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Scoping Review

The Multifaceted Effects of Flavonoids on Neuroplasticity

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Abstract. There has been a significant increase in the incidence of multiple neurodegenerative and terminal diseases in the human population with life expectancy increasing in the current times.

This highlights the urgent need for a more comprehensive understanding of how different aspects of lifestyle, in particular diet, may affect neural functioning and consequently cognitive performance as well as in enhancing overall health. Flavonoids, found in a variety of fruits, vegetables, and derived beverages, provide a new avenue of research that shows a promising influence on different aspects of brain function. However, despite the promising evidence, most bioactive compounds lack strong clinical research efficacy. In the current scoping review, we highlight the effects of Flavonoids on cognition and neural plasticity across vertebrates and invertebrates with special emphasis on the studies conducted in the pond snail, *Lymnaea stagnalis*, which has emerged to be a functionally dynamic model for studies on learning and memory. In conclusion, we suggest future research directions and discuss the social, cultural, and ethnic dependencies of bioactive compounds that influence how these compounds are used and accepted globally. Bridging the gap between preclinical and clinical studies about the effects of bioactive natural compounds on brain health will surely lead to lifestyle choices such as dietary Flavonoids being used complementarily rather than as replacements to classical drugs bringing about a healthier future.

Keywords: Invertebrates, Flavonoids, memory, learning, cognitive functions, neurodegenerative disorders, psychiatric disorders

BACKGROUND

Dependence on bioactive natural compounds for promoting human health

A report in The Lancet states that individuals diagnosed with cognitive disorders are estimated to grow by 115 million by 2050 [1]. As the World's population ages, age-related impaired executive functions and learning and memory abilities are becoming an enormous public health, social, and economic burden, representing one of the major causes of hospitalization, nursing care, and death worldwide [2–4].

Unfortunately, pharmacological interventions based on synthetic drugs only seem to alleviate symptoms of impaired neuroplasticity [5], without effectively targeting the pathophysiology of cognitive decline. Thus, determining whether and – if so – how human neuroplasticity can be preserved to match extended life expectancy more closely, is both necessary and urgent.

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Table 1
Classes of Flavonoids and their Sources

Class	Flavonoids	Sources
Flavanols	Epigallocatechin gallate Epigallocatechin Epicatechin Catechin Quercetin Kaemferol Morin Galangin	Cocoa, grapes, green tea, and red wine Tea, apples, capers, onions, broccoli, strawberries, leeks, and grapefruits
Flavanones	Eridictyol Hesperetin Naringenin Naringin	Tomatoes, grapefruits, and citrus fruits
Flavones	Luteolin Wogonin Diosmin Apigenin	Onions, broccoli, oranges, cabbage, carrot, grapefruit, parsley
Isoflavones	Equol Daidzein Genistein Glycerin	Soy and derivates
Anthocyanins	Malvidin Hirsutidin Pelargonidin Cyanidin	Red wine, berry fruits, and beans

In this complex scenario, growing evidence from translational studies confirmed the potential of dietary bioactive compounds – including polyphenols, terpenoids, polysaccharides, capsaicinoids, carotenoids and tocopherols, triterpenes and phytosterols, alkaloids, saponins, glucosinolates - in preventing and/or improving impaired cognitive functions [6]. Indeed, diet, together with genetic background, aging, hormonal states, comorbidities of chronic disorders, toxin exposures, socioeconomic profiles, and lifestyle behaviours act as a key modulator of neuroplasticity [7, 8].

This Scoping Review is not intended to be an exhaustive review of studies investigating the effects of bioactive compounds on neuroplasticity. Owing to space limitations, we have restricted our discussion to selected bioactive compounds and model organisms. In particular, we focused our attention on Flavonoids (Table 1), as these phytochemical compounds provide a new avenue of research that shows a promising influence on different aspects of brain function [9, 10], including memory, attention, and overall cognitive function [11, 12].

Flavonoids are present in many plants, fruits, vegetables, and leaves [13]. Some examples include compounds found in green tea, such as epicatechin, which have been found to improve attention and cognitive function [13]. Similarly, compounds found in berries, such as anthocyanins, have been found to improve memory and cognitive function [14, 15]. Additionally, compounds like quercetin, have been found to have anti-inflammatory and antioxidant effects, which may also contribute to cognitive enhancement and improve overall immunity and health [16–19].

Thus, in the last decade, an expanding body of research highlights enhanced cognitive performance in various age groups [20–22] after both chronic and acute interventions involving high levels of Flavonoids [23, 24]. In particular, the emerging body of evidence indicates the potential benefits of Flavonoids on attention, working memory [20, 25], and psychomotor processing speed [23, 24]. The data also suggests that the impact of Flavonoids is likely dependent on the dose and flavonoid supplementation could yield cognitive improvements within a short timeframe of 0–6 hours [23, 24]. For example, Devore et al., (2012) investigated the relationship between berry and flavonoid consumption and cognitive decline in $\geq$ 70 years women [20], by administrating food frequency questionnaires to participants every 4 years from 1980 and in 1995–2001 started measuring their cognitive functions. The study revealed that a higher intake of blueberries and strawberries (i.e., foods rich in Flavonoids [26]) and total Flavonoids was associated with delayed cognitive aging by up to 2.5 years. Thus, this study revealed that a diet rich in Flavonoids, particularly those from berries, might play a role in mitigating cognitive decline in older adults. Similar results have been obtained in the PAQUID (i.e., Personnes Agées Quid) study, which examined 1640 aged 65 or older dementia-free individuals over a 10-year period and, after accounting for age, sex, and education level, demonstrated that higher Flavonoid intake was linked to improved cognitive performances [27]. Finally, in a recent study, Godos et al., (2020) analysed the relationship between dietary flavonoid intake and cognitive health in 808 adults living in southern Italy [28]. By recutting to food frequency questionnaires, estimating polyphenol content using the Phenol-Explorer database (www.phenol-explorer.eu), and assessing the cognitive status using the Short Portable Mental Status Questionnaire [29], the study revealed a significant inverse association between higher dietary intake of total flavonoids and impaired cognitive status. Moreover, specific subclasses of flavonoids, including quercetin, flavan-3-ols, catechins,

anthocyanins, and flavonols, were linked to better cognitive health. Thus, the study suggests that greater consumption of flavonoids through diet might be correlated with improved cognitive health in adult individuals residing in the Mediterranean area [28].

Despite the promising results demonstrating the cognitive efficacies of Flavonoids, several other studies show mixed conclusions [25] and there are challenges related to their success in clinical trials [30, 31]. In particular, gaps in scientific validation, knowledge of pharmacokinetics, toxicity, and mechanism of action, are limiting the recommendation of these compounds in clinical studies [32–34]. Moreover, most Flavonoids go through a rapid metabolism, have non-specific targeting, poor solubility, as well as lack brain-blood-barrier permeability [35, 36].

In this complex scenario, translational studies are necessary to predict a direct relationship between Flavonoid intake, enhanced cognitive function, and/or protection against neurodegeneration. This may be extremely useful for both clinical treatment interventions and preventive approaches.

Thus, in the next sections, we present important discoveries on the effects of flavonoid-rich compounds on cognitive functions in different model organisms, highlighting the advantages of invertebrate models in this research field [37]. A special focus will be on the pond snail *Lymnaea stagnalis*, as – over the last decade – it has become a valuable model organism for studying the memory-enhancing effects of different bioactive compounds [37–39].

Finally, we will provide potential solutions to address research gaps and guide future research. Specifically, we will focus on the social, cultural, and ethnic dependencies on these products, the issues related to potential adverse reactions, and challenges in monitoring safety, as well as their use to complement and not as a substitute to 'classical drugs' for cognitive decline and memory loss.

MODEL ORGANISMS FOR PRECLINICAL STUDIES

To promote a better understanding of the multifaceted effects of Flavonoids on brain plasticity, research on multiple model organisms needs to occur. It must always be borne in mind that animal models no matter their origin or complexity can never fully substitute for a human central nervous system. This is especially true when the human nervous system's functionality is altered by neurodegenerative processes that result in neuropsychiatric disorders. With those caveats in mind model organisms are providing essential information on the mechanisms of action of different bioactive compounds [40–42].

The models most often used are rodent models (i.e., rats and mice) [43] as they offer genetic tools that can be useful to validate the function of specific genes, or their role in more complex functions, including neuroplasticity [44]. In this regard, Singh et al. (2022) recently reviewed the antioxidant and memory-enhancing properties of plant-derived polyphenols such as Flavonoids, phenolic acids, stilbenes, lignans, and non-phenolic compounds like bacoside-A, withaferin-A, ginkgolide-B, withanolide-A, and bilobalide [45].

In that regard, other researchers proposed the use of nano-herb conjugates to improve permeability in the brain to attenuate oxidative stress effectively overcoming the limited ability of many prospective bioactive compounds to cross the blood-brain barrier [46, 47].

Flavonoids, encompassing phytochemical compounds and dietary additions, possess substantial nutritional worth and antioxidant characteristics. These components have been applied to address oxidative stress in therapeutic contexts, aiming to alleviate the negative impacts of this stressor on the aging brain. [38–42]. For example, a recent publication [43] reviewed the therapeutic potential of phytoestrogens rich in Flavonoids, like genistein, daidzein, and resveratrol, in memory restoration in aging and different neurological disorder. Estrogen in females plays a major role in health as estrogen possesses antioxidative, anti-apoptotic, and anti-inflammatory actions [44]. There is growing evidence of the ability of estrogen and its receptors to epigenetically regulate the expressions of genes involved in memory functions [51–53]. Therefore, a reduction in estrogen signalling as occurs in menopause [54, 55] represents a risk for age-related memory decline and neurodegenerative disorders. However, phytoestrogens show neuroprotective, neurogenic, and memory restoration potential in aged estrous female rodents, Alzheimer's disease models, and human subjects [56]. Previous studies reported that menopause is responsible for multiple metabolic changes such as dyslipidemia and enhanced adiposity, leading to behavioural alterations including cognitive decline [57–60]. Unfortunately, hormone replacement therapy has not been effective, and it sometimes showed detrimental effects on memory functions [61].

In this context, Bahndari et al. (2022) reported that dietary supplementation using stem powder of *Tinospora cordifolia* (a medicinal plant belonging to the family *Menispermaceae* rich in Flavonoids, tannins, and steroids [62]) for 12 weeks improved the learning and memory behaviour in high-fat diet-fed acyclic-aged female rats [63]. Molecular analysis of the glial marker GFAP and the microglial protein Iba1 showed a significant decline in the expressions of these proteins, indicating a reduction of neuroinflammation in the hippocampus and the prefrontal cortex of *T. cordifolia*–supplemented rats, compared with high-fat diet-fed acyclic aged female rats [63]. Furthermore, those authors found a significant increase of the anti-apoptotic proteins AP-1 and Bcl-xL levels and a significant reduction of the pro-apoptotic marker p-BAD in both the hippocampus and prefrontal cortex of these animals, suggesting a pro-cell survival effect of *T. cordifolia* supplement of high-fat diet-fed acyclic aged female rats [63]. Finally, the *T. cordifolia* supplement restored the expression of neurotrophic BDNF and Trkβ in the hippocampus and the prefrontal cortex of the high-fat diet-fed acyclic-aged female rats, suggesting *T. cordifolia* as a potential therapeutic agent to prevent the adverse effects of obesity and obesity-associated brain dysfunctions [64].

Another recent study published by Huang et al., (2021), investigated the neuroprotective effect of the natural flavonoid rhoifolin in rats with streptozotocin-induced Alzheimer's-like disease [65] and found a significant improvement in memory, cognition, and spatial learning in rhoifolin-treated Alzheimer's-like disease animals. Moreover, rhoifolin treatment resulted in a significant increase in the hippocampal CA1 pyramidal layer of those animals indicating its neuroprotective properties [65].

The increase in the hippocampal CA1 area further validated the reversal of cognitive dysfunctions caused by the streptozotocin treatment. Furthermore, analysis of oxidative stress markers SOD, CAT, GPX, GRX, and MDA showed a significant improvement in oxidative stress in the hippocampus and frontal cortex.

Thus, this study provided the first evidence of the effect of plant flavonoid, rhoifolin on an Alzheimer -like disease in rat models, representing a promising therapeutic agent for the management of this terrible neurodegenerative disorder [65].

In this complex scenario, because of the complexity of mammalian brains, as well as the multimodal mechanisms of actions of different bioactive compounds, contrasting results are not too surprising [41]. Additionally, the high cost involved in mammalian studies and the increasing difficulties in obtaining ethical approvals for certain types of experimentation may result in researchers considering alternative options [66–68].

In this complex scenario, invertebrates that have a simpler nervous system and also show interesting and important variation across wild populations, represent a more ethical, faster, cheaper but still valid model organisms (with few ethical requirements) to test for the effects of bioactive compounds on brain plasticity and functioning [37].

Being simpler model organisms, the pathways that are affected by such natural compounds can be determined relatively easily [38]. However, as most of these pathways are also evolutionarily preserved and thus would show similarity across *taxa*, over the last decade, worms flies, bees, snails, and fish have proven to be extremely useful to bridge the gap between preclinical and clinical studies investigating the effects of bioactive compounds on neuroplasticity (Table 2).

Review of some of the literature on the effect of Flavonoids on brain plasticity in different invertebrate species

Over the last three decades, invertebrate models (mainly Molluscs, Arthropods, and Nematodes) have been used as screening tools for drug discovery [40, 69]. Therefore, by combining genetic amenability, low cost, and breeding conditions, these organisms allowed high-throughput screening in a physiological context, representing a needed tool to bridge the gap between traditional *in vitro* and preclinical animal assays. Thanks to the great advances in comparative genomics, it has been demonstrated that there is a high level of conservation of numerous key physiological pathways across *taxa* [87]. Thus, while maintaining the simple organization of the invertebrate nervous system [71–73], these organisms not only allowed the characterization of the conserved mechanisms through which the central nervous functions and gets sick but also elucidate the mechanisms of actions of many drugs and compounds [37, 39, 40, 74–76]. Invertebrates have been and still are of fundamental importance in understanding basic neuroscience and in accelerating the pace at which mammalian studies can be translated to humans [40].

Recently, these organisms have been used to detect the mechanisms of action of many dietary bioactive compounds.

Table 2
Some of the most relevant studies on the effects of different bioactive compounds on neuroplasticity in invertebrate model organisms

Species	Bioactive compound	Effects	Citation
Drosophila melanogaster	Adzuki bean	Restoration of the abnormal memory, movement defects, and shortened lifespan in Aβ42-overexpressing flies model of Alzheimer's disease	[78]
Drosophila melanogaster	*Citrus sinensis*, *Citrus maxima*, and *Citrus paradisi*	Improved memory index	[87]
Drosophila melanogaster	*Ganoderma lucidum, Panax notoginseng Panax ginseng*	Improvement of memory deficits induced by an inflammatory status	[88]
Drosophila melanogaster	Cyanidin, keracyanin, Kuromanin	Prevention of Aβ-induced neurotoxicity and neurite outgrowth	[89]
Drosophila melanogaster	*Garcinia binucao*	Prevention of alcohol-induced neurotoxic effects on learning, short-term memory, and motor functions	[83]
Drosophila melanogaster	*Rhodiola rosea*	Improved odor-taste reward associative memory	[90]
Caenorabditis elegans	*Acanthopanax senticosus*	Improved the long-term memory of radiation-damaged worms	[91]
Caenorabditis elegans	Cranberry extract	Preventive effects through alleviating Aβ toxicity	[92]
Lymnaea stagnalis	Quercetin	Enhancement of long-term memory formation, upregulation of the expression levels of CREB1 (a key factor for neuroplasticity), and prevention of the heat-shock-induced upregulation of HSPs	[93–95]
Lymnaea stagnalis	Epicatechin	Enhancement of long-term memory formation and reversion of the memory-impairing effects of different stressors	[96–98]
Lymnaea stagnalis	Green tea	Enhancement of long-term memory formation and reversion of the memory-impairing effects of different stressors	[98–100]
Danio rerio	Quercetin and rutin	Prevention of scopolamine-induced memory impairment	[101]
Danio rerio	Silibinin and Naringenin	Prevention of Bisphenol A-induced neurotoxicity	[102]

As reported in Table 2, most of the studies on the multifaceted effects of bioactive compounds have been performed in the fruit fly *Drosophila melanogaster*, the worm *Caenorhabditis elegans*, the pond snail *Lymnaea stagnalis,* and zebrafish (*Danio rerio*).

As previously indicated, this section is not intended to be an exhaustive collection of all the studies performed in invertebrate models on all bioactive compounds currently available. That is, for reasons of space, we have selected only recent publications in the most used invertebrate models for biomedical research.

Most of the studies using *D. melanogaster* and *C. elegans* as model organisms have been performed on animal models of neurodegenerative diseases and/or aging-related disorders [13, 77–84]. In fact, both these organisms can undergo easy genetic analysis, allowing the discovery of various mutants and the identification of the responsible genes for neurodegenerative diseases.

Therefore, the administration of dietary bioactive compounds and/or food and beverage rich in them in transgenic flies and worms allowed the characterization of the multifaceted effects of bioactive compounds on brain plasticity and functionality. That is, over the last decade, a huge number of bioactive compounds that have been analysed show antioxidant, antiapoptotic, neuroprotective, and anti-inflammatory properties. Moreover, studies involving treatments with these compounds on cognitively impaired animal models showed several beneficial effects in enhancing neuroplasticity and/or extending life span (Table 2).

On the other hand, most of the studies using zebrafish were focused on the effects of various bioactive compounds on neurotoxicity. *Danio rerio* represents an excellent *in vivo* model for studying developmental neurotoxicity [85]. Indeed, thanks to their small sizes and abundance of embryos, these organisms are ideal for high-throughput screening in which the compounds tested can simply add in the

medium of zebrafish, which will passively diffuse [86].

Importantly, comparative neurogenetic and neuroanatomical analyses reveal high degrees of conservation between the nervous systems of zebrafish and mammals [86]. Therefore, this model organism provides a valid tool in which to investigate the effects of bioactive compounds in preventing and/or modulating neurotoxicity and, on the other hand, to evaluate the potentially toxic effects of bioactive compounds themselves.

Special focus on Lymnaea stagnalis as a model system to understand the effects of natural compounds on learning and memory

Among a wide variety of invertebrate models used in Neuroscience research [37], the freshwater pond snail *Lymnaea stagnalis* (Linnaeus 1758), has been widely recognized as an ideal model system in which to investigate the action of various bioactive compounds on learning and memory formation [38, 39, 103, 104] (Fig. 1).

The rich behavioural repertoire that *L. stagnalis* uses to survive and adapt to its natural environment makes this organism a remarkable model system with which to study not only associative learning and the neuronal and molecular mechanisms of memory formation, but also how different stressors, drugs, and bioactive compounds may modulate (i.e., either enhancing or impairing) learning and memory formation [95, 103, 105–115]. *L. stagnalis* possesses relatively simple but important homeostatic behaviours whose underlying neuronal circuitry has been well elucidated [116–118]. Moreover, many of these behaviours are tractable and relatively easy to train [119, 120].

At the neuronal level, the nervous system of *L. stagnalis* consists of about 25000 large (up to 150 μm in diameter) neurons, organized in a ring of interconnected ganglia, offering a relatively large amount of biological material that can be analysed molecularly, physiologically, and morphologically [110, 121]. The neurons can be easily removed and placed in culture, where they reform the appropriate synaptic connections [122, 123]. Thus, single neurons can be identified and analysed as part of defined circuits, allowing electrophysiological dissection of the networks involved in relatively simple rhythmic behaviours, such as aerial respiration and feeding [124]. These rhythmic movements are induced by groups of central pattern-generating neurons (CPGs) [125], whose characterization is critical for understanding where and how the nervous system controls

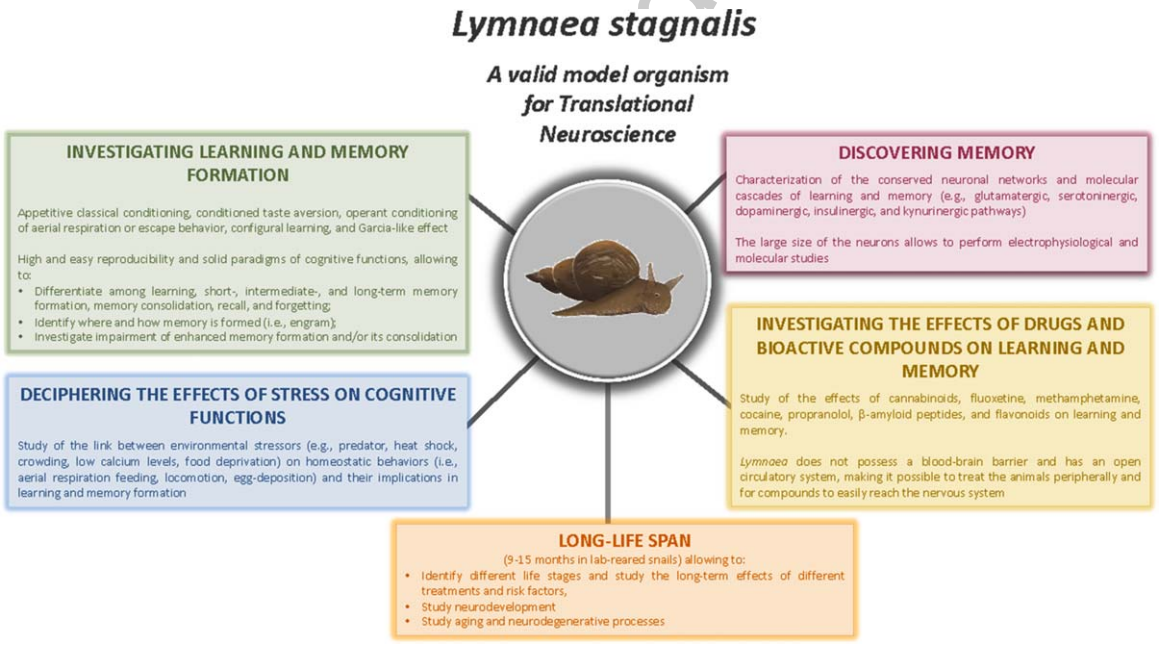

Fig. 1. Studies that can be performed using Lymnaea stagnalis as a model organism for Translational Neuroscience research, offering an array of advantages for exploring the conserved mechanisms underlying the effects of bioactive compounds (e.g., Flavonoids), drugs, and environmental stressors on cognitive functions and aging-related processes.

these homeostatic behaviours and how the interplay between CPGs and external stimuli participates in the production of adaptive learned behaviours. These CPG circuits can be plastically reconfigured via environmental changes, experiences, and conditioning procedures to optimize the output to meet specific behavioural demands [125].

Importantly, *L. stagnalis* is an aquatic invertebrate with an open circulatory system, allowing the use of membrane-permeant compounds (including bioactive compounds like Flavonoids) that can be easily absorbed, to unravel the complexity of various signalling pathways and provide new insights into how drugs and molecules can modulate different neuronal functions and behaviours [93–95, 106, 126, 127].

Furthermore, the neuronal plasticity exhibited in the CPG circuits plays an important role in regulating the initiation and temporal output of behavioural rhythms in response to rewarding/aversive stimuli (as occurs in classical conditioning) and action–outcome contingencies (as occurs in operant conditioning) [128, 129]. Therefore, by utilizing both *in vitro* and semi-intact preparations (which allow monitoring of the behaviour and neural activity simultaneously), the CPGs controlling learning-induced changes and the effects of different compounds (like drugs and bioactive compounds) can be elucidated at the single-cell level in *L. stagnalis* [123, 130, 131].

Lymnaea stagnalis serves as an excellent system because both quantitative changes in gene expression induced by conditioning and the exposure to bioactive compounds can be studied at the level of single neurons, which may be extremely useful not only for elucidating which molecules participate in the dialogue between the synapse and the nucleus and vice versa during memory and learning but also to elucidate the conserved mechanisms through which Flavonoids and other bioactive compounds exert neuroplastic effects [37, 38]. Importantly, studies such as these cannot easily be performed in most vertebrate preparations because their behaviours are more complex, and the underlying neuronal circuitries are more inaccessible to direct cellular and synaptic analyses [39, 132, 133].

In 2012, Fruson et al. demonstrated that the exposure of *Lymnaea* to 15 mg l–1 of the flavonoid (–)Epicatechin enhanced long-term memory (LTM) formation for the operant conditioning of aerial respiration, providing the first test of the effect of Flavonoids on invertebrate learning and memory [96].

Indeed, *Lymnaea* can be operantly conditioned to reduce aerial respiration, the memory of which is altered by environmentally relevant stimuli, so we can reliably assess how different factors alter memory formation [105, 120]. In particular, it has been demonstrated that when snails were operantly conditioned in (–)Epicatechin with a single 0.5 h training session, which typically results in memory lasting ~3 h, they formed LTM lasting at least 24 h [96]. Additionally, snails exposed to (–)Epicatechin also showed a significant increase in resistance to extinction, consistent with the hypothesis that this flavonoid may induce the formation of a more persistent and stronger LTM. In other words, (–)Epicatechin-enhanced LTM formed faster, persisted longer, and was more resistant to extinction. Thus, this was the first study that paved the way for a new avenue of research using L. *stagnalis* as a suitable model with which to elucidate behavioural, neuronal, and molecular mechanisms through which bioactive compounds may enhance neuroplasticity.

Additional studies demonstrated that (–)Epicatechin is only able to enhance memory if snails are either trained in (–)Epicatechin-containing pond water or exposed to it immediately after training for the operant conditioning of aerial respiration (i.e., during the consolidation period) [97].

In contrast, pre-treating snails with (–)Epicatechin 1 h before or delaying exposure to (–)Epicatechin 1 h after training did not result in the enhancement of memory formation. Thus, although (–)Epicatechin is a very powerful memory enhancer in *Lymnaea* as well as in mammals, it must be experienced either during training or immediately after training to effectively enhance memory [134].

As previously reported, learning and subsequent memory formation are influenced by both environmental and lifestyle factors, such as stress and diet [135, 136]. Therefore, while Flavonoids like (–)Epicatechin enhance LTM formation in *Lymnaea*, by contrast, ecologically relevant stressors, like low-calcium (20 mg l–1) pond water and crowding, suppress LTM formation [137–139].

Thus, in 2014, Knezevic and Lukowiak, demonstrated that exposure to (–)Epicatechin was able to overcome the negative effects of a stressor (i.e., low-calcium [137]) that blocks LTM formation in *Lymnaea* [140, 141]. Specifically, while snails trained in low-calcium pond water exhibited operant conditioning learning, they did not show LTM, but when epicatechin was added to the low-calcium pond water

an LTM enhancement was observed [140]. This was the first evidence in an invertebrate model organism that a naturally occurring bioactive plant compound was able to overcome the suppressive effects of an ecologically relevant stressor on LTM formation. Thus, this study demonstrated that the effects of a memory-impairing stressor can be overcome by diet.

As many foods, like green tea, cocoa powder, and Red Delicious apple peels [142–145] contain substantial amounts of (–)Epicatechin, Swinton et al., (2018) demonstrated that exposure to food products containing (–)Epicatechin in concentrations comparable to human consumption levels (approximately 1 g/day) during training for the operant conditioning of aerial respiration, enhanced LTM formation [127]. In particular, authors demonstrated that food substances containing (–)Epicatechin have a similar ability as the 'pure' flavonoid in enhancing memory. As UVB light inactivates (–)Epicatechin [146], following the photo-inactivation of foods containing this flavonoid, their ability to enhance LTM was blocked [127]. Therefore, these data are consistent with the hypothesis that dietary sources of (–)Epicatechin may exert positive benefits on cognitive ability and be able to reverse memory aversive states. *L. stagnalis* exhibits a higher-order associative learning called configural learning [147, 148]. That is, when snails experience two contrasting stimuli together such as predatory effluent [149] and an appetitive taste (i.e., carrot slurry), they learn and associate risk with food [112]. Thus, following the configural learning training procedure and the establishment of a configural learning LTM, the carrot slurry now elicits a fear state, sometimes referred to as a landscape of fear in the brain, rather than increased feeding [148]. Typically, configural learning memory persists for at least 3 h but not 24 h [150]. However, Batabyal and Lukowiak (2020), showed that green tea exposure (i.e., (–)Epicatechin) following the configural learning training enhances memory persistence if it occurred during the period when memory undergoes the consolidation process [150]. Thus, this study demonstrated for the first time that higher-order associative learning can be enhanced using green tea in an invertebrate taxon.

These promising results obtained by exposing snails to green tea led the researchers to investigate whether Black tea, which is a more popular beverage than green tea and which is derived from the same tea leaves, also enhances LTM formation [99, 151]. Interestingly, Zhang et al., (2018) found that black tea, unlike green tea, depressed homeostatic aerial respiratory behaviour and obstructed LTM formation for the operant conditioning of aerial respiration in *L. stagnalis* [99]. These differences may be due to the fluoride content in black tea [106, 152]. However, green tea also contains a similar amount of fluoride but it is rich in Flavonoids which are lacking in black tea, and that might lead to the differences observed in terms of cognitive enhancement. Recent studies from this model organism demonstrated the suppressive effects of black tea and fluoride on *Lymnaea*'s feeding behaviour and cognition [94, 152]. In addition, the exposure of snails to fluoride (1.86 mg/L) for 45-min before, during, or after the configural learning training procedure blocked configural learning memory formation [152]. The above-mentioned effects were long-lasting as one week after a fluoride exposure, snails are still unable to form a configural learning memory. *Why these differences?* Unlike green tea, black tea leaves go through an oxidation process called "fermentation" and this process substantially reduces (6.16 mg/100 g to 0.49 mg/100 g) the (–)Epicatechin content in black tea [153]. Furthermore, black tea contains more caffeine than green tea, but substantially more flavan-3-ols like thearubigins and theaflavins [153], which – in turn - may alter cognition [153]. These studies suggest that although both green and black teas come from the same plant (*Camellia sinensis*), the different compositions in bioactive compounds may result in different effects on neuroplasticity.

Along with (–)Epicatechin, another flavonoid widely studied in *Lymnaea* is quercetin. Quercetin (3,3′,4′,5,7-pentahydroxyfavone) is present in fruits and vegetables, such as apples, berries, onions, asparagus, capers, and red leaf lettuce [154]. Numerous studies have demonstrated quercetin's antioxidant and neuroprotective properties [155] in aged patients and animal models of neurodegenerative diseases [156]. Thus, studies performed in *L. stagnalis* may be extremely useful in exploring the effects of these compounds enhancing memory formation and recall. Recently Batabyal et al., (2021) demonstrated that the exposure of snails to quercetin for 1 h, either before or after configural learning enhanced LTM up to 48 h [150]. Interestingly, the enhanced LTM phenotype as a result of quercetin exposure in *L. stagnalis* was most pronounced when quercetin was experienced during the consolidation phase; or when snails were exposed to it during memory reconsolidation.

Consistent with these behavioural findings it was also shown that the exposure to quercetin for 1 h

induced a significant upregulation of the orthologous of the transcription factor CAMP responsive element binding protein 1 (CREB1) in the *Lymnaea*'s central nervous system. Importantly, in snails as in mammals, CREB1 plays a key role in neuroplasticity [38]. Similarly, Rivi et al., (2021) provided the first support for quercetin-modulated enhancement of cognitive function in an invertebrate model after an operant conditioning procedure [94]. That is when snails were exposed to quercetin for 1 h, 3 h before or after a single 0.5 h training session, which typically results in memory lasting $\sim$ 3 h, they formed an LTM lasting for at least 24 h [94]. Additionally, the authors assessed the effects of the combined presentation of a single reinforcing stimulus (at 24 h post-training or 24 h before training) and quercetin exposure on both LTM formation and reconsolidation.

These results suggested that, when applied within 3 h of critical periods of memory, quercetin enhances learning acquisition, memory consolidation, memory recall, and memory reconsolidation [94].

Interestingly, when those authors trained a naïve cohort of snails in hypoxic pond water and quercetin to determine whether this exposure resulted in enhanced LTM formation, quite unexpectedly, snails entered a sleep-like quiescent state that persisted for at least 2 h after ending the exposure [157]. The experiments suggest that this state might be a survival mode for these organisms when they cannot induce a physiological stress response of elevated Heat Shock Proteins' (HSPs) expression under a hypoxic environment.

Indeed, quercetin has proven to be a heat shock protein blocker [95, 108, 109, 158, 159]. In *Lymnaea*, the heat stress associated with exposure to 30°C pond water for 1 h led to a rapid (within 30 min) upregulation of the mRNA levels of both HSP40 and HSP70, reaching a peak of expression within 2–4 h of exposure [95, 160]. It was further demonstrated that the heat shock stressor-induced enhancement of LTM formation for both operant conditioning of aerial respiration and the Garcia effect (i.e., a 'special form' of conditioned taste aversion [95]) occurred as a result of the upregulation of HSPs by the heat shock stressor in snails [159]. However, the enhancing effect of the thermal stimulus on memory was obstructed if quercetin was presented before (but not after) the heat shock [95, 161]. Thus, studies from *Lymnaea* suggested that the exposure to quercetin and the heat shock results in opposite effects on LTM formation: when quercetin is applied before the heat shock, the upregulation of HSPs is blocked and LTM is not observed, whereas experiencing quercetin alone before or after the operant conditioning of aerial respiration or configural learning training, enhances LTM formation, consolidation, and recall. Thus, all these studies highlight the advantages of using *L. stagnalis* as a very useful model system in gaining an understanding of how bioactive compounds, such as the Flavonoids quercetin and epicatechin, may improve neuroplasticity in healthy organisms.

BRIDGING THE GAP BETWEEN PRECLINICAL AND CLINICAL STUDIES

Because of the ongoing process of aging experienced by modern society, the increasing prevalence of neurodegenerative diseases is becoming a global public health concern. Unfortunately, to date, there are no effective therapies to slow, stop, or reverse the progression of these diseases [162]. However, many studies have suggested that modification of lifestyle factors, such as the introduction of a balanced diet, can delay or prevent the onset of neurodegenerative diseases and psychiatric disorders. Diet is currently considered to be a crucial factor in controlling health and protecting against oxidative stress and chronic inflammation, and thus against chronic degenerative and psychiatric diseases [163].

In this context, natural bioactive compounds enhancing endogenous neuroplasticity raise hope for such therapies and preventive approaches. The preclinical studies from both mammals and invertebrates summarized in this paper have demonstrated that the neurorestorative actions of bioactive compounds (especially Flavonoids) are associated with both antioxidant and anti-inflammatory properties and also act through the activation of multiple pathways responsible for synaptogenesis and neurogenesis. Although evolutionarily quite distant from humans, invertebrates show molecular and behavioural properties that make them a wonderful model system to study the effects of dietary supplements and bioactive compounds on neuroplasticity paving the way for future studies in humans. The use of invertebrate models will limit as much as possible the use of mammalian models and allow mammals to be involved only for the validation of the results obtained from invertebrates. This will reduce by several orders of magnitude the costs of numerous studies. Thus, invertebrates as model systems provide a rapid and cost-effective experimental tool for elucidating the causal, neuronal, and molecular changes underly-

ing the effects of different bioactive compounds on neuroplasticity. Thus, these organisms may offer a translational approach that may help gain important knowledge and comprehension in the field of Clinical Neuroscience.

FINAL CONSIDERATIONS AND FUTURE PERSPECTIVES

Inter-ethnic differences in the use of bioactive compounds and their metabolism

Historically the production of medicines and pharmacological treatments began with using plant-based natural medicines (herbal medicine) and prior to the 1800 s and the advent of scientific experimentation, herbal remedies were culturally omnipresent throughout the globe [164–166]. This cultural preference for dietary bioactive compounds or alternative medicines stayed prevalent in many parts of the world [167]. In some countries, traditional herbal remedies which have been used for centuries are still deeply ingrained in the culture. In other countries, modern Western medicine is more heavily relied upon. In many Asian countries, for example, traditional Chinese medicine and Indian Ayurvedic medicine are widely used and accepted [168–170]. These traditional systems use natural compounds such as herbs, minerals, and some cases animal products in their natural medicines [171].

In contrast, many Western cultures tend to rely more heavily on pharmaceutical drugs and place less emphasis on alternative therapies although Native Americans have always relied upon natural plant-based medication for treating ailments [166]. However, there is a growing interest and acceptance of alternative medicine globally as many people are now faced with sub-optimal health conditions due to lifestyle choices and are turning to natural compounds and alternative therapies to address their health concerns. The continued use and popularity of dietary supplements in recent years may be due to various factors, including fear of adverse events associated with prescription medications, cost of prescription medications, over-the-counter availability of dietary supplements, and perceptions that dietary supplements are "natural" or "herbal" and are therefore safer to use [172].

Although the use of food supplements and bioactive compounds is increasing worldwide, cultural preferences for natural compounds or the so-called 'alternative medicines' vary greatly around the world [173]. Although dietary supplement use is a worldwide growing phenomenon, only a few studies examine why consumers choose to take bioactive compounds [174]. Thus, future studies are necessary to answer questions like: *What factors are primary motivators for the initiation of supplement behaviours as well as the decision-making related to short-term or long-term use? How does the use of bioactive compounds vary across cultures? How do motivations differ across different segments of the population? How do social norms influence and increase their use?* Answering these questions is important considering that ethical differences reflect differences in drug and bioactive compound metabolism [175]. Therefore, examining ethnic differences in metabolic processes across groups is both urgent and important to define and predict the pharmacokinetics of dietary bioactive compounds and their potential interaction with 'classical drugs'.

Issues related to potential adverse reactions and challenges in monitoring safety

Although the intake of bioactive compounds has shown promising potential beneficial effects on neuroplasticity [176], many of them remain untested and their use is poorly monitored [177, 178]. Unfortunately, there is still inadequate knowledge of their mode of action, potential adverse reactions, contraindications, and interactions with existing 'orthodox' drugs to promote both the safe and rational use of these compounds. Since safety is the major issue with the use of bioactive compounds and dietary supplements, it becomes imperative, that relevant regulatory authorities put in place appropriate measures to protect public health by ensuring that all herbal medicines are safe and of suitable quality [179]. Importantly, as by law, dietary supplements are not intended to diagnose, treat, prevent, or cure any disease, FDA-approved evidence of safety and efficacy is not needed before their appearance on the market. However, if these compounds are used improperly there could be a risk of adverse effects [180, 181]. However, their potential importance needs to be placed in scientific research to understand the nuances of the action of such compounds as most show a multifaceted effect working across different physiological pathways [182, 183]. Moreover, healthcare professionals are often poorly informed on how bioactive compounds may affect (both positively and negatively) the health of their patients and the efficiency and safety of the thera-

pies. Thus, as with other medicines for human use, it has become mandatory that bioactive compounds are covered in every country of the world by a drug regulatory framework to ensure that they conform to the required standards of safety, quality, and efficacy. This is the only way in which the use of bioactive compounds in potential complementary or alternative cognitive therapeutics and preventive approaches will be possible.

Complementary Versus Alternative

The use of bioactive compounds to prevent and/or treat disorders is not typically part of conventional medical care or training when their origins come from outside of usual Western practice. Importantly, when describing these approaches, people often use "alternative" and "complementary" medicine interchangeably. However, the two terms refer to different concepts. If a non-mainstream approach is used together with conventional medicine, it's considered "complementary", whereas if a non-mainstream approach is used in place of conventional medicine, it's considered "alternative" [184]. As most people in Western countries use bioactive compounds together with conventional drugs, the term '*complementary* should be preferred.

To sum up, this Scoping Review emphasizes the significance of different model systems that could act as valid tools for studying the diverse qualities of bioactive compounds like Flavonoids in preventing and/or treating cognitive decline. Nevertheless, there's still a lack of enough data regarding their best doses, how well the body can absorb them, distinctions between various chemical forms, and potential interactions with other dietary elements and 'traditional' drugs.

Although more research in this area is necessary, results from preclinical studies are promising and support the benefits of the intake of food products rich in these substances. Thus, we hope that in the near future, the results from preclinical studies (using both invertebrates and vertebrates) may provide important information on how to combine longer life expectancy with more years free of cognitive impairment.

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