bai et al. (2011)
Eragrostis ferruginea (Thunb.) P. Beauv.	Aerial parts	Corylin	PC12 cells, $A\beta_{25\text{-}35}$-induced neurotoxicity	>100 μM[b]	Na et al. (2010)
Euphorbia lagascae Sprengel	Seeds	Piceatannol	PC12 rat pheochromocytoma cells, $A\beta_{25\text{-}35}$-induced apoptosis	10, 20 μM	Kim et al. (2007)
Flemingia macrophylla L.	Aerial parts	Aureole	Neuronal cells Aβ-induced damage	12.09 μM[b]	Shiao et al. (2005)
		Flemingichromone		31.43 μM[b]	
Rhodiola sachalinensis A. Bor	Roots	Salidroside	Rat pheochromocytoma, Aβ-induced neuronal damage on PC12 cells	1, 5, 10, 50 μg/mL	Jang et al. (2003)
Salvia miltiorrhiza Bunge		Danshensu	PC12 cells, $A\beta_{25\text{–}35}$-induced cytotoxicity	10, 100, 200 μg/mL	Zhou et al. (2011)

[a]IC_{50} values; [b]ED_{50} values; [c]obtained results to anti-βA(25-35) and anti-βA(1-42) activities, respectively

Th-T assay Thioflavin-T assay; *LPS* lipopolysaccharide

Table 6 Bioactive compounds (from commercial origin) with reported in vivo

Bioactive molecule	Experimental models	Active concentration	Reference
Flavones			
Luteolin	Male Sprague–Dawley rat model of chronic cerebral hypoperfusion	50, 100, 200 mg/kg b. w.	Fu et al. (2014)
Flavonols			
Quercetin	Wild-type adult zebra fish scopolamine-induced amnesia	50 mg/kg b.w.	Richetti et al. (2011)
Rutin		50 mg/kg b.w.	
Hydroxycinnamic acids			
3,5-di-*O*-Caffeoylquinic acid	Male SAMP8 and SAMR1 mice	6.7 mg/kg b. w.	Han et al. (2010)
Ferulic acid	Transgenic PSAPP mouse model of cerebral amyloidosis	30 mg/kg b.w.	Mori et al. (2013)
Isoflavones			
Genistein	Male Wistar rats injected with $A\beta_{1–40}$	10 mg/kg b.w.	Bagheri et al. (2012)
Terpenes			
Hyperforin	Male Sprague–Dawley rats injected with amyloid fibrils	6 μM	Dinamarca et al. (2006)
Phenylpropanoids			
6-Shogaol	Male ICR mice $A\beta O_{1\text{-}42}$-induced microglial cell activation	10 mg/kg b.w.	Moon et al. (2014)

higher antioxidant potential, namely as free radical scavengers and also as metal quenchers and hydrogen donators (Heim et al. 2002; Grotewold 2006; Li et al. 2014).

4.1.2 Plant-Food-Derived Molecules

Tables 3, 4 and 5 show the in vitro neuroprotective effects of plant-origin phenolic and non-phenolic molecules.

In relation to phenolic compounds (Table 3), isoflavones, such as 5,7,4′-tryhydroxy-6,3′-diprenyllisoflavone (4.47 μM) and osajin (5.01 μM) obtained from *Flemingia macrophylla* L., gave the most promissory effects, followed by the lignan, olivil-4′-*O*-β-D-glucopyranoside (5; 12.5; 25 μM) and (+) pinoresinol-4-4′-di-*O*-β-D-glucopyranoside (5; 12; 25 μM), both obtained from *Valeriana amurensis* P. Smirn. ex. Kom., and, lastly, the phenolic acid, rosmarinic acid (5; 15; 25 μM), from *Rosmarinus officinalis* L.

Despite the scarce results on in vitro neuroprotective effects of non-phenolic compounds (Table 4), when compared with the first ones, they evidence a higher

Table 7 Plant-origin bioactive compounds with in vivo neuroprotective effects

Bioactive molecule	Origin	Plant part	Animal models	Active concentration	Reference
Anthocyanins					
Anthocyanins	*Vitis vinifera* L.	Fruits	Male Wistar rats, scopolamine-induced memory deficits	200 mg/kg b.w.	Gutierres et al. (2014)
Curcuminoids					
Bisdemethoxycurcumin	*Curcuma longa* L.	Rhizomes	*Drosophila melanogaster*	1 mM	Wang et al. (2014b)
Curcumin					
Demethoxycurcumin					
Flavonols					
Kaempferol	*Brassica oleracea* var. *gemmifera*	Sprouts	Mouse model-Aβ-induced memory deficit	12, 24 ppm	Kim et al. (2013)
Tannins					
1,2,3,4,6-Penta-*O*-galloyl-β-D-glucopyranose	*Paeonia suffruticosa* Andr.	Whole plant	Tg2576 APPswe transgenic mice	8 mg/kg b.w.	Fujiwara et al. (2009)
Others					
2,3-Dihydroxy-4-methoxyacetophenone	*Cynanchum paniculatum* (Bunge) Kitag.	Roots	Amnesic mice scopolamine-induced	50 mg/kg b.w.	Weon et al. (2013)

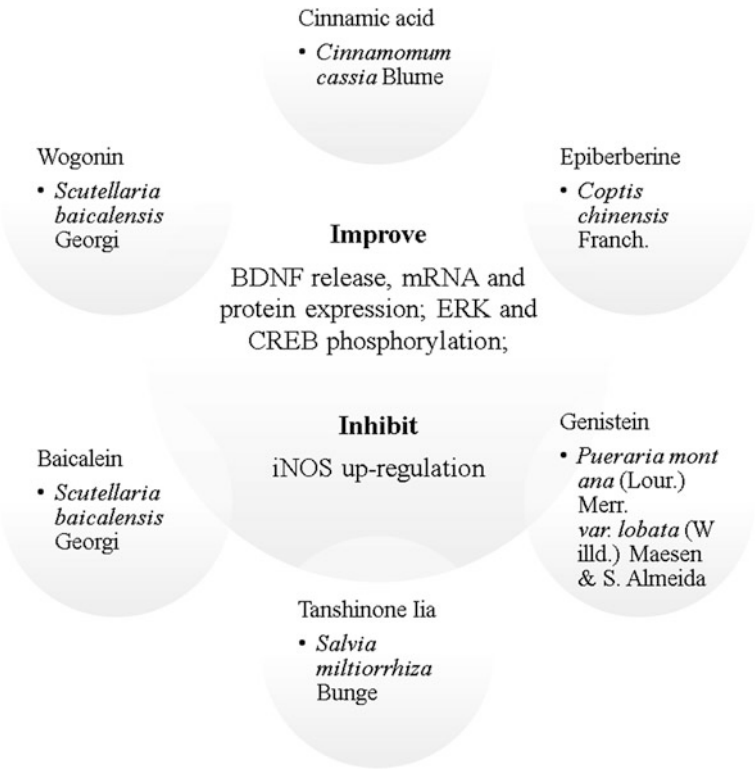

Fig. 1 Overview of the in vitro neuroregenerative effects of specific phytochemicals. Legend: *BDNF* brain-derived neurotrophic factor; *ERK* extracellular signal-regulated kinase; *CREB* cyclic AMP response element-binding protein; *iNOS* inducible nitric oxide synthase. The effects were observed by using the concentrations 0.1, 0.3, and 1 μM of each one of the tested compounds in cerebral cells from the cortex of fetal Sprague–Dawley rats (Jeon et al. 2010)

and more promissory effect. Coumarins obtained from the rhizomes of *Eleutherococcus senticosus* (Rupr. Et Maxim.) Maxim., namely isofraxidin and isofraxidin 7-*O*-glucoside, and also saponins, which include stigmasterol 3-*O*-β-D-glucopyranoside and eleutheroside E and B, exert a higher effect than phenolic compounds. Its active concentrations were for both coumarins and saponins, 1 and 10 μM.

Several terpenes, such as spirafolide (5.7 μM) from the leaves of *Laurus nobilis* L., and others obtained from the rhizomes and roots of *Valeriana amurensis* were also effective at lower concentrations (5; 12; 25 μM), being able to reduce apoptosis in human neuroblastoma cells and PC12 cells.

The bioactive constituent, (3*R*) 1,7-diphenyl-(4E,6E)-4,6-heptadien-3-ol, obtained from *Curcuma comosa* Roxb., was highly effective (0.1; 0.5; 1 μM) (Table 5), being able to reduce lipopolysaccharide (LPS)-induced NO and PGE_2 production, in a dose-dependent manner. Furthermore, the active concentrations

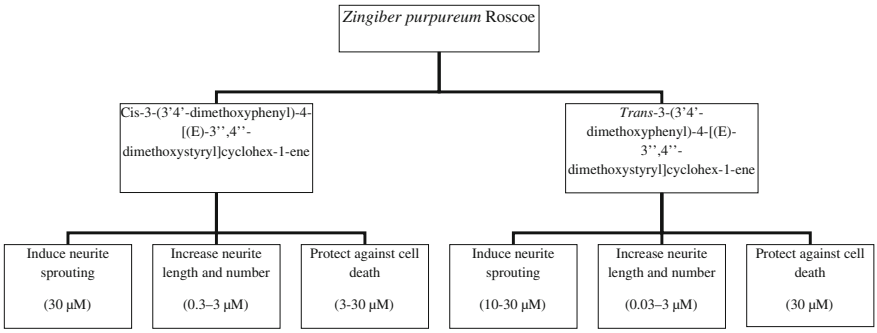

Fig. 2 In vitro neuroregenerative effects of phenylbutanoid dimers obtained from the methanol extract of *Zingiber purpureum* Roscoe. roots. *Legend* Protection against cell death and induction of neurite sprouting was assessed by using PC12 cells, while the evaluation of neurite length and number improvement was carried out in cultured primary cortical neurons of rats (Matsui et al. 2012)

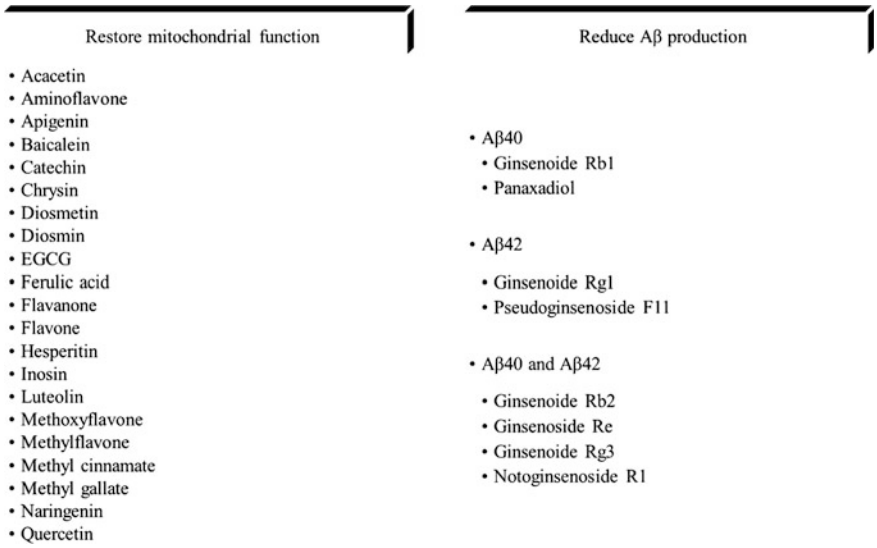

Fig. 3 Bioactive molecules from commercial sources with in vitro neuroregenerative effects. *Legend* Effects of flavonoids on the mitochondrial function were assessed by using 1 μM of each one in murine neuroblastoma N2a cells, and then, measure its activity at a level of ROS production, MMP and ATP levels (Dragicevic et al. 2011); evaluation of Aβ production was assessed by using 50 μM of each one of the tested compounds in CHO 2B7 cells (Chen et al. 2006)

were also able to reduce inducible NO synthase and cyclooxygenase 2 (COX-2). Similarly, β-sitosterol 3-*O*-β-D-glucopyranoside (1; 10 μM) obtained from the rhizomes of *Eleutherococcus senticosus* strongly inhibited neuritic atrophy induced

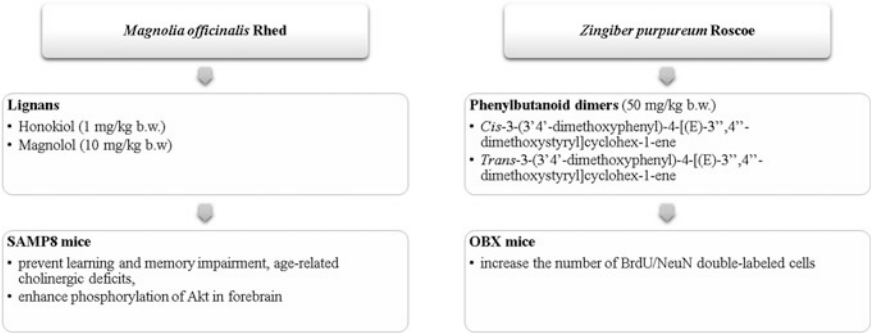

Fig. 4 Plant-origin bioactive molecules with in vivo neuroregenerative effects. *Legend Magnolia officinalis* Rhed plant (Matsui et al. 2009) and *Zingiber purpureum* Roscoe root (Matsui et al. 2012) methanol extracts

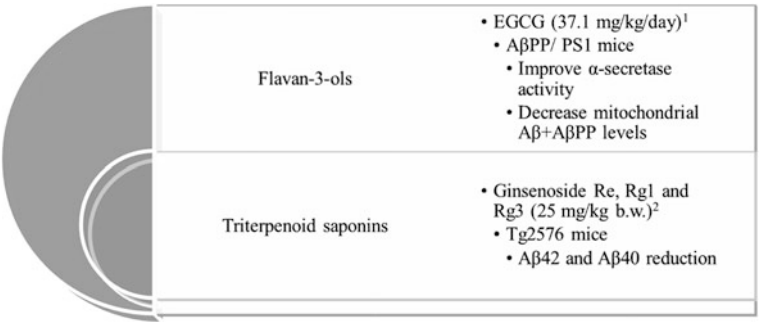

Fig. 5 Bioactive molecules (from commercial origin) with in vivo neuroregenerative effects. [1]Dragicevic et al. (2011), [2]Chen et al. (2006)

by $A\beta_{25–35}$, being clearly evident its protective effects against cognitive and memory impairments. 2,3-Dihydroxy-4-methoxyacetophenone (10.94 μM), isolated from the roots of *Cynanchum paniculatum* (Bunge), also evidenced a pronounced effect against neuronal damage and toxicity, in HT22 cells, induced by glutamate.

Overall, and comparing the efficacy and efficiency of the studied bioactive molecules in relation to its sources (commercial vs. plant origin), it is possible to conclude that plant-origin bioactive compounds possess a doubtless prominent potential. Although some of them were not studied and then compared from both sources, several examples should be highlighted. While for luteolin, derived from commercial (30 μM) and plant (30, 40, and 50 μM) sources, similar active concentrations were found, for rosmarinic acid a completely different situation was observed; the commercial molecule was effective at 23.5–50 μM, while the one from plant origin was effective at 5, 15, and 25 μM. Similarly, resveratrol isolated from *Vitis vinifera* L. was highly effective at 10 and 20 μM, while the commercial

molecule was active at 50 μM. Moreover, carnosic acid obtained from *R. officinalis* was effective at 10, 20, and 30 μM, while the commercial one was active at 50 μM. In the same line, the phenylethanoid glycosides, acteoside, and oraposide were also more effective when derived from natural sources (8.9 and 3.6 μM) in comparison with the commercial molecules (>200 μM). Finally, salidroside isolated from *Rhodiola sachalinensis* A. Bor was effective at 1; 5; 10; 50 μg/Ml, while the commercial molecules were effective at 3; 15; 30 μg/mL.

In summary, plant-food-derived bioactive molecules appear to be more effective than the commercial ones; notwithstanding, further studies are necessary to confirm this. Besides, the confirmation of the effective neuroprotective potential needs to be performed, mainly by in vivo studies, once numerous biochemical parameters influence the final bioactivity and active concentrations.

4.2 Bioactive Compounds with In Vivo Neuroprotective Activity

Tables 6 and 7 show, respectively, bioactive molecules from commercial and plant origins with reported in vivo neuroprotective effects. Comparing with the previously discussed in vitro neuroprotective effects, only commercial quercetin, ferulic acid, genistein, and hyperforin and bisdemethoxycurcumin, curcumin, demethoxycurcumin, 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose, and 2,3-dihydroxy-4-methoxyacetophenone from plant food origin were also evaluated. Higher concentrations were necessary to obtain the same effect on in vivo experiments. For example, hyperforin at 1 μM was effective under an in vitro model, while 6 μM was the active concentration in the in vivo experiment. Additionally, when compared with the in vitro reports, in vivo studies are significantly scarce. But despite this limitation, the obtained achievements need to be highlighted in order to systematize the knowledge on this area.

Phenolic compounds seem to be the most studied phytochemicals regarding neurocognitive benefits. The effects of flavonols have been evaluated using both commercial and plant-origin molecules; flavones, hydroxycinnamic acids, and isoflavones were only studied in commercial forms, while anthocyanins and tannins were obtained from natural extracts (*Vitis vinifera* L. and *Paeonia suffruticosa* Andr., respectively). Commercial terpenes and phenylpropanoids, and curcuminoids and other plant-origin biomolecules were also investigated for neuroprotective effects.

Rats and mice, followed by wild-type adult zebra fish and *Drosophila melanogaster*, including species with induced genetic variations, have been the most frequent animal models used. According to the selected animal model, several active concentrations for each bioactive molecule have been observed. Moreover, none of the studied bioactive molecules were evaluated from both commercial and plant-origin sources, being difficult to make comparisons of their effectiveness/efficiency.

Among the tested commercial flavones, luteolin showed a dose-dependent effect, mainly acting as downregulator of NF-Kβ and BACE-1, and decreased Aβ deposition (Fu et al. 2014). On the other hand, by using a standard concentration of 50 mg/kg b.w., Richetti et al. (2011) observed that both flavonols, quercetin and rutin, were able to prevent memory and cognitive impairments. Similarly, Mori et al. (2013) observed that ferulic acid (30 mg/kg b.w.) reversed transgene-associated behavioral deficits and decreased brain parenchymal and cerebral vascular β-amyloid deposits and also hyperforin at 6 μM (Dinamarca et al. 2006).

Moon et al. (2014) proved that the phenylpropanoid, 6-shogaol, at 10 mg/kg b.w. was effective in reducing microgliosis and astrogliosis, ameliorating $A\beta O_{1\text{-}42}$-induced memory impairment and elevating NGF levels, and also pre- and postsynaptic markers. In the same line, Bagheri et al. (2012) observed that genistein at the same concentration (10 mg/kg b.w.) leads to a significant inhibition of neurodegeneration and $A\beta_{1\text{-}40}$-positive aggregate formation, alleviating consequently extensive astrogliosis. The hydroxycinnamic acid, 3,5-di-caffeoylquinic acid (6.7 mg/kg b.w.), also showed a pronounced effect, being able to decrease in a significant manner escape latency time, by increasing PGK1 and mRNA expression, and also ATP production (Han et al. 2010).

In relation to plant-origin bioactive molecules, all of them were able to prevent memory and cognitive impairments, in different proportions. For example, anthocyanins from *Vitis vinifera* L. fruits extract (200 mg/kg b.w.) exerted beneficial effects mainly by preventing scopolamine-induced neurotoxic effects (Gutierres et al. 2014), while curcuminoids (bisdemethoxycurcumin, curcumin, and demethoxycurcumin) from *Curcuma longa* L. rhizomes extract, at the concentration of 1 mM, rescued morphological defects on *Drosophila melanogaster* improving the movement coordination (Wang et al. 2014b). In a similar manner, kaempferol (12 and 24 ppm), 1,2,3,4,6-penta-*O*-galloyl-β-D-glucopyranose (8 mg/kg b.w.), and 2,3-dihydroxy-4-methoxyacetophenone (50 mg/kg b.w.) obtained, respectively, from *Brassica oleraceae* var. *gemmifera*, *Paeonia suffruticosa* Andr., and *Cynanchum paniculatum* (Bunge) Kitag. markedly reduced escape latency time: the first one by its contribution on the reduction in ROS production and consequently improvement in step-through latency time (Kim et al. 2013), the second one through the inhibition of Aβ fibril formation as also destabilization of the preformed Aβ fibrils (Fujiwara et al. 2009), and the last one, related to NMDA receptor inhibition and breakdown of AChE (Weon et al. 2013).

The above-described neuroprotective benefits, both in vivo and in vitro, incite the future use of bioactive molecules from plant food origin as leaders to the AD treatment. It is also important to highlight that despite its neuroprotective and preventive effects, and even treatment/alleviation of the symptomatic conditions, these phytochemicals also possess an interesting and underexplored neuroregenerative potential, which needs to be studied in detail.

5 Plant Food Bioactive Molecules with Neuroregenerative Activity

5.1 *Bioactive Compounds with In Vitro Neuroregenerative Activity*

In addition to the previously stated promissory neuroprotective benefits of plant food bioactive constituents, its neuroregenerative effects have also been studied, but still have a low progression. Figures 1 and 2 show plant-origin bioactive molecules with prominent in vitro neuroregenerative potential, while Fig. 3 shows results of commercial molecules. Once again, is clearly evident the scarcity of the studied plant species: *Cinnamomum cassia* Blume, *Coptis chinensis* Franch., *Pueraria montana* (Lour.) Merr. *var. lobata* (Willd.) Maesen & Almeida, *Salvia miltiorrhiza* Bunge and *Scutelaria baicalensis* Georgi (Fig. 1), and *Zingiber purpureum* Roscoe. Figure 2 shows the currently recognized sources of bioactive molecules with in vitro neurodegenerative benefits. In particular, baicalein, cinnamic acid, epiberberine, genistein, tanshinone IIA, and wogonin, at low concentrations (0.1, 0.3, and 1 μM), evidenced to act synergistically on the brain-derived neurotrophic factor (BDNF) release, mRNA, and protein expression, mainly by phosphorylation of extracellular signal-regulated kinase (ERK) and cyclic AMP element-binding protein (CREB), and inhibition of inducible nitric oxide synthase (iNOS) upregulation. Jeon et al. (2010) clarified those effects by using cortex cerebral cells from fetal Sprague–Dawley rats. On the other hand, Matsui et al. (2012) by using PC12 cells observed that both isolated phenylbutanoid dimers from *Z. purpureum* (Fig. 2) were able not only to induce neurite sprouting (10–30 μM), but also to confer a significant protection against cell death (3–30 μM). Furthermore, the authors observed a pronounced induction of the number and length of neurites (0.03–3 μM) by using primary cortical neurons of rats.

Apart from the studied plant food molecules, several commercial biomolecules were also investigated, mainly in what concerns to the ability to restore mitochondrial functions and reduce Aβ production (Fig. 3). In general, phenolic compounds were the most frequently studied biomolecules toward to assess mitochondrial function restauration ability, while saponins have been studied to determine the effect on Aβ production. Indeed, and as previously mentioned, phenolic compounds are widely recognized for their antioxidant potential (mainly as free radical scavengers, metal quenchers, and hydrogen donators) (Heim et al. 2002; Grotewold 2006; Li et al. 2014). Commonly known as "powerhouse of the cells," "ATP reservoir" or "energetic factory," mitochondria contribute not only to the proper cellular function, but also to an intensive free radical production (one of the most important endogenous sources of ROS). In fact, brain cells need a higher and continuous demand for energy supply (Chaturvedi and Beal 2013). Therefore, it is of the utmost importance not only to ensure a proper neuronal function, but also to avoid cellular damages, by discovering new and effective alternatives to restore the optimum mitochondrial functions (in case of injuries). Taking into account

those features, several biomolecules have been intensively investigated. It should be pointed that, by itself, a free radical overproduction is not only a triggering factor to AD development, but also promotes Aβ production, which leads to an intense organic dysfunction and inflammation. As shown in Fig. 3, flavanones (hesperitin, naringenin), flavan-3-ols (catechin, EGCG), flavones (acacetin, aminoflavone, apigenin, baicalein, chrysin, diosmetin, diosmin, luteolin, methoxyflavone, and methylflavone), flavonols (quercetin), and phenolic acids (ferulic acid, methyl cinnamate, and methyl gallate) are among the most prominent phenolic compounds with mitochondrial function restauration ability, at the concentration of 1 μM, in murine neuroblastoma N2a cells. To evaluate the potential of those molecules, Dragicevic et al. (2011) used the levels of ROS, MMP, and ATP as positive indicators.

On the other hand, Chen et al. (2006) observed that saponins, at the final concentration of 50 μM, exerted considerable effects on Aβ40 (ginsenoide Rb1, panaxadiol) and Aβ42 (ginsenoide Rg1, pseudoginsenoside F11) and also on Aβ40 and Aβ42 (ginsenoide Rb2, Re, Rg3; notoginsenoside R1) reduction, by using CHO 2B7 cells. In spite of the great interest of these results, further studies are necessary to assess the in vivo effects, including security (mainly to saponins, which depending to the used doses, are often slightly toxic) and bioavailability, and also to establish the therapeutic doses.

5.2 *Bioactive Compounds with In Vivo Neuroregenerative Activity*

Figures 4 and 5 show the in vivo neuroregenerative effects of bioactive molecules from plant and commercial origins, respectively. Among the bioactive molecules from plant origin, only individual phytochemicals obtained from *Magnolia officinalis* Rhed and *Zingiber purpureum* Roscoe were evaluated (Fig. 4). *M. officinalis* lignans presented the better effect, namely honokiol (1 mg/kg b.w.) and magnolol (10 mg/kg b.w.) (Matsui et al. 2009), on the prevention of learning and memory impairments, age-related cholinergic deficits, as also on the improvement in Akt phosphorylation in SAM8 mice forebrain. The phenylbutanoid dimers (50 mg/kg b.w.) appear as the great contributors to OBX mice BrdU/NeuN double-labeled cell improvement (Matsui et al. 2012). In general, the authors concluded that the mentioned phytochemicals possess promissory neurotrophic effects; so, their further investigation is of the utmost importance, to be effectively used, in the near future, to threat and even to modify the course of several neurological disorders.

Among the commercial bioactive compounds (Fig. 5), the flavan-3-ols with a renowned and doubtless antioxidant potential, namely EGCG (37.1 mg/kg b.w.) from green tea (Dragicevic et al. 2011), were the most studied, and also triterpenoid saponins that include ginsenoside Re, Rg1, and Rg3 (25 mg/kg b.w.) (Chen et al. 2006).

In the first case, EGCG was able to improve the activity of α-secretase and to reduce brain mitochondrial Aβ and AβPP levels in AβPP/PS1 double-mutant transgenic mouse models. Otherwise, ginsenoside Re, Rg1, and Rg3 evidenced a higher potential to reduce not only Aβ42, but also Aβ40 brain levels in Tg2576 female transgenic mice models that overexpress the human APP gene.

Overall, and despite the described effects of the tested bioactive components, it is difficult to compare their efficacy and also efficiency once different biochemical parameters were assessed, and also biological antineuronal damage effects.

6 Neuromodulation and Neuroplasticity: Future Trends to an Optimum Brain Health

The in vitro and in vivo promissory neurocognitive benefits evidenced by plant products clearly point to an upcoming approach as future leaders on neurodegenerative diseases. In particular, their neuroprotective effects are pivotal once prevention comprises one of the most important key points on integrative intervention. Notwithstanding, in some cases, considerable changes on learning and memory abilities, and also lagged perceptions and neuronal losses, are found, which requires a therapeutic intervention (van Praag 2009; Essa et al. 2012; Yoo and Park 2012; Ahmed et al. 2015).

Otherwise, along with the disseminated idea that brain cells (such as neurons, microglia, and other glial cells) are not able to regenerate, increasing evidences have shown that they possess an interesting ability to synapse remodeling and consequently to recover its synaptic plasticity, neuronal spine density, and, therefore, cognitive improvement. Numerous signaling molecules, transporters, and codifying proteins, genes, and so on are involved on the mentioned complex process (McCoy et al. 2009; van Praag 2009; Nadim and Bucher 2014; Wester and McBain 2014). Plant-derived bioactive molecules, and also physical exercise, have shown to act as important contributors, once rest neurodegeneration, and improve neuroregenerative processes (van Praag 2009). In spite of their pivotal biological interests, the neuromodulatory and neuroplasticity abilities of numerous bioactive molecules remain poorly investigated, as also the involved modes of action. For example, it is convenient to highlight that 2,3,5,4′-tetrahydroxystilbene-2-*O*-β-D-glucoside (TSG), a phenolic compound derived from *Polygonum multiflorum* Thunb., evidenced potent cognitive improving and hippocampal synaptic plasticity promoting (Wang et al. 2011) abilities: facilitates the induction of hippocampal long-term potentiation (LTP) through activation of postsynaptic signal molecules and other signalling pathways, which contributes to the in vivo improvement of learning behavior, memory, and neuronal networks in rats. Liang et al. (2014) also showed that dihydromyricetin (DHM), a flavonoid compound, restores gephyrin (a postsynaptic anchor protein at GABAergic synaptic sites) levels, when administered in mouse models with AD. Gephyrin is directly involved on GABA receptor

functioning, once regulates its formation, plasticity and availability, as also from other signalling molecules (Liang et al. 2014). Furthermore, Zhan et al. (2014) observed that berberine, a plant alkaloid, was able to reverse synaptic deficits induced by D-galactose and rescued important intermediates (mRNA, *Arc/Arg3.1*) directly involved on normal synaptic plasticity.

Otherwise, and in association with the previous stated effects, it is also important to point out that hypothalamic neuromodulator systems are also affected/affect daily energy homeostasis. For example, under specific conditions (such as short-term fasting and other metabolic state changes), considerable synaptic circuits and respective (inter)neuronal controllers suffer from restructuration, which leads to physiological variations on energy homeostasis and may cause synaptic plasticity impairments (Horvath 2006). Thus, the above-described mechanisms of action of bioactive molecules can be also extremely useful in other contexts, such as feeding and appetite controllers. For example, plant-derived cannabinoids (phytocannabinoids) and endocannabinoids, in spite of the whole negative connotation attributed to cannabis, have shown greater contributive properties not only for physiological appetite and satiety controllers (Berry and Mechoulam 2002), but also for brain therapeutical purposes (i.e., neuromodulators, neuroprotective, neuroregenerative, and synapsis plasticity regulators) (Fisar 2009).

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