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Review Article

A POSSIBLE EMERGING ROLE OF PHYTOCHEMICALS IN IMPROVING AGE-RELATED NEUROLOGICAL DYSFUNCTIONS: A MULTIPLICITY OF EFFECTS

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Abstract—It is rare to see a day pass in which we are not told through some popular medium that the population is becoming older. Along with this information comes the "new" revelation that as we enter the next millennium there will be increases in age-associated diseases (e.g., cancer, cardiovascular disease) including the most devastating of these, which involve the nervous system (e.g., Alzheimer's disease [AD] and Parkinson's disease [PD]). It is estimated that within the next 50 years approximately 30% of the population will be aged 65 years or older. Of those between 75 and 84 years of age, 6 million will exhibit some form of AD symptoms, and of those older than 85 years, over 12 million will have some form of dementia associated with AD. What appears more ominous is that many cognitive changes occur even in the *absence* of specific age-related neurodegenerative diseases. Common components thought to contribute to the manifestation of these disorders and normal age-related declines in brain performance are increased susceptibility to long-term effects of oxidative stress (OS) and inflammatory insults. Unless some means is found to reduce these age-related decrements in neuronal function, health care costs will continue to rise exponentially. Thus, it is extremely important to explore methods to retard or reverse age-related neuronal deficits as well as their subsequent, behavioral manifestations. Fortunately, the growth of knowledge in the biochemistry of cell viability has opened new avenues of research focused at identifying new therapeutic agents that could potentially disrupt the perpetual cycle of events involved in the decrements associated with these detrimental processes. In this regard, a new role in which certain dietary components may play important roles in alleviating certain disorders are beginning to receive increased attention, in particular those involving phytochemicals found in fruits and vegetables.

Keywords—Memory, Learning, Aging, Phytochemicals, Polyphenolics, Free radicals

INTRODUCTION

The human brain executes the vast array of cognitive and behavioral functions demanded of it through an intricate network of nearly 100 billion neurons and supporting glial cells (i.e., astrocytes and microglia). Despite comprising only 2% of the adult body weight, it requires and utilizes a substantial amount of energy. In fact, it has been reported to receive almost 15% of the cardiac output and accounts for up to 30% of the resting metabolic rate [1]. This high demand of energy may well be required to maintain efficient functioning of its complex and diverse active chemical processes. It is the changes in the functional integrity and/or optimum efficiency of

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these processes that contribute towards impairments in brain function, neuronal signaling, and subsequent behavior.

Continued research still indicates the occurrence of neuronal and behavioral deficits during aging, even in the absence of neurodegenerative disease. Among those, neurotransmitter receptor sensitivity has been reported to be altered with age, examples of which include the dopaminergic [2], muscarinic [3,4], opioid [5], and adrenergic [6] systems. Declines in motor functions such as those controlling balance and coordination have also been reported [7,8]. Furthermore, impairments in cognitive behaviors [9], in particular those that require the use of spatial learning and memory [10,11] have also been shown to correlate with alterations in receptor sensitivity. Indeed, these characterizations have been supported by a great deal of research in both animals [9–11] and humans [12,13].

Consequently, there has been a growing interest in a number of pharmacological approaches to help slow the rate of both cognitive and functional declines associated with aging with view towards maintaining a positive quality of life. For example, in the case of Alzheimer's disease (AD), a number of agents have been proposed to slow down its progression. These include antioxidants, monoamine oxidase inhibitors, anti-inflammatory agents, cholinergic agents, estrogens, or neurotrophic factors [14–23]. In the case of Parkinson's disease (PD), specific agents such as selegiline or deprenyl, L-DOPA, catechol-O-methyltransferase inhibitors, and apomorphine have received great attention [24–30]. However, while pharmaceutical companies continue to invest enormous resources into identifying agents that could be used to alleviate debilitating neurodegenerative disorders that continue to afflict numerous people around the world, a source of potentially beneficial agents, namely phytochemicals, would appear to have significant benefits that have yet to be fully exploited.

Phytochemicals have long been recognized to possess many properties, including antioxidant, antiallergic, anti-inflammatory, antiviral, antiproliferative, and anticarcinogenic [31–35]. However, with respect to over all health-promoting benefits, considerable interest over the past decades has primarily been focused on examining their roles in reducing risk factors associated with cancer and heart disease [34]. Consequently, there still remains a paucity of studies that have investigated their role in brain functions such as learning and memory, decrements in which, as alluded to above, are likely to have a negative impact on the quality of life. Of those phytochemicals having been investigated, those most familiar to the general public are Chinese herbal remedies such as Ginkgo biloba (EGb 761) and ginseng. While continued research is being undertaken to further understand the biological actions of these extracts, the underlying beneficial effects of phytochemicals from other dietary sources such as fruits and vegetables, with respect to brain performance, are only beginning to receive increased attention. This review is directed towards familiarizing the reader with the available literature pertaining to the beneficial role(s) performed by phytochemicals in improving certain age-related neurological dysfunctions.

PHYTOCHEMICALS

Polyphenolics

Polyphenolic compounds (flavonoids) occur ubiquitously in foods of plant origin, with over 4000 different structures having been identified and described [36]. Although polyphenolic research has spanned several decades, it has recently intensified due to our increasing understanding of the potential beneficial effects that these compounds promote towards improving human health [32,34,37]. However, all too often, a simplistic approach to the biological importance of the dietary antioxidants has been investigated. Many investigators appear to be satisfied by merely implying that an increase in antioxidant status following dietary consumption is sufficient evidence to suggest that there will be an overall benefit to biological systems and processes. While this may be true in part, corroboration of such claims with observable beneficial outcomes to validate the true beneficial potential that consumption of dietary antioxidants afford, in particular those pertaining to the brain, are lacking.

Fruits and vegetables

Animal studies. Investigations of the potential effects of fruit and vegetable components and cognitive functions have, until recently, been limited. With this in mind, we, together with colleagues at the University of Colorado, initiated an innovative trial to assess the effects of fruits and vegetables on forestalling behavioral and neurological parameters in aging rats from adulthood to middle age. In these initial studies [38] rats were fed from adulthood (6 months) to middle age (15 months) with diets supplemented with extracts of strawberry (SE) or spinach (SPN), each containing identical antioxidant content (based upon mmol Trolox equivalents). Parameters known to be sensitive to oxidative stress were then examined. These included receptor sensitivity, that is, oxotremorine (OX)-enhanced DA release in isolated striatal slices [2], cerebellar Purkinje cell activity [39], calcium buffering capacity [39], and changes in signal transduction assessed by carbachol-stimulated GTPase coupling/uncoupling in striatal membranes. Cognition, also identified to decline with aging [11,40], was examined using performance in the Morris water maze, which measures spatial learning and memory by requiring the rat to use spatial cues to find a hidden platform that is located just below the surface of the water. Results showed that SPN-fed rats demonstrated the greatest retardation of age-effects on all parameters with the exception of GTPase activity, where SE had the greatest effect. Strawberry and vitamin E showed significant but equal protection against the onset of age-induced deficits on the other parameters.

In follow-up studies [41–43], supplementation with SE, SPN, or blueberry (BB) extracts to aged rats was found to be effective in *reversing* certain age-related deficits in the neuronal and behavioral parameters, that is, memory and learning, described above. Interestingly, BB extract appeared most effective in these reversals on all of the parameters assessed, in particular OX-enhanced DA release in isolated striatal slices. This observation is particularly striking because maintaining the functional integrity of the striatum, in particular that of the dopaminergic system, has been reported to have a major impact on several behavioral parameters [4,7,44]. Furthermore, it is known that reduced release of dopamine from the decline in the number of dopaminergic neurons within the substantia nigra that forms projections into the striatum, plays a major role in PD [45]. As such the ability of BB extract to enhance DA release upon stimulation may also have important implications in the etiology of this disease. What remains to be examined is if this increase in DA release is due to increased neuronal sensitivity and/or possible increase in neurogenesis in striatal neurons.

Evaluation of cerebellar β-adrenergic receptor augmentation of γ-amino butyric acid (GABA) responding (i.e., cerebellar Purkinje cell activity), and motor learning, were also examined. It has been postulated that the cerebellar noradrenergic system, which shows age-related changes in β-adrenergic function may underlie certain age-related deficits in motor learning [46]. Norepinephrine potentiates GABA-induced inhibition of cerebellar Purkinje neurons via the β-adrenergic receptor. In aged rats, β-adrenergic potentiation occurs in only 30% of the recorded cerebellar Purkinje cells as compared with 70–80% in younger animals. The results from this study found that this decline was prevented in animals whose diets had been supplemented with BB or SE [42,43].

Interestingly, in these studies, diets were supplemented based on equal antioxidant activity, as determined by the ORAC assay [47]. Based on our findings, this would suggest that antioxidant activity was not predictive in assessing the potency of certain compounds at being beneficial against certain disorders affected by aging. Furthermore, supplementation of diets with ST, SPN, or BB extracts of equal antioxidant potency, were not similar in their abilities to protect against hyperoxia-induced declines in motor and learning skills [42]. This result, together with differences in protective capacities afforded to neuronal and cognitive parameters assessed in our lab, would indicate that a simple measure of antioxidant activity, (e.g., ORAC), should be carefully scrutinized, and perhaps combined with functional assessments, in order to ascertain potency of agents thought to have high antioxidant activity, and perhaps that potency be corroborated with other functional measures. Moreover, one must be careful in assuming that protection afforded against these various decrements in neurological and cognitive functions, known to be sensitive to aging and oxidative stress, are a result of antioxidative activity. In this regard, when two indices of antioxidant activity ROS production and glutathione levels in the striatum and cerebellum were examined [41], it was found that the supplementations only resulted in modest effects that could not totally account for the efficacy of these treatments.

Hence, there may be other properties of these extracts aside from antioxidative properties, that account for their different efficacies. One possibility is the actual polyphenolic composition. Based upon this idea, findings from a recent study showed that two different cultivars of BB, though supplemented at the same concentration, afforded different degrees of protection against memory and learning declines in aging rats [48]. Overall, the observations made in this latter study further supported the original finding that dietary polyphenolics improve age-related decrements in neurological functions.

Aged garlic extract and red bell pepper: Senecence accelerated mouse (SAM) model

Aged garlic extract (AGlE, *Allium sativum*), which contains S-allycisteine, S-allymercaptocysteine, allicin, and diallosulfides, has been reported to exhibit beneficial effects towards cognitive impairments in a novel strain of senescence accelerated mouse (SAM) [49–52]. This SAM model is particularly useful, as it has been shown to exhibit both morphological and neurological impairments observed in normal aging [53–57]. Initial studies found SAM supplemented with AGlE (2% w/w), displayed both increased lifespan and improved learning as assessed by active and passive avoidance tests [52]. Further beneficial effects of AGlE administration have been observed in SAM models, where morphological changes in the brain, which included prominent atrophy in the neocortex, olfactory cortex, and amygdala [50,51, 58,59], (areas thought to be involved in cognition and emotion) were not observed. This protection by AGlE was found to be most predominant in the frontal brain areas, thus likely contributing to the observed improvements in cognitive and behavioral tasks. While a direct protective effect cannot be dismissed, the beneficial effects promoted by AGlE could also be attributed to improved antioxidant activity within brain regions, which potentially could result in a reduction in membrane lipid peroxidation, an observation that has been observed with AGlE in vitro [60,61]. As such, protection of neuronal cells from free radical damage may contribute to improvement in certain brain functions. However, in our studies using fruit and vegetable extracts [38,41, 48], no increases in antioxidant capacities within brain structures (e.g., striatum and cerebellum) were observed, despite improvements in cognitive performances. This would suggest that, similar to the findings with fruit and vegetable extracts, there might indeed be properties in *addition* to antioxidant characteristics that are promoted by these extracts in improving age-related impairments in cognitive function.

It has been argued that in addition to antioxidant activity, changes in the immune response may contribute to a number of age-related impairments in cognitive performance [62,63]. In this regard, a recent study by Zhang and colleagues [49] found that thymectomized mice supplemented with AGlE displayed marked improvement in a number of markers of immune function. AGlE treatment was found to prevent the reduction of thymectomy-induced antibody production and improve thymectomy-induced deterioration of learning behaviors (performance in a passive avoidance and spatial memory task). Interestingly, both AGlE and a high molecular protein fraction of AGlE have been reported to increase oxidative burst in murine macrophages [64], and enhance T-lymphocyte [64] and human lymphocyte [65] proliferation. Together this evidence would suggest that AGlE may exert some protective effects in SAM through immunomodulatory mechanisms, since it has been shown that unfavorable changes in the immune system result in impairment of learning and memory functions [62,63].

In addition to AGlE, red bell pepper (*Capsicum annuum* L.) has also been employed in the SAM model, and beneficial effects were observed in both memory and aqusition performance [66]. Thus, to the extent that the SAM model is effective in aging, both garlic and red bell pepper may have positive benefits on age-related deficits.

Tea

While increased consumption of polyphenolics from tea has been found to correlate with reduced incidence of certain cancers [67,68], they have also been suggested to elicit potentially beneficial effects towards improving brain function(s). A study by Matsuoka and co-workers [69] found that intracisternal injection of epicatechin improved the memory impairment induced by intracisternal glucose oxidase, and iv injection of catechin or epicatechin improved deficits induced by the cerebral ischemia. One could argue that the protection afforded by tea polyphenolics against ischemic damage was due in part to inhibition of oxidative and inflammatory processes [70–72], both of which are characteristic events during/following ischemic insults [73–76], that ultimately effect behavior [62]. Interestingly, despite the fact that these constituents were supplied via iv, and hence not representative of normal dietary consumption, there is evidence to suggest that tea polyphenolics can localize within the brain following dietary consumption [68] and thus be available to promote actions resulting in cognitive improvements as reported by Matsuoka and co-workers [69].

Carotenoids, vitamin E and vitamin C

Very few reports have actually investigated the effect(s) of dietary supplementation of vitamin E and C or carotenoids on age-related cognitive impairments. The majority of studies having identified their role(s) on brain functions have done so through dietary deficiency. Nonetheless, numerous epidemiological studies have reported some positive benefits of dietary carotenoids on age-related impairments in memory and learning performance (Table 1). In parallel with these assessments, correlations with flavonoids and vitamins E and C have also been reported with mixed results. There is, however, growing evidence to suggest a potential beneficial effect of these compounds, in particular vitamin E, against the damaging effects of neurodegenerative disorders such as AD and PD [77].

For the most part, it is difficult to establish from these epidemiological studies reported in Table 1, whether changes in β-carotene [78,79], vitamin E [80–82], or vitamin C [79,82,83] preceded or are the result of impaired cognition. Even more difficult to ascertain are the mechanism(s) by which CNS protection, if any, is afforded. In addition, although the tests used in these studies are valid indicators of cognitive impairments and can measure substantial declines that may result in a strong risk factor, certain dietary factors that may be associated with small effects on cognitive performance may not be detected. Furthermore, these findings could have reflected unmeasured confounding, measurement error, or a change in food habits resulting in unreliable food frequency information, which too may have resulted from rather than preceded the onset of cognitive impairment.

Table 1. Epidemiological Studies Reporting Correlations Between Dietary Carotenoids, Vitamin E, and Vitamin C and Cognitive Declines

Study	Dementia type	Cognitive measures	Blood measures	Dietary measures	Nutritional changes associated with increased dementia	Ref.
Rotterdam study[a]	Aging	Mini-Mental State Examination (MMSE)	-	β-carotene	Reduced	[78]
				Vitamin E	No association	
				Vitamin C	No association	
Zutphen elderly study[a]	Aging	MMSE		β-carotene	No association	[175]
				Vitamin E	No association	
				Vitamin C	No association	
				Flavonoids	No association	
				Linoleic Acid	Reduced	
Etude du viellissement arteriel study[a]	Aging	Trail-Making Test & Digit Symbol Substitution	Carotenoids	–	Reduced	[176]
			Vitamin E		No association	
Basle longitudinal project IDA[a]	Aging	Working memory, free recall and WAIS-R	β-carotene	–	Reduced	[79]
			Vitamin E		No association	
			Vitamin C		Reduced	
Austrian stroke study[a]	Aging	Mattis Dementia Rating Scale (MDRS)	–	Carotenoids	No association	[80]
				Vitamin E	Reduced	
				Vitamin C	No association	
3rd National Health and Nutrition Examination Survey[a]	Aging	Wechsler Memory Test (WMT)	–	Carotenoids	No association	[81]
				Vitamin E	Reduced	
				Vitamin C	No association	
New Mexico aging process study[a]	Aging	WMT and Halstead-Reitan Categorie Test	β-carotene	–	No association	[83]
				Vitamin E	No association	
				Vitamin C	Reduced	
New Mexico aging process study[a]	Aging	WMT and Shipley-Hartford Intelligence Test (SHInT) Rey-Osterrieth Complex Figure Test	Vitamin E		No association	[82]
			Vitamin C		Reduced (WMT only)	
				Vitamin E	Reduced (WMY and SHInT)	
				Vitamin C	No association	
Nun study	Aging	Self-care performances[b]	Carotenoids	-	Reduced (lycopene only)	[177]
			Vitamin E		No association	

[a] Results adjusted for possible confounders including age, sex, month of blood sampling, years of education, smoking, lipid status, and major risk factors for stroke.
[b] Self-care assessments included those that required assistance with bathing, walking, dressing, standing, toileting, and feeding.

Ginkgo biloba (EGb 761)

EGb 761 is a standardized extract of dried leaves of Ginkgo biloba. It has also been shown to be an effective free radical scavenger and a potent inhibitor of lipid peroxidation [84]. As mentioned in the introduction, it is one of the most extensively studied extracts with respect to cognitive performance in animal and human studies [85–100]. A number of very good review articles have recently been published that are solely directed to discussing Ginkgo and its various pharmacological actions, and the reader is referred to these for a comprehensive overview of the literature [84,90,101].

Various properties that EGb 761 has been reported to elicit include the reduction in levels of ROS [102–104], which have been reported to impair brain function [105]; increasing cerebral blood flow [96,106] Eckmann, 1990 #263 [107–111], thereby increasing the amount of oxygen and glucose delivered to the brain, thought to decline through aging and necessary for efficient functioning of the various brain structures; modulation of membrane fluidity, possibly through protection of membrane fatty acids [97,112–115], changes in which have been shown to correlate with cognitive performances [116–118]; interactions with the muscarinic cholinergic system [119, 120], which has been shown to be involved in the performance of spatial tasks [121–123]; antagonism of platelet activating factor [124–127], thereby inhibiting platelet aggregation, neutrophil degranulation, and ROS production, which would otherwise lead to increased microvascular permeability of detrimental agents through the blood brain barrier; protection of the striatal dopaminergic system [128,129]; and inhibition of monoamine oxidase activity [89,130,131], which consequently results in the protection of monoamines such as NE, 5-HT, and DA, which are known to play essential roles in a variety of brain functions.

Ginseng

Panax ginseng is one of the mostly widely used herbs in traditional Chinese medicine. Currently, sales within the US amount to over $300 million annually. Some of the actions reported to be elicited by ginseng include an ability to induce effects within the CNS that control functions related to stamina, fatigue, and physical stress; and to modulate immune function and functions such as memory, learning, and behavior [132]. A number of different cognitive tests have shown the potential beneficial effects of ginseng on memory and learning in performance in a variety of animal species [92,133–136]. In addition, herbal mixtures that contain ginseng have been shown to improve cognitive performance. These include S-113m [137,138], which consists of *Biota orientalis*, *Panax ginseng*, and *Schizandra chinesis* (1:1:3 w/w/w), and DX-9386 [139–144], which consists of *Panax ginseng, Polygala tenuifola, Acorus gramineus*, and *Paoria cocos* (1:1:25:50 w/w, dry).

It has been suggested that one potential mechanism by which ginseng improves various neurological functions is through an interaction with the cholinergic and serotoninergic neurotransmitter systems. This theory is supported by studies that have shown that selective damage to serotonergic neurons affects certain aspects of memory functions, in particular spatial working memory [145,146]. Furthermore, one of the behavioral paradigms found to be improved by ginseng supplementation was that against electroconvulsive shock, which is known to modulate the cholinergic neurotransmitter system [147], in particular within brain areas such as the hippocampus, known to be involved in spatial memory tasks [148–151]. It has also been speculated that ginseng acts by enhancing cholinergic systems such as choline acetyltransferase, also thought to be important in the formation of memory [149,152–154].

In addition to the use of the whole root extracts from *Panax ginseng,* studies have also shown that behavioral impairments can be forestalled using individual ginsenosides [136,155–164]. Indeed, it is from studies with these individual components that considerable insight has been gained into the mechanisms by which ginseng is likely to promote its beneficial actions. In this regard, further support of the theory that ginseng may be improving age-related impairments in cognitive performance through interactions with neurotransmitter systems has come from reports having shown that ginsenosides increase muscarinic-cholinergic receptor density, together with an ability to increase levels of acetylcholine in the brain [165].

Although there have been a number of studies highlighting the potential beneficial effects of ginseng on cognitive performance in animal models, few epidemiological studies have been performed to compliment these findings. Indeed, a comprehensive survey of the literature found only five studies investigating ginseng on human cognitive performance [166–170], in three of which significant improvement in mental arithmetic and abstraction tests were reported [167–169].

*Dinh lang (*Policias fruticosum *L.)*

While ginseng (Panax ginseng) is probably one of the best known medicinal plants used as a traditional remedy, an abrupt reduction in its natural supply, as well as inherent difficulties in methods of cultivation, stimulated the study of other species of the Araliaceae family that could potentially elicit similar pharmacological responses. Subsequently, a medicinal remedy from an ornamental Vietnamese tree, Ding lang, was identified. In fact, the Ding lang root extract (DLRE) was found to be the most pharmacologically active. Among the actions promoted by DLRE was its beneficial effect on brain performance (active and passive avoidance tests) in aging rodents [171]. Yen suggested that one possible mechanism behind this improvement may have been due to stimulation of neurotransmitter release, because in a previous study, DLRE was found to stimulate sexual performance of aged male rats [172], a behavior that is stimulated by catecholamines and inhibited by serotonin in the brain [173].

As discussed earlier, age-related impairments in memory and learning tasks have been attributed to an oxidative stress component. A subsequent study by Yen [174] showed that DLRE administration elevated the activity of the endogenous antioxidant enzyme superoxide dismutase in the striatum and cerebellum, while those of glutathione peroxidase and catalase were unaltered. Oxidative stress-induced declines in striatum functions have been shown to result in cognitive impairments, hence an increase in antioxidant status following DLRE may explain in part the beneficial effects observed in the initial study by Yen on learning performance [171].

SUMMARY

Dementia already represents a major burden on our society, whether it is from normal aging or as a consequence of a neurodegenerative disorder. These disorders resulting in memory loss are often associated with a loss of independent functioning. Given the current demographic trends, the outlook for most of us over the next few decades does not appear favorable. Moreover, the possibility that nutritional deficiencies may play a role in cognitive deficits in old age has been recognized for several years. Hence, identification of potentially modifiable protective factors for memory deficits or dementia is becoming an increasingly important task. However, there is only limited information available about nutrition-cognition associations.

To date, the major focus made with respect to health-promoting effects of phytochemicals has often been towards reducing risk factor associated with the onset and/or progression of diseases such as cancer and heart disease [34]. It has only been during the latter part of the 20^{th} century that research has begun to include investigating the potential role between phytochemicals and neurological functions. Unfortunately there still remains a paucity of studies within this area, but this review has highlighted those in which positive effects have been observed. For the most part, major emphasis to date has been primarily directed towards investigating the role of herbal remedies such as ginkgo and ginseng. The findings with respect to these remedies are promising, and as such have received considerably interest together with substantial funding in an attempt to further elucidate their mechanisms of action. Although this approach is important, research should not be *solely* directed to this end, but also expanded to delineate and exploit the putative beneficial effects on age-related cognitive deficits promoted by other dietary phytochemicals. Among those reported in this review to have exhibited protective effects towards neurological impairments are: polyphenolics from strawberry, spinach, blueberry, tea, red bell pepper, aged garlic extract, and herbal remedies aside from ginkgo and ginseng, such as ding lang root extract. Unfortunately, what comes with the novelty in this particular area of research is only a partial understanding of their underlying mechanism(s) of action. In general the findings to date appear to strongly indicate potential associations with neurotransmission and/or receptor function [38,41,48,119,120,147,165,171], possible immunomodulatory effects [49,64,65], and alterations in the brain's antioxidant status [69,174]. Interestingly, studies performed in our lab appear to suggest that the antioxidant properties of these polyphenolics may comprise only a small part of the beneficial effects they promote, since no alterations in antioxidant status within brain regions utilized to control cognitive tasks such as the striatum were observed, while having antioxidant effects in the cerebellum. Clearly, one explanation may be differences in the bioactivities of the individual phytochemicals, which together display antioxidant properties in vitro, but in vivo may exhibit additional properties beneficial to improving neurological functions.

It is also possible that there is a regional specificity in their antioxidant effects. What remains to be examined is if these actions are resulting from a direct interaction with these systems or are being mediated indirectly. Of course to be able to suggest a direct interaction, further studies are required to identify that indeed the polyphenolics are able to cross the blood-brain barrier, which to date has only been observed with certain tea polyphenolics [68]. What these findings indicate is that one must be careful to not assume that their antioxidant activity, often assessed in vitro, is the sole basis upon which their health benefits be judged.

On face value one might argue, with respect to brain function, that there are no definitive beneficial outcomes following consumption of dietary phytochemicals. Yet, the fact that the various phytochemicals discussed above in some way improved either cognitive and/or motor functions, clearly highlights a *potential* health effect, because an inability to perform day-to-day tasks that require efficient cognitive and motor performance inevitably results in loss of independence and often institutionalization within a care facility. However, this is not a reason to dispute their potential, but rather reason to further study their physiological properties. Of course a true test of their effectiveness will come from future epidemiological studies. Prior clinical studies examining associations between antioxidants and cognition have primarily focused on vitamin C, vitamin E, and β-carotene [78–83,175,176]. Although no one specific nutrient stands out, an association between certain dietary phytochemicals, such as carotenoids, was observed in improved cognition in aged subjects. However, with careful planning, studies can be designed to specifically investigate the role of polyphenolic dietary supplementation and age-related cognitive impairments, and the results may prove more insightful. Yet, in order to ensure that such studies yield valuable nutritional information more preliminary studies using appropriate model systems are required to validate those having already reported positive effects.

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ABBREVIATIONS

AD—Alzheimer's disease
AGlE—aged garlic extract
BB—blueberry
DA—dopamine
DLRE—Ding lang root extract
EGb 761—Ginkgo biloba
GABA—γ-amino butyric acid
5-HT—serotonin
MDRS—Mattis Dementia Rating Scale
MMSE—Mini-Mental State Examination
MWM—Morris water maze
OS—oxidative stress
OX—oxotremorine
PD—Parkinson's disease
ROS—reactive oxygen species
SAM—senescence accelerated mouse
SE—strawberry extract
SPN—spinach extract