



Polyphenols Beyond Barriers: A Glimpse into the Brain



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Abstract: Background: Ageing can be simply defined as the process of becoming older, which is genetically determined but also environmentally modulated. With the continuous increase of life expectancy, quality of life during ageing has become one of the biggest challenges of developed countries. The quest for a healthy ageing has led to the extensive study of plant polyphenols with the aim to prevent age-associated deterioration and diseases, including neurodegenerative diseases. The world of polyphenols has fascinated researchers over the past decades, and *in vitro*, cell-based, animal and human studies have attempted to unravel the mechanisms behind dietary polyphenols neuroprotection.

Methods: In this review, we compiled some of the extensive and ever-growing research in the field, highlighting some of the most recent trends in the area.

Results: The main findings regarding polypolyphenols neuroprotective potential performed using *in vitro*, cellular and animal studies, as well as human trials are covered in this review. Concepts like bioavailability, polyphenols biotransformation, transport of dietary polyphenols across barriers, including the blood-brain barrier, are here explored.

Conclusion: The diversity and holistic properties of polypolyphenol present them as an attractive alternative for the treatment of multifactorial diseases, where a multitude of cellular pathways are disrupted. The underlying mechanisms of polypolyphenols for nutrition or therapeutic applications must be further consolidated, however there is strong evidence of their beneficial impact on brain function during ageing. Nevertheless, only the tip of the iceberg of nutritional and pharmacological potential of dietary polyphenols is hitherto understood and further research needs to be done to fill the gaps in pursuing a healthy ageing.

Keywords: Bioavailability, blood-brain barrier, healthy ageing, neurodegenerative disorders, neuroprotection, polyphenols.

INTRODUCTION

Neurodegenerative disorders (NDs) collectively refer to debilitating, life-threatening conditions that affect brain cells. As chronic and progressive neurological syndromes, they are caused by nervous system dysfunction resulting from neuronal cell failure [1], leading to impaired mental functioning (dementia) or movement complications (ataxia). These diseases can arise from hereditary or sporadic conditions, having a complex pathogenesis that triggers atrophy of central or peripheral structures of the nervous system [2]. Disease-modifying therapies to delay or reverse disease progression are not yet available, there is only a paucity of pharmacotherapy strategies focused on symptomatic relief.

More than 600 disorders have been described to afflict the nervous system such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), brain cancer, degenerative nerve diseases, encephalitis, epilepsy, genetic brain disorders, head and brain malformations, hydrocephalus, stroke, and prion diseases. They are heterogeneous

and multifactorial pathologies, which affect different brain structures and have different etiologies. AD, PD and HD, as well as ALS, share the aggregation of misfolded proteins as common pathological processes, being collectively designated as protein conformational disorders [2, 3].

AD is a clinical syndrome characterized by the progressive degeneration of hippocampus and neocortical brain neurons [4], which is responsible for the major disease symptoms – memory loss and cognitive decline. AD pathological hallmarks include the accumulation of extracellular amyloid plaques, majorly composed by amyloid- β peptides (A β 40 and A β 42) [5], and intracellular aggregates of hyperphosphorylated tau microtubule-binding protein, designated neurofibrillary tangles [6].

PD is the most common motor neuron disease. Its clinical symptoms include muscle rigidity, bradykinesia, resting tremor and postural instability, caused by the loss of dopaminergic neurons in the *substantia nigra pars compacta* [7]. The cytoplasmic inclusions designated Lewy bodies (LBs), predominantly enclosing aggregated α -synuclein (α Syn) [8], are the major pathological hallmark of the disease. α Syn is highly expressed in the brain and its function is thought to be involved in the regulation of dopamine neurotransmission and synaptic function/plasticity [9-14].

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HD displays a wide variety of symptoms including chorea, dementia, and emotional disturbance [15, 16]. It is characterized by neuronal demise especially in the striatal region of the basal ganglia. Genetic mutations causing HD are linked to the expression of N-terminal polyglutamine (polyQ)-expanded huntingtin (Htt) beyond a critical length of ~35 glutamine residues. The cleavage of these polyQ tails generates cytotoxic fragments with high propensity to cross-link and form protein aggregates in both neuronal and glial cells [17, 18].

ALS is a fatal motor neuron disease leading to death usually within 3-5 years after the disease onset, mostly due to respiratory failure. It is characterized by progressive muscle weakness, which frequently starts in the limbs, axial, bulbar, or respiratory muscles and afterwards generalizes relentlessly causing a gradual disability. The disease is caused by progressive loss of cortical, bulbar, and ventral cord motor neurons, with the major genetic risk factors being mutations in the genes encoding the superoxide dismutase SOD1 [19], the TAR-DNA-binding protein [20] and the fused in sarcoma or translocated in liposarcoma protein (FUS/TLS) [21, 22].

Epidemiology of Neurodegenerative Disorders

Dementia is responsible for the greatest burden of NDs, a recent estimation indicates that there is nearly 46.6 million people worldwide living with dementia [23]. The same study reveals that the number of new cases will almost double every 20 years, with 65.7 million by 2030 and 115-130 million cases foreseen in 2050 [23, 24]. Given the huge social and economic impact of dementia in our society, it becomes imperative to develop strategies to prevent cognitive decline and to improve life quality of patients suffering the devastating effects of dementia-associated disorders.

AD represents the primary cause of dementia accounting for nearly 70% of known dementia cases and being one of the leading causes of mortality worldwide. Disease prevalence is estimated at 5.3 million Americans in 2015 [25], ranging between 3-7% in Europe and the US [26]. The incidence rates vary between 5-8 per thousand persons-years, which corresponds to half of new dementia cases each year [27, 28]. Following AD, PD is the second most common ND. The Parkinson's Disease Foundation predicts that PD affects 7-10 million people worldwide. The prevalence rates vary from circa 50-300 per 100,000 individuals whereas the incidence rates are about 10-20 new cases per 100,000 people annually [29, 30]. As a rare neurodegenerative condition, the global HD prevalence is 2.71 per 100,000 individuals, being higher in Europe, North America and Australia (5.70 per 100,000) than in Asia (0.40 per 100,000), and the worldwide disease incidence rates are estimated at 0.38 per 100,000 individuals-year [31]. Consistent with the very limited survival of patients suffering ALS, prevalence is quite low, ranging between 4-5 people out of 100,000 and accounting for 1/300 to 1/400 of all deaths in the US. The median annual incidence of the disease in Europe and the US is estimated at 0.7-2.5 per 100,000 individuals [29, 32].

Altogether, these data reinforces the concomitant burden that NDs present in the develop world and the trend to increase over time. The need for novel therapies assisting to

retard and prevent the development of NDs is imperative and must be the focus of research in this area, rather than finding new alternatives to treat symptoms in later stages of disease progression.

Neurodegenerative Disorders and the Ageing of Population

Ageing is a central risk factor in the development of degenerative processes associated to NDs. According to the Organization for Economic Co-operation and Development [33], the likelihood of developing dementia increases from 0.002-0.010% before the age of 65 [34] to 50% over the 95s in Europe [33]. Demographic ageing, incremented by the advances in medical care and living conditions, has therefore a profound impact on the increase of NDs prevalence [35]. Indeed, the expected increase in dementia prevalence to about 115 million by 2050 is largely correlated to population ageing as it is projected that the number of individuals aged above 60 years will reach 1.25 billion in the same period, accounting for 22% of the world's population [24], with a particularly rapid increase in over-80s population.

Though ageing is considered a primary process in neurodegeneration, it differently influences the onset of the various NDs. Advancing age is the leading risk factor for AD, and disease onset usually occurs at the age of 65 [25]. Reports indicate that the risk of developing this disease almost doubles every five years after this age, as inferred by the incidence rates from 3 to as much as 69 per thousand individuals-year between the age of 65-69 and over the 90s, respectively [27, 28]. Likewise, PD majorly afflicts individuals over the 60s with higher median prevalence rates over 65s (9.5 per 1,000 persons) than in the overall population (max. 3 per 1,000 persons) of US and European countries [29]. As a consequence, median PD incidence ratios are also much higher in individuals over the 65s (160 per 100,000 person-years) than in the overall population (14 per 100,000 person-years) [29]. On the other hand, HD is a midlife disease usually diagnosed in adults between 35-50 years of age. Age-specific prevalence and incidence studies considering the global population are scarce, being restricted to particular countries. For example, a study performed in Taiwan found that HD incidence peaked between 40-49 year-old age in men (0.23 per 100,000 per year) and 50-59 year-old age in women (0.24 per 100,000 per year) [36]. Epidemiologic reports on ALS indicate acceleration in the upward trend for prevalence and incidence rates in individuals over the 40s, with prevalence estimations around 5 per 100,000 population over 70s [29].

Socio-Economic Impact of Age-Related Disorders

The global cost of dementia, both in terms of financial costs and the burden of the disease, is huge and set to rise further as a consequence of demographic ageing, representing the fastest growing major cause of disability globally. Due to the close association of ageing and neurodegenerative disorders, ageing has been considered the greatest social and economic challenge of the 21st century and dementia has also become a key policy priority for countries worldwide.

According to Alzheimer's Disease International, the burden of dementia affect society at the level of patient

itself, its family and caregivers, and at last the wider society, majorly impacting patient's welfare as well as the quality of life of caregivers [23]. Dementia has significant social and economic implications in terms of direct medical, social care as well as informal care spending. Direct medical costs include hospital/nursing-home care, diagnostic and medication; direct nonmedical costs are associated to in-home day care; and indirect or intangible costs take into account the psychological pain of the patient and the loss of productivity of both patient and caregivers [37, 38]. For these reasons, dementia, especially AD, has been considered one of the costliest diseases for society at least in Europe and the United States [39, 40]. The current global costs associated to dementia are estimated at US\$ 818 billion, 35.4% higher compared to the 2010 estimations (US\$ 604 billion), representing 1.09% of global gross domestic product (GDP) [23]. It was estimated that in 2015 AD direct costs to American society would total circa US\$ 226 billion and, unless measures are taken, in 2050 AD is projected to cost over US\$ 1.1 trillion [25]. Regarding PD, the annual direct and indirect costs are estimated to be nearly US\$ 25 billion in the US alone. Unlike AD, direct medical costs represent a substantial portion of the costs associated to PD, according to Parkinson's disease Foundation.

In almost all the cases, as neurodegenerative diseases advance, there is an increase in dementia severity accompanied by increasingly deeper behavioural disturbances. The worsening of symptoms leads to the increase of caregiving time required for the provision of physical care. Therefore, measures to decrease cognitive decline, delay institutionalization or reduce caregiver needs will certainly provide economic benefits. Thus, the long-term goal of dementia policy is to develop effective preventive treatments and, if possible, to find a cure for these devastating diseases. In a short-term, a special attention has been given to the improvement of the quality of life of patients. In this frame, dementia is one of the priority conditions in the World Health Organization – WHO – Mental Health Gap Action Program (mhGAP), whose objective is to scale up care for dementia-associated neurological disorders [33]. Indeed, it is estimated that the development of treatments reducing severe cognitive impairment in older people by just 1% per year would cancel out the projected increases in the long-term care costs due to our ageing population (Alzheimer's Research Trust).

Healthy Ageing and Transition to Disease

Ageing is a complex, irreversible, progressive and natural process, which is characterized by morphological, psychological, functional and biochemical changes affecting the welfare and health of the individual. The WHO describes the quality of life associated with ageing as a "broad and subjective concept that integrates physical health, psychological state, level of independence, social relationships, personal beliefs and convictions and their relationship with important aspects of the environment". The WHO also defines "Active Ageing" as the process of optimizing opportunities for health, participation and social security, to improve the quality of life with ageing. The maximization of the functional capacity and health of the elderly is conditioned by factors such as nutrition, physical and social activity,



Fig. (1). Determinants of healthy ageing. The quality of life associated with ageing integrates different variables such as nutrition, physical and social activity, education, genetic background, and their relationship with the environment. Except for the genetic background, which is not modifiable, all the other aspects are subject to change. Nutrition has been increasingly considered a key aspect for a healthy ageing and emerges as a critical modifiable risk factor to be explored in research.

education, and genetic background (Fig. 1), which ultimately define healthy ageing. Some of these factors are not modifiable, such as genetic ones, while others (nutrition, physical and social activity, *etc.*) are subject to change (*i.e.* environmental, psychological, social and lifestyle). In this sense, nutrition and other environmental factors have a huge impact on health and wellbeing. The nutritional status of elderly people has been increasingly considered a key aspect for a healthy ageing and, therefore, nutrition emerges as a critical modifiable risk factor to be exploited in policy strategies to prevent or delay the onset of neurodegenerative disorders and dementia [41]. There are several evidences that a continuous and prolonged intake of fruit and vegetables, rich sources of compounds named polyphenols, may help in the prevention of several degenerative pathologies such as diabetes, cardiovascular diseases, neurodegenerative diseases and cancer, and to prevent symptoms associated to ageing and menopause [42, 43].

If we consider the normal process of evolution of a healthy state to a disease state, we may resume that the evidences indicate an active role of dietary polyphenols to homeostasis maintenance, delaying or even reversing the transition from a healthy to a pathological state (Fig. 2). Then, nutrition and in particular bioactive polyphenols identified in the diet, are strong contributors to the maintenance of a healthy condition. Moreover, polyphenols can also constitute lead compounds as basis for developing new drugs and therefore contribute to a pharmacology intervention (Fig. 2). Thus, pharmacological and nutritional approaches can be considered for the study of polyphenols. The next sections will be dedicated to review the evidences for both approaches on a neuroprotection perspective.

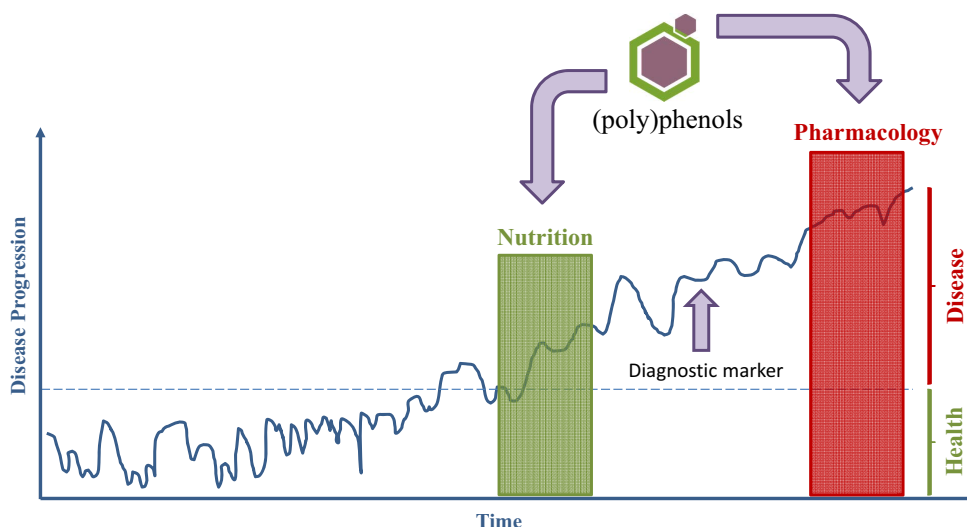


Fig. (2). Polyphenols in a nutritional or pharmacological approach: disease progression and transition from a healthy to a disease state. Through nutrition polyphenols can act in the prevention of disease, or in the restoration of a healthy state in earlier disease stages, even before detection of diagnostic markers or drug administration. Polyphenols can also be the basis for developing new therapeutic compounds and therefore contribute to pharmacological interventions.

POLYPHENOLS AND NEUROPROTECTION

Phenolic compounds, commonly referred as polyphenols, constitute one of the most extensive and ubiquitous group of secondary metabolites in the plant kingdom. These compounds are characterized structurally by the presence of, at least, one hydroxyl functional group (-HO) linked to an aromatic ring [44]. Some compounds that do not present structural characteristics of polyphenols are commonly integrated in the group of polyphenols as “honorary”, such as phenolic acids or stilbenes. For this reason, recently the term “polyphenols” has been rewritten as “(poly)phenols” [45-47].

Polyphenols represent an extremely differentiated group not only in terms of chemical structure but also in terms of their biological activity. They occur conjugated with sugars, carboxylic and organic acids, amines, lipids and other phenols. Different groups are classified in terms of the number of phenol rings that they encompass and according to the structural elements binding these rings [48, 49]. The main classes are represented in Fig. (3) and include phenolic acids, stilbenes, flavonoids, coumarins and lignans.

Hydroxybenzoic and hydroxycinnamic acids represent the two different groups of phenolic acids. The first ones can be found in plants, both free and esterified. Examples are gallic acid, present in fruits, herbs, tea and wine, or more complex compounds, the hydrolysable tannins such as ellagic acid, gallotannins and ellagitannins [50]. Hydroxycinnamic acids are generally represented by *p*-coumaric, caffeic, ferulic and sinapic acids, usually found glycosylated or conjugated with quinic, shikimic and tartaric acids [48, 50]. Chlorogenic acid, an ester of caffeic and quinic acids can be found in several fruits and vegetables and is highly abundant in coffee. Ferulic acid is present in large amounts in cereal grains [50, 51]. Stilbenes frequently present in roots, barks, rhizomes and leaves, are not routinely consumed. By opposition we have a highly valued stilbene, resveratrol, present in grapes and in red wine [52].

The largest group of phenolic compounds in plants are flavonoids, with more than 10,000 different structures being identified [53]. The main classes of flavonoids are flavonols, flavones, isoflavones, flavanones, anthocyanins and flavanols. Monomers of flavanols (catechins), such as (+)-catechin and (-)-epicatechin, are relatively abundant in fruits, wine, chocolate and green tea [50, 54]. Proanthocyanidins, also known as condensed tannins, are constituted by dimers, oligomers and polymers of catechins. Proanthocyanidins can be found in fruits such as apples and grapes, in wine, cider, tea and beer, and also in cocoa [55]. Anthocyanins are glycosylated pigments, responsible for the colours of some flowers and fruits.

Cognitive Health and Dietary Polyphenols: Epidemiological and Population Based Studies

The beneficial effects resulting from polyphenol intake have been extensively studied, as in the studies concerning the Mediterranean Diet (MeDi). MeDi is characterized by a high consumption of fruits, vegetables, and grains, as well as sea-fish on regular bases. It also includes a modest consume of wine and olive oil as the principal source of fat, both highly enriched in polyphenols. Additionally, the intake of meat, dairy products, sweets and convenience food is rather low in the MeDi [56, 57].

A survey of studies reporting the effects of MeDi, carried out by WHO, revealed that it is a promising strategy to prevent diseases and to enhance quality of life (World Health Organization, 2009). Furthermore, epidemiologic studies over the last decades have supported the positive correlation between Mediterranean eating patterns and a large number of health benefits [58, 59], including (i) decreased risk of developing NDs; delayed AD and PD onset; (iii) lowered mortality in AD patients; and (iv) improved cognitive function [41, 60-62].

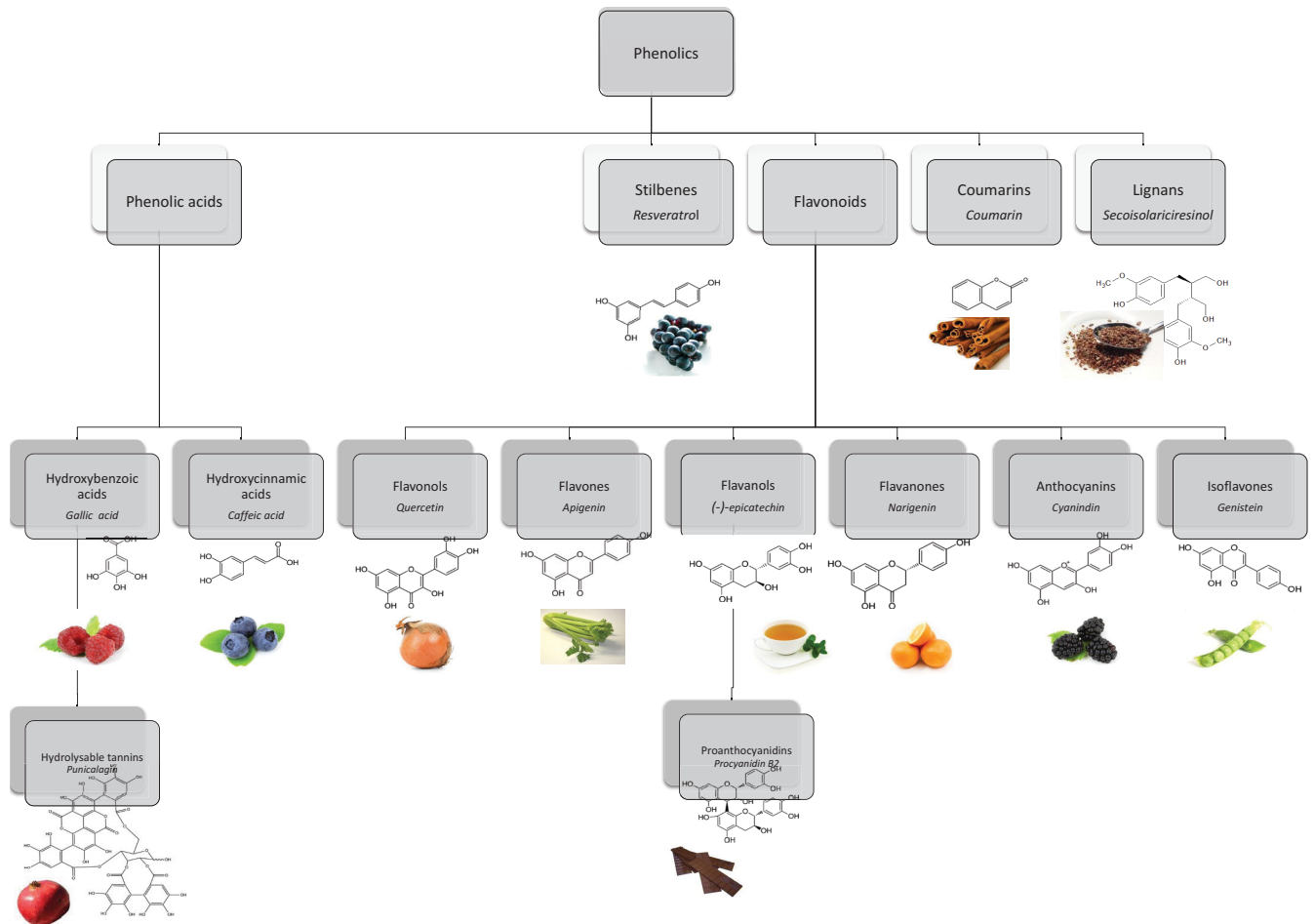


Fig. (3). Main polyphenol classes with structure, name of representative compounds (in italic) and examples of food sources.

Polyphenols are abundant in MeDi and are believed to contribute to the beneficial effects of this diet when adopted in a regular basis, as revealed by studies showing that polyphenol-rich diets improve cognition, memory, learning, and vascular function in elderly people [63, 64]. The regular consumption of flavonoid rich-foods, representing the most common group of polyphenolic compounds in the human diet, has been associated to enhanced cognitive abilities and reduced risk of cognitive decline in aged individuals [65, 66]. Indeed, a large-scale population study indicated that flavonoids intake decreased dementia as well as premature death due to dementia [66]. Remarkably, it was found a correlation between high polyphenol concentrations in urine samples of older adults and lower risk of cognitive decline in global cognitive function in a prospective population-based study over a 3-year period [67].

Berries are a great source of polyphenols and wild blueberry diet supplementation was proved to improve cognitive function in older adults [68]. Increased consumption of berries and anthocyanins, as well as total flavonoids, was shown to be associated to a slower progression of cognitive decline in a large prospective cohort of older women [69].

Also, it was demonstrated that high anthocyanin consumption is associated with reduced risk of developing PD [70].

Collectively, these epidemiological and population based studies support the hypothesis that polyphenol-rich foods or supplements have a positive impact towards NDs. How it is processed and by which mechanisms diet alterations may exert protective effects is still a field of intensive research that, in the future, may change our perspective of an effective treatment for NDs.

Nutritional Relevance and Bioavailability of Polyphenols

Although polyphenols are not essential for humans, they have a positive impact on human nutrition. Polyphenols are widely spread in food, and the total polyphenols dietary intake could be as high as 100-150 mg per day, which is much higher than that of all other classes of phytochemicals [50]. Just for perspective, this is one order of magnitude higher than the intake of vitamin C and two orders of magnitude higher than the intake of vitamin E and carotenoids [71, 72]. Polyphenols main dietary sources are fruits and plant-derived beverages such as fruit juices, tea,

coffee, and red wine. Vegetables, cereals, chocolate, and dry legumes also contribute to the total polyphenol intake [50]. The amount of research that has emerged in the past years in order to better understand polyphenols health benefits discloses a glimpse of the huge potential they may present [73-75]. However for a deeper understanding of the effect of polyphenols in human health, their absorption, distribution, metabolism and excretion in the human digestive tract needs to be studied.

The most common polyphenols present in the human diet are not necessarily the most active inside the body, either due to a low inherent activity or due to their poor absorption, extensively metabolism and rapid excretion [50]. Throughout digestion, polyphenols suffer several chemical modifications and metabolism, and the bioavailable metabolites found in blood and tissues may diverge from the native compounds in terms of biological role. Many different models are used to obtain a deeper knowledge about these mechanisms, ranging from *in vitro* enzymatic activities, cellular models, animal models or even the man himself. Although many differences can be seen between human and other animals' digestive process, animal studies have been essential for the current understanding gathered so far on polyphenols bioavailability and effects.

One of the major difficulties on studying the bioavailability of polyphenols relies on their structural differences, resulting in different metabolic fates among compounds. Although some reactions could be common, several differences in the polyphenols metabolism can occur among classes or even within the same class.

After ingestion, the availability of polyphenols, often associated with fibre or complex carbohydrates in the food matrix, can be modified in the oral cavity by amylase digestion and, perhaps, by particle size reduction [76]. Afterwards, the effective release of the phenolic compounds in the stomach maximizes the potential for absorption in the small intestine [76]. Absorption occurs mainly at the duodenum and at the proximal half of jejunum, where enterocytes are the predominant cells, being responsible for the absorption (Fig. 4). Being lipophilic compounds, most flavonoid aglycones and phenolic acids permeate intestinal cells by passive diffusion [42, 77, 78]. Polyphenols in the form of esters, glycosides or polymers, usually present in plants, cannot be directly absorbed and they probably resist to acid hydrolysis in the stomach, being able to reach the duodenum [50].

The absorption of glycosylated compounds is usually preceded by the hydrolysis of the glycoside and release of the aglycone (Fig. 4), by the enzyme lactase phloridzin hydrolase (LPH) in the brush-border of the small intestine epithelial cells. After hydrolysis, the free aglycone can enter the epithelial cells by passive diffusion [79]. Otherwise, glycosylated compounds are supposed to enter epithelial cells via the sodium-dependent glucose transporter, SGLT1, and be hydrolyzed by the cytosolic β -glucosidase (CBG), depending on the glycoside [80]. By opposition, the highly stable oligomeric and polymeric flavanols during digestion, are thought to have a very low absorption [81].

Compounds that are not absorbed in the proximal gastrointestinal tract can reach the large intestine where

absorption can also happen (Fig. 4). However, colonic microbiota can degrade complex polyphenols into low molecular weight phenolics, aromatic acids [82], and also into oxaloacetate and CO_2 [83].

As usually happens with xenobiotics, polyphenols can undergo enzymatic reactions known as 'biotransformations', phase I and phase II reactions [84] (Fig. 4). The resulting compounds are frequently less lipophilic so the body can more easily excrete them.

Phase III transporters are responsible for the final step in the elimination and/or detoxification of xenobiotics, resulting in the removal of the undesired compounds in faeces, urine and bile [85] (Fig. 4). These transporters are mainly constituted by the ABC protein family, including P-glycoprotein (P-gp), the multidrug resistance-associated proteins (MRP2, BCRP), and also by the solute carrier family (SLC) transporters [86, 87].

Importantly, most of the conjugated-polyphenols are excreted in urine. However, the mechanisms by which these conjugated-polyphenols can return into the intestinal lumen or to bile, by the action of intestinal cells or liver parenchymal cells, respectively, should also be considered (Fig. 4). Several polyphenols were shown to be considerably better absorbed in the presence of additional polyphenols, interfering with efflux transporters (P-gp, MRPs, BCRP), which normally reduce the intracellular concentration of such "xenobiotics" and, in that case, lead to their excretion to the apical side [88, 89]. On the other hand, transporters to the basolateral side are poorly understood. Compounds excreted into bile are eventually emptied in the duodenum. Usually, they are not absorbed in the small intestine, and reach the colon, where they can either be excreted into the faeces or be degraded by the colon microbiota, and be ultimately reabsorbed [90].

Bioavailability of polyphenols is thus a multi-stage process comprising de-conjugation and possible catabolism, absorption, conjugation and excretion (Fig. 4). Moreover, the possible sequestration of some polyphenol metabolites inside tissues has been recurrently undetermined and may contribute to underestimation of the their bioavailability. The accessibility of polyphenol metabolites to the central nervous system is an example where the presence of an additional barrier, the blood-brain barrier (BBB), reduces even more polyphenols bioavailability, in addition to the described metabolism. This aspect will be further discussed below. Therefore, controlled target delivery to central nervous system (CNS) is desirable to optimize polyphenols in terms of efficiency, specificity and safety.

Formulations and methods for enhancing polyphenols bioavailability, solubility and stability in the human body have been patented, creating new derivatives with improved biological activity and stability [91]. Encapsulating polyphenols in nanoparticles can be a promising solution by enhancing their bio-distribution, solubility, and stability in the human body, while reducing their extensive metabolism. Nanoparticles-loaded polyphenols constitute an active area of research, with the goal to increase the oral bioavailability of poorly absorbed phenolic compounds. Sahni and co-workers summarized the neurotherapeutic applications of nanoparticles loaded with curcumin, catechins or resveratrol for AD [92].

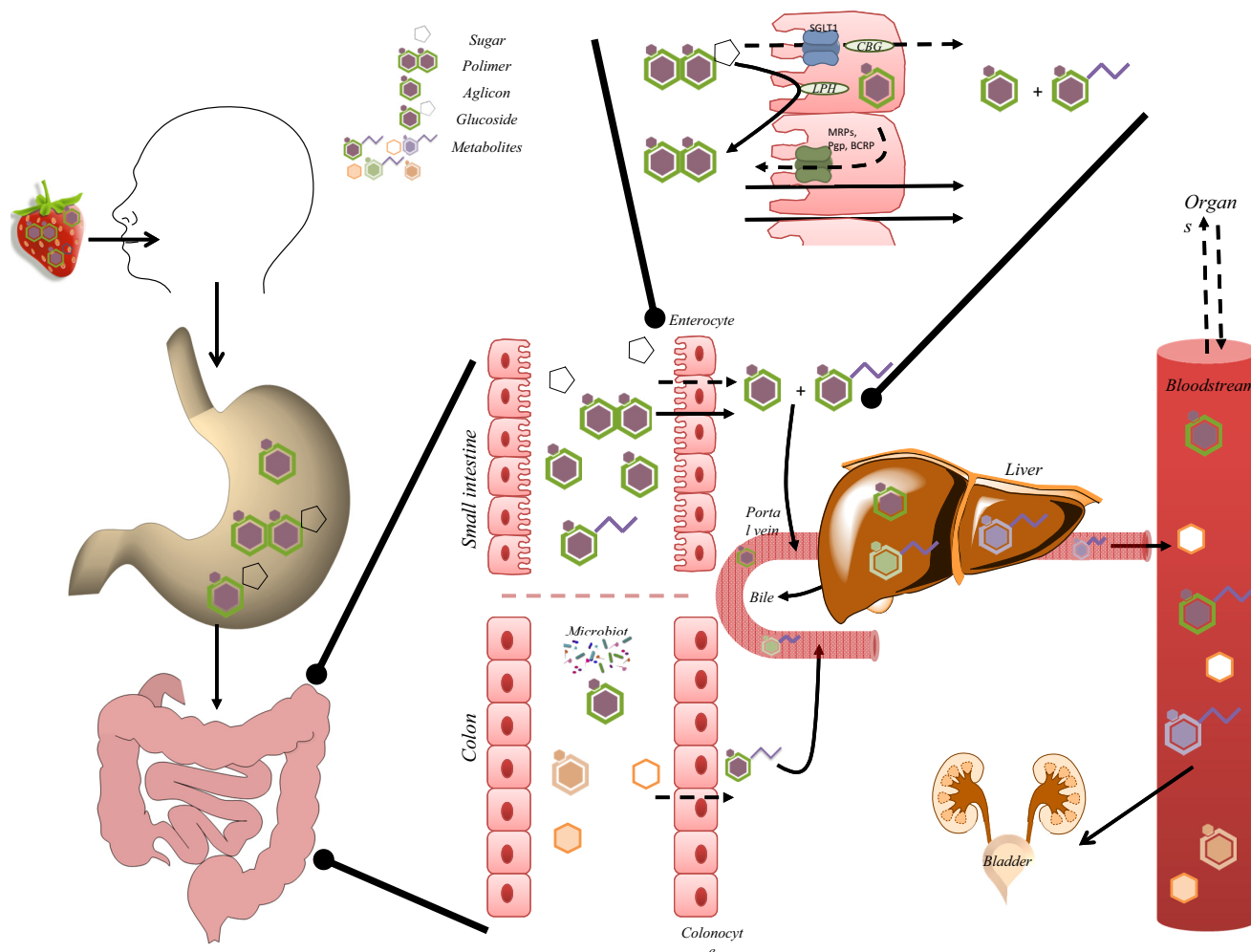


Fig. (4). Schematic representation of absorption, biotransformation and excretion of polyphenols in the human body. Along the digestive process, polyphenol-rich food suffers transformations, starting in the mouth, stomach and throughout the entire gastrointestinal tract. The gastrointestinal tract is covered by the mucosa, which functions as a physical barrier, determining bioavailability of xenobiotics like polyphenols. This function is mediated by physical walls, metabolism and passive (solid arrows)/active (dashed arrows) transport mechanisms. Absorption occurs mainly at the duodenum and the proximal half of jejunum, in enterocytes. Enterocytes apical cell membranes contain microvilli, which increase the surface area of absorption. Passive intestinal permeability occurs mainly for aglycones and simple phenolic acids. Absorption of glycosylated compounds is usually preceded by release of aglycone through hydrolysis by lactase phloridzin hydrolase (LPH). Free aglycone can then enter the epithelial cells by passive diffusion. Alternatively, glycosylated compounds enter epithelial cells by the active sodium-dependent glucose transporter SGLT1 and are hydrolyzed by the cytosolic β -glucosidase (CBG). Once inside enterocytes, polyphenols can be extruded into the lumen by efflux transporters (P-gp, MRPs, BCRP). Compounds not absorbed reach the colon where they can be extensively metabolized by microbiota. Several transformations in polyphenols structure can occur. Most of the colonic metabolites are excreted in feces, although absorption can still take place. Then, polyphenols can undergo phase I and phase II reactions. Phase I reactions include oxidative and reductive reactions. Glucuronidation, sulfation and methylation are the most frequent phase II reactions. The conjugates, being more water soluble, are rapidly excreted through bile or urine [84]. Metabolites can then be transported into the bile (enterohepatic recirculation) and secreted back to the duodenum. Degradation of metabolites in the intestine generates catabolites available for reabsorption.

NEUROPROTECTIVE POTENTIAL OF POLYPHENOLS

In addition to the epidemiological evidences already mentioned, neuroprotective evidences for polyphenols also result from *in vitro*, cellular, animal and clinical studies [63, 93]. Another aspect to consider is that polyphenols can be studied either in a pharmacological or nutritional perspective as valid strategies to supply them to humans. Besides the form of delivery/route of administration we can consider

studies focusing on pure compounds in contrast to the use of mixtures or whole extracts. Target and nontargeted metabolomic profiling have evolved and allowing identification of new potential bioactive metabolites and the definition of absorption kinetics [94-97].

Neurodegeneration is a multifactorial process and polyphenols present pleiotropic effects (antioxidant, anti-inflammatory, immunomodulatory properties) [98] due to their ability to modulate the activity of multiple targets

involved in pathogenesis, thereby halting the progression of these diseases. For many years, polyphenols were thought to protect cell constituents against oxidative damage through direct scavenging of free radicals. Such idea has become very popular leading to the appearance of several studies exploring extensively this property of polyphenols for NDs, since oxidative stress constitutes an important hallmark of these diseases. However, this concept now appears to be an oversimplified view of their mode of action. There is an emerging acceptance that polyphenols, as well as their metabolites, exert modulatory actions in proteins/enzymes through direct interaction with receptors or enzymes involved in signal transduction, such as protein kinase and lipid kinase signalling pathways [99]. Moreover, several neurochemical mechanisms underlying the protective action of plant polyphenols have been described: iron chelating properties [100]; modulation of signalling pathways related with neuronal survival and differentiation [99, 101]; inhibition of neuropathological processes [102, 103]; and regulation of mitochondrial function [104-106]. A recent review also addressed other positive effects of dietary polyphenols regarding brain health and cognition. Other mechanisms by which flavonoids can be neuroprotective include their positive role on peripheral and cerebrovascular blood flow, ultimately affecting synaptic plasticity processes and cognitive function [107].

Mixtures vs. Pure Compounds

The study of pure compounds is limited to their molecular mechanisms in neurodegeneration cell models, and their specific biological effects in animal models. On the other hand, studies using pure polyphenols miss the synergies among different polyphenols. The presence of synergism and prodrugs in an extract can be misleading by using pure compounds [108]. Total extract from *G. biloba*, a well-known matrix used for treating peripheral vascular diseases and cerebrovascular insufficiency in the elderly, is more active than its isolated polyphenols [109, 110]. St John's Wort extract is another example, since no single compound or even a group of compounds has been found to be responsible for its activity [108, 111]. Therefore, studies with polyphenol-enriched fractions can be not only useful to identify sources to isolate pure bioactive compounds but also for identifying mixtures of bioactive compounds. Since polyphenols are emerging key compounds for the development of novel therapeutic agents for NDs, the identification of the molecular targets of isolated polyphenols or identification of novel sources of neuroactive polyphenols has become an important area of research.

In the next sections, it will be summarized the evidences pointing out the neuroprotective activities of polyphenols regarding different types of studies: *in vitro*; cellular models and primary cell cultures; *in vivo* animal assays; and human trials. The approach used, either nutritional or pharmacological, will be highlighted.

In Vitro Studies

The consensus fact that free radical-mediated reactions play an important role in both ageing and in the pathophysiology of most NDs lead to the extensive study of

polyphenols chemical scavenging activity. One of the best studied source of plant polyphenols is *G. biloba* and its extract (EGb 761), which has been described to scavenge reactive nitrogen and oxygen species (RNOS) [112] and peroxy radicals [113]. Direct scavenging of RNOS and peroxy radicals was also described for green tea [114] and for rosmarinic acid [115], respectively.

Substantial presynaptic cholinergic deficit is a feature registered in most NDs [116]. Malfunction of the cholinergic system may be tackled pharmacologically through inhibition of acetylcholinesterase [117], which catalyses the hydrolysis of the neurotransmitter acetylcholine (ACh) to choline. Therefore, AChE inhibition has been reported to ameliorate the symptoms of some NDs and has been used as a rationale to develop drugs to treat AD [118]. Green tea and white tea digested metabolites were described to inhibit AChE [119]. Additionally, a variety of plants with diverse phytochemistry features have been reported to exhibit AChE inhibitory activity [120] and, in some of these studies, polyphenols were the compounds associated with the plant extract activity [118, 121-126].

Another common pathological hallmark of many NDs is the generation of aberrant misfolded proteins with formation of intra- or extra-cellular high-ordered insoluble fibrils deposits [127, 128]. Potent activities towards the several steps of fibrils formation are modulated either by plant extracts or by isolated compounds. For instance, inhibition of A β -peptide aggregation and fibril formation was described for: isolated catechins and procyanidins and fractions of EGb761 extract containing these flavonoids [129]; blueberry anthocyanins enriched extract [130]; grape seed extract [131]; epigallocatechin gallate (EGCG) [132, 133]; myricetin [134]; resveratrol derivatives [135-139]; gallotannins and some derivatives [140]. Moreover, the ability to destabilize preformed fibrils *in vitro* was also described for curcumin [141], catechins and procyanidins [129]. Similarly, the protein α Syn is an amyloidogenic polypeptide that forms cytotoxic oligomers and quercetin was described to reduce α Syn fibrillization [142]. It was also shown that EGCG redirect the aggregation of α Syn monomers and remodel α Syn amyloid fibrils into disordered oligomers [132, 143]. Recent studies also reported that *Corema album* polyphenolic extract acts as inhibitor of α Syn fibrillization by the stabilization of non-toxic α Syn oligomers [144]. Furthermore, quercetin has raised interest as therapeutic for cerebral ischemia/reperfusion (I/R) injury due its predicted inhibitory effects on MMPs activation and acid sensing ion channel 1a channels mediated downstream survival/damage mechanisms [145].

In vitro studies are particularly relevant to determine the effect of polyphenols in specific pathological processes, without the interference of other cellular pathways. However, *in vitro* findings must be interpreted with caution, as some are not translated into cell and animal models. For instance, polyphenols present a very promising *in vitro* antioxidant capacity leading to the misconception that their cellular protection was mainly due to direct antioxidant scavenging. Studies with cellular and animal models were valuable to demystify this concept, and now we know that the mode of action of polyphenols go far beyond their antioxidant potential [146].

Cellular Models and Primary Cell Cultures

Cellular models, although less physiological than animal studies, are very important to unravel the molecular mechanisms underlying the polyphenol protective effects observed in animals. Cellular assays allow to study the cross-talk between pathways affected by polyphenols, giving a more integrated view of the metabolic pathways affected by these compounds. In contrast to *in vitro* studies, focused on a particular aspect or protein/enzyme function, in cellular models the whole cellular metabolism is evaluated. The complexity of these studies increases when analysing a mixture of compounds, as food extracts, in contrast to studies with pure compounds.

Several *in vitro* studies refer a general protection from oxidative stress effects either by direct scavenging activity or induction of antioxidant defences by plant polyphenolic extracts (see Table 1). Moreover, the effects of these extracts have also been explored for specific mechanisms hallmarks of NDs.

Protection from neurotoxicity induced by A β was observed for: *G. biloba* EGb 761 extract, in the neuroblastoma cell line Neuro2a [147], PC12 cells [148] and in hippocampal primary neurons [149]; green tea extracts, in primary rat cortical neurons [150]; blueberry anthocyanin-rich extract, in Neuro2a cells [130]; and Korean black soybeans anthocyanin-rich extract, in hippocampal HT22 cell line [151]. Other mechanisms impaired by A β were also described to be ameliorated by some of these plant extracts. For example, EGb 761 improves oxidative phosphorylation performance and restores from A β -induced mitochondrial dysfunction [152]. Also, blueberry anthocyanin-rich extract increase microglial A β clearance, inhibit its fibrillation and suppress microglial activation in murine cell culture [153]. Similarly, the rescue of α Syn aggregation toxicity was described for *C. album* polyphenols extract in human neuroglioma cells [144].

Neuroinflammation, another important hallmark of neurodegeneration, is also reduced by plant polyphenols extracts. Blueberry extracts attenuate inflammatory responses, inhibiting NO production and the release of the cytokines interleukin-1 β and tumour necrosis factor- α in mouse brain BV-2 microglial cells [154]. Another anthocyanin-rich extract from *açai* reduce inflammatory stress signaling in BV-2 microglial cells by the down-regulation of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), p38 mitogen-activated protein kinase (p38-MAPK), tumour necrosis factor- α (TNF α), and nuclear factor κ B (NF- κ B) [155].

The studies described in this section have in common the use of complex mixture of compounds, most of them of dietary origin. However, these studies do not consider polyphenols metabolism and therefore they could only be considered in a pharmacological perspective with controlled target delivery to central nervous system (CNS). In fact, the described effects seen in these *in vitro* studies could be completely altered by metabolism. For example, blackberry extracts submitted to a simulated gastro-intestinal digestion reveal that neuronal protection to oxidative insult can be unrelated to the modulation of reactive oxygen species

(ROS) and glutathione (GSH) levels, suggesting a pre-conditioning effect by the induction of caspase activity [156, 157]. On the other hand, *Phellinus igniarius* polyphenols also provided protection in a mouse stroke model [158].

Studies with pure isolated compounds also revealed more specific and targeted potential neuroprotective applications. Catechins increased neuronal viability by modulation of signal transduction pathways, cell survival genes and mitochondria functions [reviewed in [159, 160], reduction of neurotoxins, and A β toxicity in several cell lines and primary cultures (Table 2). EGCG, in particular, prevented A β fibril formation [161] and inhibited caspase activation mediated by A β in hippocampal neurons, leading to increased viability [162].

As a pure compound, the potential of resveratrol in NDs prevention have been extensively exploited. It was shown to reduce A β mediated accumulation of ROS and apoptosis in cell models [163], being its protection related with the modulation of NF- κ B and SIRT1 pathways [163-165]. In yeast, resveratrol mimics caloric restriction, described to slow the pace of ageing, by stimulating Sir2 (the homologue of SIRT1), increasing DNA stability and extending life span by 70%, being therefore associated with a mitigation of age-related diseases, including neurodegeneration [166].

Curcumin has also been pointed as a polyphenol with a plethora of protective activities. It exhibits intracellular antioxidant activities, anti-amyloid activities [167, 168] and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) protective activity [169]. Moreover, studies reveal that curcumin also presented anti-inflammatory activity through inhibition of COX-2 in both rat primary microglial and murine BV2 microglial cells [170], suppressed iNOS and inhibited NF- κ B and AP-1 activation [171].

The flavonoid quercetin is also among the well-characterized polyphenols in terms of biological activity. It increased cell survival upon treatment with H₂O₂, hydroperoxide, tert-butyl hydroperoxide (TBHP), IL-1 β and PD related toxins [reviewed in [172, 173]. Pre-treatment of primary hippocampal cultures with quercetin significantly attenuated A β -induced cytotoxicity, protein oxidation, lipid peroxidation and apoptosis [174].

A limited number of studies have revealed the protective activity of other phenolics (see Table 2). Chlorogenic acid, a polyphenol present in coffee, was shown to protect cortical primary neurons against glutamate neurotoxicity, with potential for ischemic stroke treatment [175]. The 3-O-caffeoylquinic acid reduced neuroinflammation by reducing microglia mediated ROS production and neuronal excitotoxicity [176], whereas hesperetin, a flavanone glycoside abundant in citrus fruits, have also revealed neurprotective effects in mouse primary neurons [117] and in a rotenone-induced apoptosis human neuroblastoma SK-N-SH cells, considered a cellular model of PD [177]. Other study detected protective activity by less representative flavonoids (chrysin, puerarin, naringenin, genestein) in mesencephalic cultures from injury by MPP+ also a model of PD [173].

Cellular models are indispensable to understand the molecular mechanisms of polyphenols and how they affect

Table 1. Neuroprotective evidences (*in vitro*, cellular models and animals) for the most representative plant polyphenolic extracts.

Plant Extract	<i>In Vitro</i>	Cellular Models and Primary Cell Cultures	Animal Model
Ginkgo biloba/EGb 761	<ul style="list-style-type: none"> * Scavenged RNOS [112] and peroxy radicals [113] * Inhibited of Aβ peptide aggregation and destabilized of preformed fibrils [129] 	<ul style="list-style-type: none"> * Protected from neurotoxicity induced by Aβ in N2a [147] and PC12 cells [148] and in hippocampal neurons [149] * \downarrow Neuroinflammation [147] * Improved mitochondrial function [152] * Protection from oxidative stress [345] 	<p>AD rodent models:</p> <ul style="list-style-type: none"> * \uparrow spatial learning and memory [178] * \downarrow decreased APP in the cortex [179] <p>PD rodent models:</p> <ul style="list-style-type: none"> * Potent neuropreventive/neurorecovery effects against neurotoxicity induced by MPTP/MPP⁺ [180, 181, 219] <p>ALS rodent models:</p> <ul style="list-style-type: none"> * Impart neuroprotective effects [182] <p>Cerebral ischemia in rodents:</p> <ul style="list-style-type: none"> * Protects neuronal destruction in the hippocampus [183] <p>Hyperthermic brain injury:</p> <ul style="list-style-type: none"> * \downarrow Inducible nitric oxide synthase (iNOS) expression [346]
Green tea	<ul style="list-style-type: none"> * Scavenged RNOS [114] * Inhibited AChE [119] 	<ul style="list-style-type: none"> * Scavenging intracellular RNOS and induced endogenous antioxidant defences preventing DNA damage [114] * Protects primary rat cortical neurons against Aβ-induced cytotoxicity [150] 	<p>Ageing and neurodegeneration models:</p> <ul style="list-style-type: none"> * \downarrow Protein/lipid oxidation [184] * \uparrow Spatial learning [184] * Modulation of glutathione levels and antioxidant enzyme activities [185] * \uparrow CREB activation [185] * \uparrow BDNF and Bcl-2 levels [185] * \uparrow Cognitive and behavioural capacities [186] * Protects against deltamethrin-induced neurotoxicity in rat [187] <p>AD rodent models:</p> <ul style="list-style-type: none"> * \downarrow Aluminium chloride toxicity [220] <p>PD non-human primates model:</p> <ul style="list-style-type: none"> * Alleviate motor impairments, dopaminergic neuronal injury, and aSyn aggregation [188]
Grape seed extract and derivatives	<ul style="list-style-type: none"> * Inhibited Aβ aggregation and cytotoxicity [131] 	<ul style="list-style-type: none"> * \uparrow IL-6 and respective mRNAs in primary culture of astrocytes, which functions as a neuroprotective paracrine, protected neuronal cells from death by oxidative stress [347] * Protects neuronal cells against low extracellular Mg²⁺ concentration and oxygen glucose deprivation-induced neurotoxicity, in cultured rat hippocampal neurons mediated by inhibition of glutamate-induced calcium signaling and NO formation [348] 	<p>AD rodent model:</p> <ul style="list-style-type: none"> * \downarrow cognitive deterioration [103] * \uparrow cognitive function [189] * \downarrow oligomerization of Aβ peptides and amyloid plaques [103] * \downarrow microglial activation [190] * \downarrow extracellular-signal-regulated kinases (ERK) 1 and 2 in the brain, suppressing tau neuropathy [192] * Interferes with the assembly of Aβ peptides into neurotoxic aggregates [194] * \uparrow Spatial memory performance, \downarrow cognitive deterioration and Aβ neuropathy [195] <p>HD rodent model:</p> <ul style="list-style-type: none"> * Neuroprotective following oral administration [193]
Berries and anthocyanin rich extracts	<ul style="list-style-type: none"> * Inhibit the formation of Aβ peptide fibrils [130, 137-139] 	<ul style="list-style-type: none"> * \downarrow Toxicity of Aβ aggregates toward Neuro2a cells [130] * \uparrow Aβ aggregates clearance, \downarrow fibrillization and suppressed microglia activation, in murine cell cultures [153, 154] * Protection of neuronal cultures from oxidative stress [349] * \downarrow Neuroinflammation [155] * \downarrow Neuronal death in cells expressing Aβ by improving cellular metabolism [151] 	<p>Ageing and neurodegeneration rodent models:</p> <ul style="list-style-type: none"> * Reverse age related deficits in spatial working memory (\uparrowCREB activity, \uparrow BDNF, phosphorylation of hippocampal Akt, activation of TOR and \uparrow expression of Arc/Arg3.1 [196] * Delayed age-related motor and cognitive behavioural deficits [200, 201, 350, 351] <p>AD rodent model:</p> <ul style="list-style-type: none"> * \downarrow cognitive degeneration [130] * Reverses Aβ-induced effects on protein expression: mitochondrial apoptotic pathway (Bax, cytochrome C, caspase-9 and caspase-3) and AD markers (Aβ, APP, P-tau and BACE-1) [151] * Pomegranate juice oral intake improved spatial learning, and reduced Aβ plaques [202]

Table 2. Neuroprotective evidences (*in vitro*, cellular models and animals) for the most representative pure polyphenols.

Polyphenol	<i>In Vitro</i>	Cellular Models and Primary Cell Cultures	Animal Model
Cathecins (mainly EGCG)	<ul style="list-style-type: none"> * Prevent Aβ fibril formation [132] * Redirect the aggregation of αSyn monomers and remodel αSyn amyloid fibrils into disordered oligomers [132, 143] 	<ul style="list-style-type: none"> * \uparrow neuronal viability, modulation of signal transduction pathways and mitochondria functions [160] * \downarrow neurotoxins and Aβ toxicity in cell lines and primary cultures [162, 173, 186, 352-354] * \downarrow caspase activation mediated by Aβ in hippocampal neurons [162] 	<p>Ageing and neurodegeneration rodent models:</p> <ul style="list-style-type: none"> * Prevention of spatial learning and memory decline [203] * \uparrow life span [204]; * Prevention brain inflammation [355] <p>AD rodent model:</p> <ul style="list-style-type: none"> * \downarrow amyloidosis [102]; * Rescue memory impairment (\downarrow NF-κB pathway and \downarrow oxidative stress [161] * Restored mitochondria function in the brain hippocampus, cortex and striatum [206] <p>MS rodent model:</p> <ul style="list-style-type: none"> * Neuroprotective effects by modulating neuroinflammation and attenuating neural damage [205] <p>Cerebral ischemia rodent model:</p> <ul style="list-style-type: none"> * Ameliorated redox imbalance and limited inflammation [205] * EGCG improved age-related cognitive decline and protected against ischemia/reperfusion [221]
Resveratrol	<ul style="list-style-type: none"> * Inhibited the formation of Aβ peptide fibrils [130, 137-139] 	<ul style="list-style-type: none"> * \downarrow Aβ toxicity [163] * Modulation of NF-κB and SIRT1 pathways in cell models [163-165] 	<p>AD rodent model:</p> <ul style="list-style-type: none"> * \downarrow formation of amyloid plaques, without affecting APP levels [209] * Protection from Aβ neurotoxicity by inhibiting iNOS [222] * \downarrow hippocampal neurodegeneration [164] <p>PD rodent model:</p> <ul style="list-style-type: none"> * \downarrow neural inflammation (\downarrow mRNA levels of COX-2 and TNF-α in the <i>substantia nigra</i>) [210] * \downarrow oxidative stress, lipid peroxidation, and protein carbonyl [225] <p>HD rodent model:</p> <ul style="list-style-type: none"> * SIRT1 activation [214] <p>MS rodent model:</p> <ul style="list-style-type: none"> * \downarrow neural damage (\uparrow SIRT1) [212] * Prevention neural loss without immunosuppression [213] <p>Cerebral ischemia rodent model:</p> <ul style="list-style-type: none"> * Improve brain energy metabolism [223] * Modulation of the release of neurotransmitters and neuromodulators [224] <p>Non-human primate study: supplementation increased spatial memory performance [211]</p>
Curcumin	<ul style="list-style-type: none"> * Destabilized preformed αSyn fibrils [141] 	<ul style="list-style-type: none"> * Intracellular antioxidant activities and anti-amyloid activities [7, [168] and MPTP protective activity [169] * anti-inflammatory (\downarrowCOX-2) in both rat primary microglial and murine BV2 microglial cells [170] * \downarrow iNOS and inhibition of NF-κB and AP-1 activation [171] 	<p>AD rodent model:</p> <ul style="list-style-type: none"> * \downarrow Aβ plaques, oxidized proteins and Interleukin-1 beta (IL-1β) [141, 227] <p>HD rodent model:</p> <ul style="list-style-type: none"> * Counteract huntingtin aggregates formation and partial improvement of transcriptional deficits, as well as an amelioration of rearing deficits [215]

(Table 2) Contd....

Polyphenol	In Vitro	Cellular Models and Primary Cell Cultures	Animal Model
Quercetin	* ↓ α Syn fibrillization [142]	<ul style="list-style-type: none"> * ↓ Aβ induced cytotoxicity, protein oxidation, lipid peroxidation and apoptosis in cultured neurons [174] * Protected cells from oxidative insults, IL-1β and PD related toxins [172] * Control immune response via modulation of IL-1β and TNF-α and reduced the proliferation of peripheral blood mononuclear cells isolated from MS patients [356]. 	Neurodegeneration rodent models: <ul style="list-style-type: none"> * ↑ memory and synaptic plasticity upon chronic lead exposure [232] * Protection against colchicine-induced cognitive impairment [216] * Improved motor function in a model of acute spinal cord injury [228] AD rodent model: <ul style="list-style-type: none"> * ↑ Performance on learning and spatial memory tasks and greater risk assessment behaviour [233] * ↓ Extracellular β-amyloidosis, tauopathy, astrogliosis and microgliosis in the hippocampus and the amygdala [233] * ↓ Plaque burden and mitochondrial dysfunction (\uparrowAMPK activity) and \uparrow cognitive impairment [357] PD rodent model: <ul style="list-style-type: none"> * Neuroprotective by inducing antioxidant defences and ATPases [217] Cerebral ischemia rodent model: <ul style="list-style-type: none"> * ↓ Lesion [229] * ↓ Hippocampal neuronal death [230] * ↓ Apoptosis (activation of BDNF-TrkB-PI3K/Akt signalling pathway) [231]
Rosmarinic acid	* Scavenging peroxynitrite [115]	* Protects neurons from oxidative stress [235, 358]	AD and ALS rodent model: <ul style="list-style-type: none"> * Alleviated memory impairment, delayed disease onset and \uparrow lifespan [201, 234]
Hesperetin		<ul style="list-style-type: none"> * Cytoprotective effects in mouse primary neurons [117] * Cytoprotective in a cell model of PD induced by rotenone [177] 	AD rodent model: <ul style="list-style-type: none"> * Restore deficit in non-cognitive nesting ability and social interaction; attenuation on β-amyloid deposition, plaque associated APP expression, microglial activation and TGF-β immunoreactivity [218]

cellular homeostasis. By studying pure polyphenols in cellular models specific mechanisms could be followed and attributed to the target compound. However, only by pharmacological approaches can be consider the scenario of the presence of these compounds in neuronal tissues. Studies are lacking to evaluate the effects of nutritional metabolites at the brain cells. Yet, in order to design nutritional or pharmaceutical approaches using polyphenols, it is mandatory to translate their benefits into animal models, and to study their effects at the level of the whole organism.

In Vivo Animal Assays

Most of the evidences for neuroprotection in animal studies come from studies were foods or plant extracts are given orally to animals. Those are defined as nutritional (nutraceutical) interventions since polyphenols will cross the gastro-intestinal barrier and will be metabolized as dietary compounds. Only encapsulated compounds, intravenous or other forms of delivery were considered in a

pharmacological perspective. The reason for that is related with the significant impact that digestion and metabolism impose to the biological effects of polyphenols as described in the previous sections.

Nutritional/Nutraceutical Interventions

EGb 761 has been shown to exert a protective effect in many models of neurodegenerative pathologies. In an AD transgenic mice, oral intake of *G. biloba* extract improved spatial learning and memory [178], and decreased APP in the cortex [179]. In PD animal models, EGb 761 exerted potent neuropreventive/neurorecovery effects against neurotoxic induced by MPTP/MPP⁺ [180, 181]. Oral administration of EGb 761 improved motor performance and survival, and protected against a loss of spinal-cord anterior motor horn neurons, in a mouse model of ALS carrying a mutation in *SOD1* gene [182]. Protection was also observed in rodent models of cerebral ischemia and other neurodegenerative disorders [reviewed in [183].

Oral administration of green tea in animal models of ageing and of neurodegeneration prevented several dysfunctions, such as protein/lipid oxidation [184], improved spatial learning [184], modulated glutathione levels and antioxidant enzyme activities [185], increased cAMP response element-binding protein (CREB) activation [185], raised brain-derived neurotrophic factor (BDNF) and b-cell lymphoma 2 (Bcl-2) levels [185], as well as improved cognitive and behavioural capacities [186]. Oral ingestion of green tea extract also protected against deltamethrin-induced neurotoxicity in rat by improving the oxidative status and DNA fragmentation [187].

Interestingly, a recent study provided the first evidence that tea polyphenols administered by oral gavage alleviate motor impairments, dopaminergic neuronal injury, and cerebral α Syn aggregation in MPTP-intoxicated parkinsonian monkeys [188].

Another source of polyphenols in the stardom is grape and its derivatives. Oral ingestion of grape seed polyphenol extract improved cognitive function [189] and reduced cognitive deterioration [103], A β oligomerisation [103], amyloid plaques and microglial activation in animal models of AD [190]. Moreover, its incorporation in diet attenuated extracellular-signal-regulated kinases [191] 1 and 2 signalling in the brain, suppressing AD tau neuropathy [192]. Oral administration of grape seed also exhibited potential for HD treatment by improving lifespan in a *Drosophila* model and attenuating motor skill decay in a rodent model of HD [193]. Recent studies reported that rat intestinal microbial metabolites from grape seed extract accumulated in brains and interfered with the assembly of A β peptides into neurotoxic A β -amyloid aggregates, with relevance to AD pathogenesis [194]. A derivative of grape, red wine, was shown to increase spatial memory performance, reducing cognitive deterioration and A β neuropathy in an AD transgenic mouse model [195].

A blueberry-supplemented diet was also shown to reverse age-related deficits in spatial working memory through the increase of CREB activity, BDNF, the modulation of phosphorylation of hippocampal Akt, the activation of target of rapamycin (TOR), and the regulation of Arc/Arg3.1 [196]. To define the causal agents in the cognitive benefits of blueberry, the same authors tested diets with the pure flavanols, (-)-epicatechin and (+)-catechin and pure anthocyanins, and concluded that they were associated to the beneficial effects on memory in aged rats [197]. Furthermore, a diet containing blueberry anthocyanins prevented the cognitive degeneration in AD mice [130].

Intake of berries such as pomegranate, strawberry, blueberry and blackberry ameliorated several aspects of memory and learning [198], delayed age-related motor and cognitive behavioural deficits in rodent models [199-201]. Pomegranate juice oral intake also improved spatial learning, and reduced A β plaques in transgenic mice expressing A β -amyloid peptide [202]. In rats receiving anthocyanins orally, it was observed the reversion of A β -induced effects on the expression of proteins related with the mitochondrial apoptotic pathway (BCL2-associated X protein (Bax), cytochrome C, caspase-9 and caspase-3) and AD markers (A β , P-tau and

Beta-secretase 1 (BACE-1) [151]. Administration of a cocoa polyphenolic extract orally to aged rats delayed the onset of age-related cognitive deficits and increased lifespan with improvements in cognitive performances [51].

Several animal studies have been also performed for individual polyphenols present in the most neuroprotective extracts described earlier (catechins from tea, resveratrol from grapes and wine products, *etc.*) through dietary interventions. For instance, oral administration of catechin prevented spatial learning and memory decline in aged mice [203] and increased the lifespan in a senescence-accelerated mice model [204]. It also ameliorated redox imbalance and limited inflammation in rats with cerebral ischemia [205]. Catechin oral administration also rescued memory impairment induced by A β , through inhibition of the NF- κ B pathway, and mitigated oxidative stress in the brain [161]. Furthermore, EGCG oral intake restored mitochondria function in the brain hippocampus, cortex and striatum of a transgenic mouse model of AD [206]. An EGCG diet rescued transgenic mice of trisomy from morphogenesis defects, low BDNF levels and mnemonic deficits [207]. It also exhibited neuroprotective effects by modulating neuroinflammation and attenuating neural damage in an *in vivo* model of multiple sclerosis (MS) (gavage administration) [208].

In an animal model overexpressing APP, a resveratrol rich diet reduced the formation of amyloid plaques, without affecting amyloid peptide levels [209]. Furthermore, oral administration of resveratrol exhibited a positive effect in PD animal models, as it reduced neural inflammation by lowering mRNA levels of COX-2 and tumour necrosis factor (TNF- α) mRNA in the *substantia nigra* [210]. In a non-human primate, diet supplementation with resveratrol for 18 months increased spatial memory performance compared to placebo [211]. In agreement with this, in animal models of MS, resveratrol oral intake was found to attenuate neural damage through SIRT1 activation [212] and prevented neural loss without immunosuppression [213]. Regarding HD, oral gavage of resveratrol also shown a beneficial effect via SIRT1 activation in a transgenic mouse model [214].

Curcumin also reduced A β plaques, oxidized proteins and Interleukin-1 beta (IL-1 β) in AD transgenic mice, by administrating curcumin to diet [141], whereas it counteracted HD aggregates formation [215].

Quercetin protects against colchicine-induced memory impairment and oxidative damage in rats [216]. In PD *in vivo* models, quercetin oral administration showed to be neuroprotective by inducing antioxidant defences and ATPases [217].

Hesperidin, a flavanone glycoside found abundantly in citrus fruits, was orally given to a transgenic mouse model of cerebral amyloidosis for AD [218]. Fascinatingly, after a relatively short-term treatment of 10 days, hesperidin significantly restored deficits in non-cognitive nesting ability and social interaction. A significant attenuation on β -amyloid deposition, plaque associated amyloid peptide expression, microglial activation and transforming growth factor beta (TGF- β) immunoreactivity was observed in the brains of mice [218].

Pharmacological Interventions

Several attempts were done with a more pharmacological approach, by direct injection of bioactive polyphenols to the organism with the aim to circumvent its metabolism and improving their efficacy. Some examples are explored below in this section.

In a mice model of PD, EGb 761 administered by intraperitoneal injection before or after MPTP treatment protects against nigrostriatal dopaminergic neurotoxicity involving the inhibition of brain monoamine oxidase [219].

Green tea extract injected into the hippocampus region of rat brain reduced aluminium chloride toxicity, associated with AD [220]. In animal models, EGCG administered by intraperitoneal injection improved age-related cognitive decline and protected against ischemia/reperfusion [221] as well from amyloidosis in AD mice models [102].

In an AD mouse model injected with A β , intracerebroventricular injection of resveratrol protected from A β neurotoxicity by inhibiting iNOS [222]. Reduced hippocampal neurodegeneration has also been shown after intracerebroventricular injection of resveratrol in rodent models of AD/tauopathies [164]. In rat models of ischemic injury, intraperitoneal injection with resveratrol improved brain energy metabolism [223], along with modulation of the release of neurotransmitters and neuromodulators [224]. Resveratrol was also tested by intraperitoneal injection on a 6-hydroxydopamine (6-OHDA)-induced Parkinson's disease (PD) in rats and revealed attenuation of oxidative stress, lipid peroxidation, and protein carbonyl content [225]. Recently, resveratrol was shown to reduce cell death in ovariectomized female rats subjected to chronic cerebral hypoperfusion [226].

Notably, curcumin when injected in the tail vein of an AD rodent model was able to cross the BBB, target and disrupt existing plaques in [227] and also reduced A β plaques, oxidized proteins and IL-1 β in AD transgenic mice [141].

Intraperitoneal administration of quercetin improved motor function in a model of acute spinal cord injury [228], reduced ischemic lesion [229], as well as hippocampal neuronal death [230], and cell apoptosis in a rat model of cerebral ischemia [231]. By the same route, quercetin improved memory and synaptic plasticity upon chronic lead exposure in rats [232]. In a triple transgenic AD model, quercetin was able to reverse the histopathological hallmarks of AD and to ameliorate cognitive and emotional impairments [233].

A rosemary phytochemical, rosmarinic acid, alleviated memory impairment mediated by A β , delayed disease onset and increased lifespan in AD mouse models [234]. Rosemary extract and rosmarinic acid also prevented ALS degeneration in mouse models of the disease after intraperitoneal injection [201]. Carnosic acid, also present in rosemary, crossed BBB and preserved GSH levels in mouse models of ischemia/reperfusion after intraperitoneal injection [235].

An integrated view of *in vitro*, cellular and animal model studies either with food or plant extracts (Table 1) or pure compounds (Table 2) reveals the whole panorama of knowledge gathered for polyphenols, and clearly reinforces

their neuroprotective potential. Although human trials are more reliable and the closest approach to human physiology, they are time and cost consuming. The animal *in vivo* and cellular assays have constituted an unparalleled tool to dissect mechanisms of action, and for genetic and compound screening assays. On the other hand, the *in vitro* assays are crucial to understand the interaction of polyphenols with proteins, metals or other small molecules, by excluding cell components interference and serving as a fundamental tool to tune the overall picture revealed by cell studies.

Human Trials

Human clinical trials to ascertain the impact of polyphenols in neurodegenerative diseases and ageing are still very scarce. Although allusive of a protective role in neurodegeneration, there is still too many fragmented evidences to build an integrated picture with the mechanistic studies.

Most of the human trials with *G. biloba* were inconclusive [236] and its long-term oral intake did not affect the prevalence of cerebral A β deposition [237]. Nevertheless, recently, positive results were obtained with *G. biloba* extract in ischemic stroke [238] and in children with attention deficit hyperactivity disorder [239]. A recent systematic review and meta-analysis about the efficacy and adverse effects of *G. biloba* for cognitive impairment and dementia concluded that it stabilizes or decelerates the decline in cognition, function and behaviour, at 22-26 weeks administration, especially for patients with neuropsychiatric symptoms [240].

Concerning green tea extracts, human studies revealed the increase of brain activity in the dorsolateral prefrontal cortex, an area involved in memory processing [241]. Recently, consumption of green and black tea by healthy volunteers increased the brain theta waves as measured by a simplified electroencephalogram, suggesting a role in cognitive function, specifically alertness and attention [242]. Moreover, EGCG reduced cognitive deficits in a pilot study with Down syndrome individuals, with effects on memory recognition, working memory and quality of life [243].

Recently, Brickman and co-workers [65] reported that a high cocoa flavanol-containing diet over 3 months enhanced memory function and improved related activation in the dentate gyrus, the hippocampus region characterized by life-long neurogenesis, in comparison to a cocoa diet low in flavanol, in a randomized study with healthy old subjects using functional magnetic resonance imaging (MRI). In the Cocoa Cognition and Ageing (CoCoA) study, consumption of cocoa flavonols for 8 weeks improved cognitive performance in a group of cognitively intact older adults [244].

In an intervention study, blueberry juice supplementation improved memory in older adults [68]. Also, supplementation with Concord grape juice enhanced neurocognitive function in older adults with pre-described mild cognitive impairments, which was supported by studies on brain activity using functional magnetic resonance imaging [245].

There are several studies examining flavanols and anthocyanins neuroprotective properties in humans but little investigation into the flavonoid subclass known as flavanones.

This is an incredible gap because orange juice, a rich source of flavanones, is one of the most-commonly consumed juices throughout the world. A recent study evaluated the consumption of flavanone-rich orange juice over 8 weeks and concluded that there was an association with benefits for global cognitive function in healthy older adults, in comparison to the consumption of a low-flavanone control juice [246]. Moreover, the same authors observed that ingestion of a flavonoid-rich orange juice promoted acute cognitive benefits over 6 h in healthy middle-aged adults [247].

Only a few placebo-controlled interventional studies are available to date concerning resveratrol cognitive improvements. Kennedy *et al.* (2010) [248] assessed the effects of oral administration of resveratrol on cognitive performance, in a randomized control trial crossover study in 22 healthy adults, with the result that even single doses of orally administered resveratrol could modulate cerebral blood flow variables, measured using MRI [248].

A recent study examined the effects of curcumin on cognition and mood in a healthy older population. Working memory and mood were significantly improved following 4 weeks treatment, confirming the potential psychological and cognitive benefits of curcumin in an older population [249].

On the other hand, a contradictory study in a large community sample, with a 12-week supplementation of quercetin, provided evidence that quercetin may not have an ergogenic effect on neurocognitive functioning [250], consistent with a growing body of literature raising concerns about the generalization of findings from *in vitro* and animal quercetin research to human populations.

Some human studies have been performed for dietary formulations that include mixtures of polyphenols or polyphenols with other compounds, highlighting possible synergies between constituents. For instance, in a double-blind, clinical trial with older adults by Small and colleagues [251], the intake of a pill-based nutraceutical that contained a proprietary formulation of blueberry, green tea, carnosine, vitamin D3 and biotin, resulted in significantly increased processing speed. Also, in healthy overweight older individuals, a daily intake of a formulation containing resveratrol and quercetin significantly improved memory performance [252].

However, for polyphenols to reach the brain they have to be able to cross BBB. An increasing body of evidence regarding this subject has been collected and discussed in the next chapter.

POLYPHENOLS AND RESTRAINS: INTERACTION WITH BARRIERS AND BEYOND

The extensive metabolism to which dietary polyphenols are submitted once ingested, either in the intestine, liver and or in cells, leads to the arise of a broad range of polyphenol derivatives. Despite accumulating evidence concerning polyphenols neuroprotection (see Tables 1 and 2), and assuming the effective transport/distribution/delivery of dietary polyphenol metabolites to target tissues, we also need consider the existence of other barriers that must be crossed

by these polyphenols metabolites or, at least, be able to alter the surrounding environment in order to induce responses in the target organs.

Blood-Brain Barrier

The existence of three layers of barrier at the CNS limits and regulates molecular exchanges between the blood and the neuronal tissue, or its fluidic spaces: i) the BBB, majorly constituted by cerebrovascular endothelial cells, located between the blood and the brain interstitial fluid; ii) the choroid plexus epithelium, located between the blood and ventricular cerebrospinal fluid; iii) and the arachnoid epithelium, located between the blood and subarachnoid cerebrospinal fluid [3]. In particular, the choroid plexus is responsible for the transport of vitamins, small peptides, amino acids, inorganic ions and hormones to the cerebrospinal fluid [253]. Among the different barriers of the CNS, the BBB exerts the highest control over the close microenvironment of brain cells, since its surface area is 5000 times larger than the blood-cerebrospinal fluid barrier, having a dominant role in providing nutrients for the brain, as well as controlling metabolites, like polyphenols, accessibility to neuronal cells [254].

The BBB is a dynamically selective and complex interface, protecting the CNS from toxic compounds and pathogens, acting as a border between the periphery and the brain [255]. Besides the microvascular endothelial cells that comprise the anatomical basis of the BBB, it is surrounded and interacts with pericytes, astrocytic endfeet, microglia and neurons, which constitute the neurovascular unit (Fig. 5) [254, 256, 257]. The neurovascular unit complexity, together with the tight control exerted by the brain endothelium due to the presence of intracellular tight junctions, lack of fenestrations, low pinocytotic activity and efflux pumps, controls the passage of the smallest polar molecules and macromolecules [254, 258, 259] (Fig. 5). Polyphenols are no exception, in order for them or their metabolites to access the brain, they must cross a tightly regulated, selectively permeable endothelial layer. As a growing number of biological effects have been attributed to these molecules in the past few years, attention to their role as modulators of the transport capacity of epithelial barriers has also received great attention.

Youdim and co-workers have elucidated the polyphenols permeation through the BBB [260, 261]. They suggested that polyphenols transmembrane diffusion *in vitro* is related with its lipophilicity, where less polar derivatives (*e.g.* methylated derivatives) are capable of higher brain uptake than more polar metabolites (*e.g.* sulphated and glucuronides). Accumulating evidence of polyphenols uptake by the BBB reinforces their putative potential in a neurological context. Nevertheless, it is not yet totally clear whether the primary route by which polyphenols cross the BBB is simple diffusion or carrier-mediated transport [262]. To date, only a few compounds from each flavonoid subclasses have been studied, and there is limited knowledge on the effects of flavonoid structure on their bioavailability at the brain level. Therefore, the true mechanisms by which flavonoids and their circulating

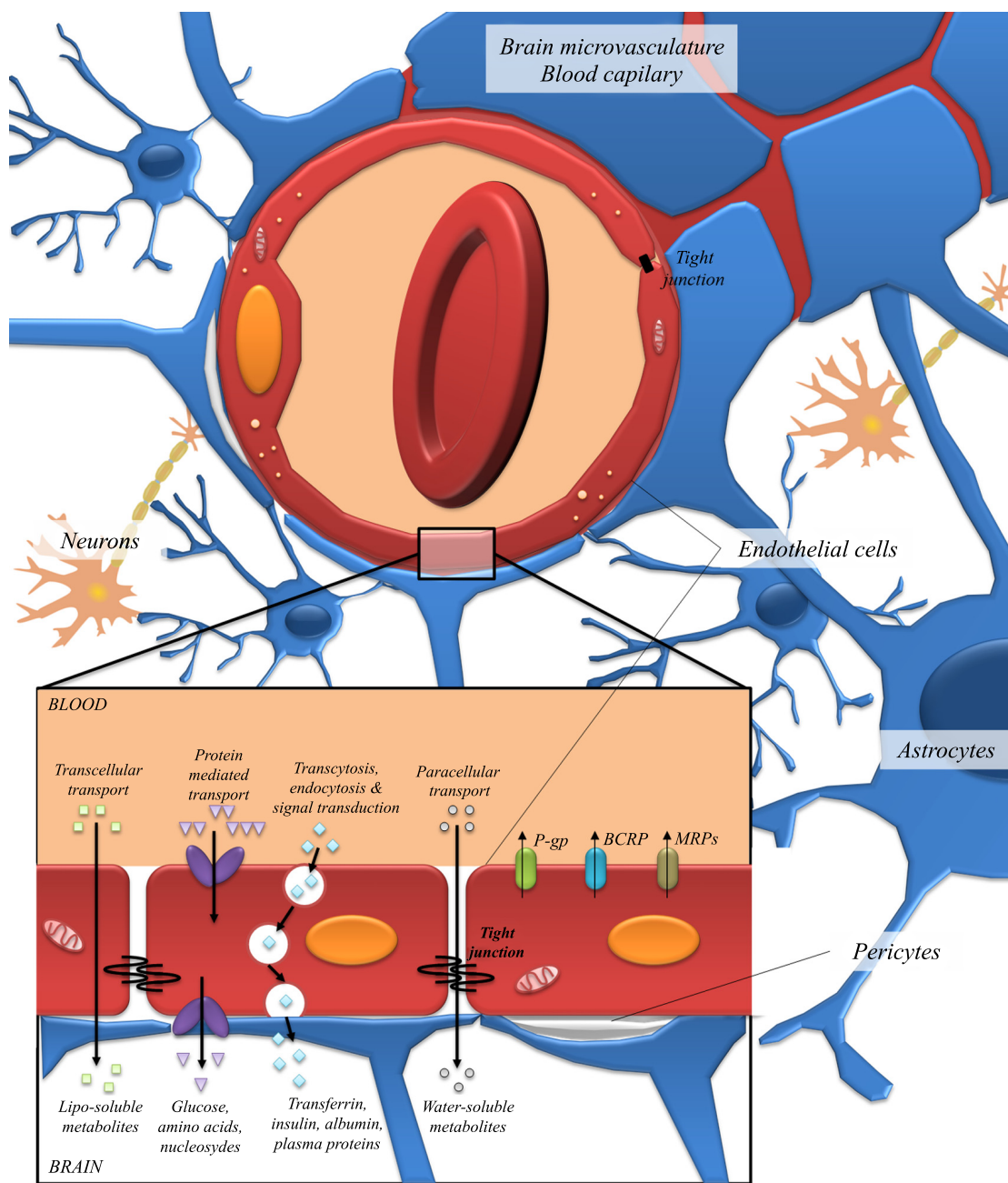


Fig. (5). The neurovascular unit. The BBB is composed by endothelial cells, astrocytes and pericytes, where endothelial cells form a boundary between the blood and the CNS. The flux of nutrients and metabolites from the blood to the CNS is regulated by the BBB, which controls their availability by transport systems. Transport across the BBB occurs via several pathways: lipid-mediated diffusion (transcellular transport), paracellular diffusion, carrier-mediated transport through proteins, receptor-mediated transcytosis and absorptive-mediated transcytosis. Besides these pathways, active efflux transport through ABC transporters such as P-gp, BCRP and MRPs family also takes place, in order to prevent the entry and accumulation of harmful substances to the brain.

metabolites interact with the BBB remain a hot topic in neuroscience research.

Considering polyphenol and their metabolites permeability across the BBB, the existence of different specialized transporters in the plasma membranes of luminal (blood) and abluminal (brain) sides of the endothelial cells should be taken into account. The endothelial cells permeability to polyphenols is particularly influenced by the expression profile, functionality and precise location/orientation of efflux

transporters, solute carriers and organic-anionic transporters [263]. Nevertheless, there are strong evidences of the effective capacity of polyphenols to reach the brain and exert neuroprotection, and it is an ever-growing field of investigation (Table 3).

In terms of uptake, there is evidence suggesting that transport mediated by glucose transporter 1 (GLUT1), organic anion transporters (OATs) and organic anion-transporting polypeptide (OATP1A2) may affect the distribution of

Table 3. Evidences of polyphenol transport at the BBB and neuroprotective potential, concerning interaction studies with ABC efflux transporters expressed in endothelial cells at the BBB. P-gp - P-glycoprotein, MRP - multidrug resistant protein, BCRP - breast cancer resistant protein, BMEC - brain microvascular endothelial cells, TR-rats - transport deficient rats.

Polyphenol	Evidence of BBB Penetration	Evidence of Neuroprotection	Efflux Transporter Interaction	Experimental Setup	Refs.
Apigenin	Yes [307]	Yes [307]	P-gp inhibitor	Rat BMEC	[307]
			P-gp inhibitor	CCRF-CEM, CEM/ADR5000 leukemia cells	[308]
			BCRP inhibitor	MDA-MB-231-BCRP cells	[308]
Catechin / epicatechin	Yes [278]	Yes [309, 310]	P-gp activator	NIH-3T3-G185 cells	[189]
			MRP2 substrate	Caco-2 cells	[311]
			MRP1/MRP2 substrate	MDCKII/MRP1 cells & MDCKII/MRP2 cells	[312]
Chrysin	N. D.	Yes [313, 314]	P-gp inhibitor	Mouse BMEC	[315]
			MRP2 substrate	Caco-2 cells	[316]
			BCRP inhibitor	MCF-7 MX100 cells	[317]
Curcumin	Yes [227]	Yes [318]	P-gp inhibitor	MCF-7 cells	[319]
			BCRP inhibitor	Rat brain capillaries	[320]
Fisetin	Yes [321]	Yes [321]	MRPs inhibitor	Caco-2 cells	[322]
Genistein	Yes [323]	Yes [324, 325]	P-gp inhibitor	MCF7/BC19-3, rats	[326, 327]
			MRP2 inhibitor	TR-rats	[328]
			BCRP inhibitor	K562/BCRP cells	[329]
Hesperitin	Yes [260]	Yes [330]	P-gp inhibitor	Mouse BMEC	[315]
			BCRP inhibitor	ABCG2 over-expressing cells	[331]
Kaempferol	Yes [307]	Yes [332]	P-gp inhibitor	Mouse BMEC	[315]
			MRPs inhibitor	Human glioblastoma cell line T98G	[333]
			BCRP inhibitor	MDCK/Bcrp1 cells	[334]
Myricetin	Yes [335]	Yes [335]	P-gp inhibitor	MCF-7/ADR cells	[336]
			BCRP inhibitor	HEK293/ABCG2 cells	[280]
Naringenin	Yes [287, 337]	Yes [338]	P-gp inhibitor	Mouse BMEC	[315]
			MRPs inhibitor	HEK293/ABCG2 cells	[280]
Quercetin	Yes [261]	Yes [339]	P-gp inhibitor	Mouse BMEC	[315]
			MRPs inhibitor	HEK293/MRP1, HEK/MRP4, HEK/MRP5 cells	[340]
			BCRP inhibitor	ABCG2 over-expressing cells	[331]
Resveratrol	Yes [341]	Yes [342]	P-gp inhibitor	MCF-7/ADR cells	[343]
			BCRP inhibitor	ABCG2 over-expressing cells	[331]
Rutin	Yes [307]	Yes [344]	P-gp inhibitor	Rat BMEC	[307]

flavonoid glucuronides into the brain, in a similar fashion to other glucuronidated metabolites [264, 265]. In fact, the presence of these glucuronidated metabolites can be partially derived, due to the high expression of both GLUT1 and OAT1A2 on both luminal and abluminal membrane of

endothelial cells. In a recent study, the authors successfully localized quercetin-3-O-glucuronide, a major phase-II metabolite of quercetin, in human brain tissue, namely at epithelial cells of the choroid plexus and also in macrophages [266].

Microdialysis sampling in rats also showed that (+)-catechin and (-)-epicatechin could pass through the BBB [267]. In fact, several polyphenols have been identified in different brain regions of the rat [268, 269] and pig [270, 271], usually accumulating in a nonregion-specific manner [272]. Several animal studies also indicate that polyphenols are able to cross the BBB and co-localize within the brain tissues independently of their route of administration: epigallocatechin gallate [273], epicatechin [274], and anthocyanins [269, 275] were detected in the brain after oral administration; naringenin and its glucuronide were identified in the cerebral cortex, after intravenous administration [276], and intravenously administered hesperetin was also detected in the brain, especially in the striatum [277].

Another study has examined the permeability of flavonoids and their known circulating metabolites across an *in vitro* model of the BBB [260]. Hesperetin, naringenin, and their respective *in vivo* glucuronides, as well as the anthocyanins cyanidin-3-rutinoside and pelargonidin-3-glucoside, all showed measurable permeability. In another study, both catechin and epicatechin could cross a cellular model of BBB in a time-dependent and stereo-selective manner, with epicatechin presenting a substantially higher transport than catechin [278]. *In vitro* transmembrane transport of different flavonoids (flavonols, flavan-3-ols and anthocyanins) and some of their methylated and glucuronidated metabolites was also observed, where in most cases the metabolites exhibited higher transport efficiency than their parent compounds [279]. All these collected data strongly suggests the effective uptake of dietary polyphenols and their metabolites through the BBB endothelium, reinforcing their ultimate neuroprotective potential.

Polyphenols as Modulators of Membrane Transport

Importantly, polyphenols have also shown to be able to modulate the activity of some ATP-binding cassette transporters (ABC transporters). The ABC transporters are efflux pumps responsible for controlling the bioavailability of many xenobiotics, being vastly present in the epithelia of the gut, placenta and BBB, as well as in cancer cells. Cancer cells tend to overexpress these ABC transporters, which confers them bigger resistance to chemotherapy [280].

Several studies have demonstrated inhibition of ABC transporters by flavonoids (Table 3). The interaction between flavonoids and ABC-transporters could be advantageous for poorly absorbed drugs; otherwise, this interaction could also lead to drug intoxication, particularly in the context of drugs with a narrow therapeutic window. Additionally, some flavonoids are themselves substrates of the most pharmacologically relevant ABC transporters: P-gp, multidrug resistant protein type 2 (MRP2) and breast cancer resistant protein (BCRP) [281].

For example, it was shown that extracts from St John's Wort upregulate the expression of P-gp at intestinal level, which could ultimately reduce the bioavailability of substrate pharmaceuticals [282]. On the other hand, diterpenes, triterpenes and carotenoids, naturally occurring lipophilic phytochemicals, were able to inhibit human P-gp *in vitro* at a low range, while other combinations had a synergistic

activity [146, 283]. Quercetin, hypericin and kaempferol were shown to promote the cellular uptake of ritonavir on P-gp overexpressing cells [284]. Besides, both *in vitro* and *in vivo* assays (only with short-term exposure) with these polyphenols inhibited the action of efflux pumps and increased substrate bioavailability; *in vivo* assays of chronic exposure boosted the expression of P-gp and lead to a reducing bioavailability of substrate drugs [285, 286].

Besides their modulation of ABC transporter function, polyphenols can also be substrates of these transporters, a property that can dramatically limit their bioavailability. Youdim and co-workers have showed the limitations that quercetin has to BBB transposition: when co-administrated with a P-gp or BCRP inhibitor, this polyphenol was able to enter epithelial cells of the BBB, possibly by passive diffusion due to its hydrophobicity, but was then specifically exported by the BCRP [260]. Such phenomenon explains, at least in some extent, why quercetin and resveratrol presented very limited bioavailability, despite the amount ingested [287, 288].

Taking all this information into account, it could be interesting to explore the combination of an inhibitor of the ABC transporters and a beneficial polyphenol, in order to increase the accumulation of such polyphenol in the target region and potentiate its efficiency. The co-administration of a quercetin-rich product and an inhibitor of BCRP may increase quercetin's access into the brain and then unleash novel bioactivities from this polyphenol [289]. In addition, if the inhibitors of ABC transporters themselves are orally bioavailable, they may assist polyphenols transport through the BBB [261].

Blood-Testis Barrier & Placenta

Besides brain integrity, mainly protected by the presence of the BBB, the insurance of life perpetuation and preservation must not be disrupted by foreign molecules in the human body. The presence of barriers protect germ cells and foetus, saving from harm the new life-to-be inside pharmacological sanctuaries. These pharmacological sanctuaries have highly restricted access to exogenous compounds, and where polyphenols, contrarily to other metabolites, may have an open door.

The blood-testis barrier (BTB) is one of the tightest blood-tissue barriers in the mammalian body and it separates the seminiferous epithelium into the basal and the apical compartments [290]. A specialized and unique micro-environment is safeguarded by the BTB, where meiosis, spermiogenesis and spermiation occur. BTB controls the entry of nutritional compounds, vital molecules (such as hormones and electrolytes) and also harmful toxicants, into the compartment in which post-meiotic germ cell development takes place [290].

On the other hand, the placenta constitutes the link between the mother and the developing foetus, performing several strict functions that are essential for the maintenance of pregnancy and normal foetal development. The placenta mediates the uptake of nutrients between the mother and the foetus, eliminating metabolic waste fetal products. This

capacity is mediated due to the presence of transporters at the maternal-facing brush-border membrane and at the foetal-facing epithelial basal membrane. It is the activity of these specialized transporters that will largely determine the extent at which organic compounds will cross the placenta and enter the foetal blood circulation [291].

Recently, it was demonstrated that prenatal stress can reduce mitochondrial content and antioxidative capacity, while increasing oxidative stress in the hippocampus of offspring, contributes to decreased neurogenesis and cognitive function. Impressively, maternal hydroxytyrosol administration successfully promoted cognitive function, through modulation of mitochondrial content and phase II enzymes in the progeny [292]. Such observations evidence that the drastic alterations that polyphenol supplementation induce are more dramatic than what was initially thought: the effects of polyphenols are transversal, affecting not only the animal itself but also its offspring, leading to benefits that can only be explained by its capacity to cross the placenta.

Neuroprotective effects of resveratrol on prenatal stress were also investigated in the brain of neonatal rats. Administration of resveratrol during pregnancy inverted the memory impairment caused by prenatal stress, as well as the oxidative damage and loss of neurons at the dentate gyrus [293].

Already in 2005 such kind of neuroprotective potential in neonatal brains was assessed. It was seen that maternal dietary supplementation with pomegranate juice was neuroprotective in an animal model of neonatal hypoxic-ischemic brain injury [294]. This dietary supplementation resulted in markedly decreased brain tissue loss, with the highest pomegranate juice dose having substantial statistical significance ($p \leq 0.001$). Pomegranate juice also diminished caspase-3 activation in the hippocampus and in the cortex. Ellagic acid, a polyphenolic component in pomegranate juice, was detected in plasma from treated pups but not in control pups [294].

Contrarily, other authors showed that flavanol metabolites were abundant in maternal placenta but were detected at low levels in foetuses and amniotic fluid. This study was performed in pregnant rats subjected to acute intake of a grape seed proanthocyanidin extract [295]. Additionally, flavanol metabolism appears to be less active in the liver during pregnancy, and altogether the data suggests that transport across the placenta is not efficient for flavanols and their metabolites, where the placenta seems to act as a barrier. However, these compounds target the foetus and are excreted in the amniotic fluid [295].

Beyond the putative neuroprotective effects of polyphenols to the offspring, in a study of Keating and co-workers [296] it was evidenced the benefits on folic acid absorption, once folic acid is critically important for normal foetal development. The authors suggested a detrimental effect of short-term exposure to epicatechin and isoxanthohumol on placental folic acid absorption and, on the other hand, a beneficial effect of a long-term exposure to xanthohumol, isoxanthohumol and quercetin on folic acid absorption at the

placental level [296]. The effect of isolated polyphenols on placental transport of glucose was studied as well: several polyphenolics compounds were found to affect the apical uptake of deoxy-D-glucose in a trophoblast cell model. Rutin, catechin and epicatechin increased deoxy-D-glucose uptake and, when tested in a long-term exposure (48 h) rutin and myricetin increased apical uptake of deoxy-D-glucose. This observation was true for the isolated compounds or the combination of both. Chrysin and quercetin decreased deoxy-D-glucose uptake in a concentration dependent manner [297].

Moreover, several studies highlighted the protective potential of polyphenols in ensuring the integrity of germ cells. It was found that, in irradiated tests, EGCG ameliorates several parameters related to spermatogenesis in mice [298]. This study determined the effects before and after radiation treatment on spermatogenesis in the testicles: pre-treatment seems to be crucial to protect spermatogenesis against radiation, while post-treatment appears to be able to support spermatogenic rescue from radiation [298]. Altogether, EGCG seems to prevent germ cells from radiation-induced cell death by multiple mechanisms, and the use of this bioactive polyphenol can present an attractive strategy to preserve fertility in males exposed to conventional radiation therapy [298].

In another study, the administration of 10 μmol [3H] epicatechin to rats resulted in major amounts of radioactivity in the large intestine and caecum at 24 h, and little radioactivity was observed in the stomach, plasma, small intestine, blood and testes [299]. The relatively high concentration of epicatechin metabolites found in the testes of rats subjected to a cocoa-enriched diet (mainly epicatechin glucuronide), highlighted the BTB putative permeability to this polyphenol metabolite, and shows that its accumulation could occur [300].

Beyond Barriers

In the light of today's knowledge, novel mechanisms of action for polyphenols are proposed far beyond the classical direct antioxidant radical scavenging power. In fact, polyphenol concentration at cerebrospinal fluid rarely exceeds 1-5 μmol . Therefore, it is highly improbable that polyphenol intracellular concentrations in neurons and glial cells would exceed the micromolar-nanomolar range, which is not enough to exert significant direct antioxidant effects. Nevertheless, such concentrations are in fact beneficial, pointing out that polyphenols and their metabolites modulate other cellular parameters and pathways at the CNS level, even at low concentrations [262].

The noteworthy effect of polyphenols and their metabolites in cellular signalling pathways at concentrations as low as 1 μmol has been reported already [301], reinforcing the idea of indirect mechanisms that could be involved in polyphenols neuroprotection. The activation of hormetic responses and effects on peripheral systems of the body, that culminate in changes in the CNS function are the proposed indirect mechanisms of action of polyphenols and degradation metabolites. Hormesis describes a process in which exposure to a low dose of an agent, that is toxic at higher doses,

induces a beneficial effect on the cell or organism [301]. Direct evidence for hormesis induction *in vivo* has already been reported in mammals: pre-treatment of mice with epicatechin significantly reduced the negative impact of stroke induction in wild-type but not nuclear factor erythroid 2 (Nrf2) knock-out animals, as the transcription factor Nrf2 is one of the key regulators responsible for the induction of antioxidant and cell protective genes [302]. Additionally, the regulation of brain integrity and function must not be seen as an isolated process, but instead as strongly dependent on feedback information (in the form of hormones, nutrients, metabolites and, of course, sensory neuron signalling of the body periphery).

Furthermore, evidences of the metabolism of polyphenols at the BBB level has already been reported with the detection of the compounds conjugated with glucuronic acid [278]. The hypothesis that polyphenol metabolites resulting from biotransformation in endothelial cells, are the key actors in neuroprotection, arises as a novel creed in a nutritional/nutraceutical perspective. The physiological role of conjugated-flavonoids is discussible, but there is the possibility of their presence in the extracellular fluid in the CNS, and exerting biological effects. In fact, some reports have suggested that flavonoid metabolites possess more biological activity than the intact form [303, 304]. Noteworthy, biotransformation processes may constitute an essential step to convert polyphenols into more water-soluble metabolites, and subsequently facilitate its elimination from the body or, oppositely, allow an easier xenobiotic transport and delivery around the body.

In a pioneer pharmacokinetics study, 23 polyphenols microbial metabolites were administered intravenously to rats, to reliably reproduce a physiological post absorption situation [305]. Remarkably, the brain was found to be a specific target organ for 10 of the 23 polyphenol metabolites injected, which significantly increased in the treated animals and most compounds were excreted into the urine [305].

In that sense, it is imperative to adjust the study of polyphenols beyond the reductionist dogma of polyphenol-effect: research should focus not only in the study of polyphenols but also the metabolites arising from digestion and metabolism. Dietary and colonic metabolites derived from polyphenols present in foods and drinks can reach considerable concentrations in circulation, usually higher than their parent compounds, and such physiologically-relevant concentrations must be studied, taking into account the multiplicity of interactions inside the human body as an overall beneficial outcome to the CNS.

CONCLUSION

The diversity and holistic properties of polyphenol present them as an attractive alternative for the treatment of multifactorial diseases, where a multitude of cellular pathways are disrupted. The main findings regarding polyphenols neuroprotective potential performed using *in vitro*, cellular and animal studies, as well as human trials are covered in this review. The underlying mechanisms of polyphenols for nutrition or therapeutic applications must be further consolidated, however there is strong evidence of their beneficial impact on brain function during ageing. Nevertheless, there is an

unmet need for clinical trials regarding polyphenols in the context of neurodegenerative diseases [63, 306]. Pandora's box is ajar and new evidence are revealing polyphenols impact in the brain beyond barriers. Offspring cognitive improvements after maternal ingestion of polyphenols is a new amazing unexplored route of effects. Understanding how the presence of polyphenols during embryonic development impacts in infancy, adult and advanced life is still an enigma to solve.

LIST OF ABBREVIATIONS

ABC	=	ATP-binding cassette
Ach	=	Acetylcholine
AChE	=	Acetylcholinesterase
AD	=	Alzheimer's disease
ALS	=	Amyotrophic lateral sclerosis
ASIC1A	=	Acid sensing ion channel 1A
BACE-1	=	Beta-secretase 1
Bax	=	BCL2-associated X protein
BBB	=	Blood-brain barrier
Bcl-2	=	B-cell lymphoma 2 (Bcl-2)
BCRP	=	Breast cancer resistant protein
BDNF	=	Brain-derived neurotrophic factor
BTB	=	Blood-testis barrier
CBG	=	Cytosolic β -glucosidase
CNS	=	Central nervous system
CoCoA	=	Cocoa, cognition, and ageing
COX-2	=	Cyclooxygenase-2
CREB	=	cAMP response element-binding protein
EGCG	=	Epigallocatechin gallate
ERK	=	Extracellular-signal-regulated kinases
FUS/TLS	=	Fused in sarcoma/translocated in Liposarcoma
GDP	=	Gross domestic product
GLUT1	=	Glucose transporter 1
GSH	=	Glutathione
HD	=	Huntington's disease
Htt	=	Huntingtin
IL-1 β	=	Interleukin-1 beta
iNOS	=	Inducible nitric oxide synthase
LPH	=	Lactase phloridzin hydrolase
MeDi	=	Mediterranean diet
mhGAP	=	Mental health gap action program
MMPs	=	Metalloproteinases

MPTP	=	1-methyl-4-phenyl-1,2,3,6-tetrahydro-pyridine
MRI	=	Magnetic resonance imaging
MRP2	=	Multidrug resistant protein type 2
MS	=	Multiple sclerosis
NDs	=	Neurodegenerative disorders
NF-kB	=	Nuclear factor kappa B
Nrf2	=	Nuclear factor erythroid 2
OATP	=	Organic anion-transporting polypeptide
OATs	=	Organic anion transporters
P-gp	=	P-glycoprotein
PD	=	Parkinson's disease
PolyQ	=	Polyglutamine
RNOS	=	Reactive nitrogen and oxygen species
ROS	=	Reactive oxygen species
SIRT1	=	Silent mating type information regulation 2 homolog 1
SLC	=	Solute carrier
TBHP	=	Tert-butyl hydroperoxide
TGF- β	=	Transforming growth factor beta
TNF- α	=	Tumor necrosis factor
TOR	=	Target of rapamycin
WHO	=	World health organization
α Syn	=	α -Synuclein

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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