

Review Article

The Role of Dietary Polyphenols on Adult Hippocampal Neurogenesis: Molecular Mechanisms and Behavioural Effects on Depression and Anxiety

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Although it has been long believed that new neurons were only generated during development, there is now growing evidence indicating that at least two regions in the brain are capable of continuously generating functional neurons: the subventricular zone and the dentate gyrus of the hippocampus. Adult hippocampal neurogenesis (AHN) is a widely observed phenomenon verified in different adult mammalian species including humans. Factors such as environmental enrichment, voluntary exercise, and diet have been linked to increased levels of AHN. Conversely, aging, stress, anxiety and depression have been suggested to hinder it. However, the mechanisms underlying these effects are still unclear and yet to be determined. In this paper, we discuss some recent findings addressing the effects of different dietary polyphenols on hippocampal cell proliferation and differentiation, models of anxiety, and depression as well as some proposed molecular mechanisms underlying those effects with particular focus on those related to AHN. As a whole, dietary polyphenols seem to exert positive effects on anxiety and depression, possibly in part via regulation of AHN. Studies on the effects of dietary polyphenols on behaviour and AHN may play an important role in the approach to use diet as part of the therapeutic interventions for mental-health-related conditions.

1. Introduction

A long-standing dogma in the brain sciences stated that new neurons were only generated during development. However, in the mid-1900s new evidence indicated the need for a change in this doctrine, as an unknown capacity in the adult mammalian brain started to be unraveled: adult neurogenesis.

Two regions in the adult mammalian brain, including human [1], can be pointed as neurogenic sites [2]: the subventricular zone (SVZ), located along the sides of the lateral ventricles, and the subgranular zone (SGZ) of the dentate gyrus (DG) in the hippocampus.

The new neurons generated in the SVZ migrate through a precise route, the rostral migratory stream (RMS), and integrate into the olfactory bulb, where they continuously replace local neurons [3]. In the DG, new neurons are generated from two types of progenitors or precursors located in the SGZ [4]: type 1 hippocampal progenitors, which extend a radial process across the granular layer, ramifying in the inner molecular layer, and type 2 cells, which are hippocampal progenitors with short processes (Figure 1, also showing the 3 types of progenitor cells lying adjacent to the ependymal cell layer in the SVZ: type B cells, which are GFAP positive; type C transit amplifying cells; type A, which are migrating neuroblasts) [4].

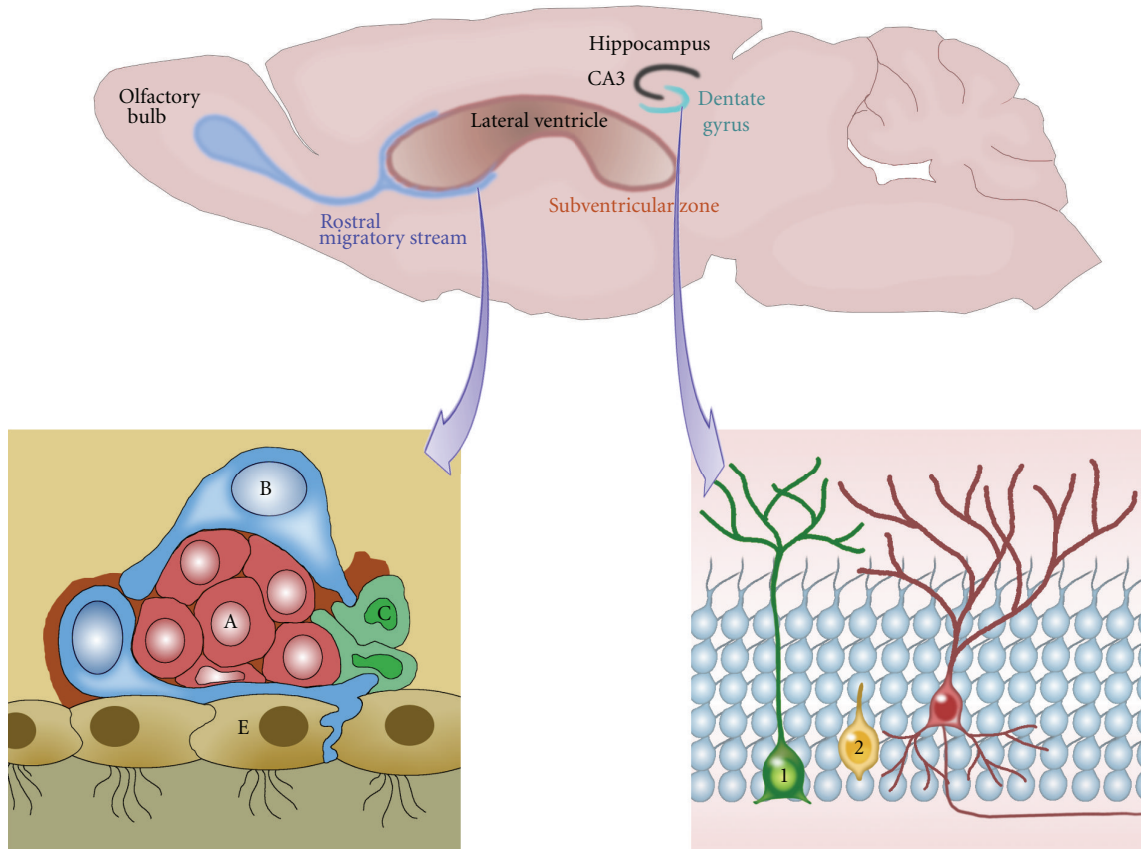


FIGURE 1: *Adult neurogenesis in the mammalian brain.* The figure illustrates the two well-known neurogenic sites in the brain: the subventricular zone (SVZ) and the dentate gyrus of the hippocampus (DG). Three types of progenitor cells are found lying adjacent to the ependymal cell layer (E) in the SVZ: A subset of relatively quiescent GFAP+ radial cells (type B cells) in the SVZ has the potential to serve as adult NSCs and generate rapidly dividing, transit-amplifying nonradial NSCs (type C cells), which in turn give rise to neuroblasts (type A cells) that migrate through the rostral migratory stream toward the olfactory bulb. In the adult SGZ, a population of GFAP+ Sox2+ radial cells corresponds to quiescent NSCs (type 1 cells). They coexist with actively proliferating, GFAP+ Sox2+ nonradial NSCs (type 2 cells) that generate both astrocytes and neuroblasts. Neuroblasts then migrate into the granule cell layer and mature into neurons (red cell).

The new neurons generated in the adult hippocampus, specifically in the SGZ of the DG, migrate to the inner layer of the granule zone, where they send/receive synaptic contacts [5].

Adult neurogenesis is a widely preserved phenomenon, being verified in different mammalian species such as mice, rats, guinea-pigs, monkeys, and humans [1, 6–12]. In both mentioned neurogenic sites, adult neurogenesis follows defined stages, identified as proliferation, cell fate determination, migration, and synaptic integration [5]. Many factors can impact the regulation of these different steps, possibly via the influence of factors released from vasculature [13, 14] and complex cell-cell interactions, between progenitor cells and other progenitors, astrocytes, and local/distal neurons [4].

Some environmental factors have been shown to influence adult hippocampal neurogenesis (AHN), such as voluntary exercise, enriched environment, and caloric restriction that increase the rates of AHN [15–17], whereas stressful conditions like aging or stress itself have a decreasing influence [8, 18].

Stress is one of the most potent negative modulators of hippocampal neurogenesis, as demonstrated in several species of mammals [19]. This effect has been demonstrated by different paradigms, such as exposure to predator odour [20], resident-intruder model of stress [8], psychosocial stress [21], inescapable shock [22], and others (reviewed in [23]). However, the mechanisms involved in this deleterious effect have not yet been totally clarified. There is evidence of a role for hormones and cytokines released during stress in modulating AHN. Indeed, AHN is very sensitive to the increase in corticoid levels [19], with these hormones negatively regulating it. It is also known that the hippocampus plays a role on the regulation of endocrine functions, possibly promoting a negative regulation of the hypothalamus-pituitary-adrenal (HPA) axis [24]. This involvement of the hippocampus is evidenced by the high concentration of glucocorticoid and mineralocorticoid receptors in this brain structure (reviewed in [25]). However, there is also evidence of a role for the newly generated neurons buffering the stress response. Indeed, a recent study has shown that the ablation of AHN led to a modulation of glucocorticoid levels after

moderate stress, with a sustained increase in the levels of these hormones even after a significant period following the stressful event [26]. This reinforces the modulating role of the hippocampus on the HPA axis through both AHN and the more established negative feedback via glucocorticoid receptors. This same study has suggested a relation between neurogenesis and the aetiology of depression. As stated, it has been proposed that depressed individuals have reduced hippocampal volume [27, 28]. In addition, there is increasing evidence from animal research that antidepressants might exert a proneurogenic effect in the hippocampus [29], and the ablation of neurogenesis has led to depressive behaviour in animals tested in the forced swimming test (FST) and in the sucrose preference test (SPT) [26, 30].

The role of AHN is still intensely debated. While several contradictory findings emerge when analyzing the literature, evidence in favour of a relevant role of adult-born neurons in hippocampus-dependent learning is compelling; spatial and associative memory is impaired in rodents under conditions that decrease AHN, whereas hippocampus-dependent learning tasks are solved better under conditions that increase AHN (reviewed in [31]).

AHN is also said to play a role in different neurodegenerative, neurological, and psychiatric disorders such as Alzheimer's and Parkinson's disease, anxiety, and depression. With regard to the latter, a small reduction of hippocampal volume has been found in human patients suffering from depression, suggesting an involvement of the hippocampus in mood disorders [27, 28]. Reduced AHN in different animal models of depression supports this observation as well as the ability of antidepressants to restore it [22, 28]. However, data from different studies are still controversial and the specific features that characterise the involvement of AHN in depression and anxiety are not absolutely clear. On the one hand, decreased AHN does not necessarily induce depressive behaviour in laboratory rodents [30, 32] and on the other hand, minimally normal levels of AHN have been shown to be necessary for the successful effect of some antidepressants [30, 33], and for buffering depressive behaviour [26].

Several studies during the last 5 years suggest that changes in diet can have a positive influence on neurogenesis, learning, and memory as well as cognition and mood (reviewed in [34]). As mentioned, laboratory rodents that were fed under calorically restricted conditions had a higher amount of AHN than *ad libitum* fed fellows, a process most likely regulated via the brain-derived neurotrophic factor (BDNF) [17]. Other positive effects on brain function were achieved by omega-3 fatty acids and vitamins, as well as by polyphenolic components of grapes, blueberries, cocoa, or teas (reviewed in [35, 36]). Polyphenolic compounds are phytochemicals known for their biological antioxidative, neuroprotective, and cognitive properties. For instance, it has been shown that different polyphenols can increase synaptic plasticity in the context of AHN [37–40] and also promote hippocampal long-term potentiation [41]. In addition, it has been verified that polyphenols can enhance learning and memory [42, 43] and reduce the risk of developing age-related neurodegenerative diseases [44, 45], possibly via a

decrease in reactive oxygen species (ROS) production and inflammation in models of aging [46, 47].

Besides antidepressant drugs, different polyphenolic compounds such as catechins (flavanols/flavonoid from green tea), curcumin (nonflavonoid from tumeric/*Curcuma longa*), and resveratrol (stilbenoid produced naturally by several plants when under attack/found high in red grape skin) have been observed to have antidepressant-like effects in rodents and human [48–52]. This suggests that polyphenols could be key compounds for the improvement of psychiatric disorders like depression or anxiety.

The facts that polyphenols have been shown to be helpful compounds against depression and that they can increase AHN suggest that these molecules might affect mood, and not only cognition, via AHN. In this way, this paper aims to address this hypothesis, discussing the effects of dietary polyphenols on mental health, particularly on depression and anxiety, and the possible molecular mechanisms underlying these effects via AHN regulation.

2. Polyphenols and AHN

2.1. Effects of Polyphenols on AHN. Many of the studies about the impact of polyphenols on the hippocampus have relied on the antioxidant properties of these molecules and their neuroprotective effect in different models of brain injury [53–61] (see Table 1 for details), with the majority of them not having addressed AHN. However, the emerging evidence of hippocampal plasticity offered by the mechanisms underlying AHN has made this phenomenon a promising target for pharmacological, environmental, and nutraceutical interventions, such as polyphenolic diet, raising the need for studies focusing on how these factors could impact the ability of the adult hippocampus to generate new functional neurons.

A positive role of a diet enriched in polyphenols and polyunsaturated fatty acids (LMN diet) on adult mice neurogenesis has been shown [37]. Following 40 days of LMN diet, different markers of AHN have been found to be increased in comparison to mice under control diet, such as the number of newly generated cells in the SGZ (as well as in the SVZ), with significantly more cells expressing the neuroblast marker doublecortin, suggesting that the LMN diet had an effect on neuronal populations. Indeed, the rise in neuronal differentiation was confirmed by the increased colocalization of the cell proliferation marker 5-bromo-2'-deoxyuridine (BrdU) and NeuN—expressed in mature neurons—in neurons of the granule layer of animals fed with the polyphenolic/fatty acid-enriched diet. Although more is yet to be specifically clarified, one of the possible mechanisms suggested for the increase in AHN by this special diet could be the induction of hippocampal plasticity factors such as insulin-like growth factor-1 (IGF-1) and its receptor (IGF-1R), as previously shown by short-term blueberry supplementation in rats [62]. In addition, the neurogenic potential of the LMN diet has also been suggested in a recent study that showed it to be capable of increasing to 70% the rate of cell proliferation in the SVZ of a mouse model of Alzheimer's disease [54]. However, since

TABLE 1: Effects of polyphenols, particularly green tea/epigallocatechin and curcumin, on different neurochemical and morphological aspects of the hippocampus. BB: blueberry; EGC: epigallocatechin; GT: green tea.

Reference	Polyphenol	Treatment	Model	Effect on hippocampus	Proposed molecular mechanism(s)
Xu et al. 2009 [53]	Curcumin	Curcumin (5, 10 and 20 mg/kg, p.o.) or imipramine (10 mg/kg, i.p.)	Sprague-Dawley rats	Curcumin prevented hippocampal dendritic remodeling under conditions of chronic stress	Normalizing corticosterone levels and downregulating pCaMKII and glutamate receptor levels
Fernández-Fernández et al. 2011 [54]	LMN diet (polyphenols and fatty acids)	Control or LMN diet for 5 months	Tg2576 male mice as a model of AD crossing them with 129S1/SvImJ females	Reduction of A β plaques in the hippocampus when administration of diet occurred before plaque formation	—
Joseph et al. 2010 [55]	Blueberry	HNCs treated with BB extract, BB fractions (e.g., proanthocyanidin, PAC) or control medium were exposed to dopamine (DA, 0.1 mM), amyloid beta (A β 42, 25 μ M) or lipopolysaccharide (LPS, 1 μ g/mL)	NeuroPureTM E18 primary rat hippocampal cells	Results indicated that the degree of protection against deficits in Ca $^{2+}$ recovery varied as a function of the stressor and was generally greater against A β 42 and LPS than DA	Prevention of deficit in Ca $^{2+}$ buffering, normalization of cyclic CREB, protein kinase C γ (PKC γ) and increased expression of ERK
Narita et al. 2011 [56]	Grape seed extract (GSE: Koshu and Muscat Bailey)	50 mM glutamate for 30 min, in the presence or absence of various concentrations of GSEs	Hippocampal tissue isolated from newborn mice (C57/B6; P1)	Koshu: alleviated the acute inactivation of Erk1/2 and dendrite retraction in cultured hippocampal neurons exposed to a toxic concentration of glutamate (1.0 ng/ml) Muscat Bailey: no neuroprotective effect	High-affinity molecular targets
Fujishita et al. 2009 [57]	Grape seed extract (GSE, Koshu)	0, 1, 10, 30, 100 μ g/mL for 24 h or 0, 1, 10, 30, 100 μ g/mL for 2, 6, or 12 h.	Culture of hippocampal neurons and astrocytes	GSE upregulated (concentration (100 μ g/mL) and time-dependently); various mRNAs for cytokines, particularly for interleukin-6 (IL-6)	GSE could protect neuronal cells from death by oxidative stress via upregulated IL-6 production in astrocytes
Assunção et al. 2011 [58]	Green tea/epigallocatechin	19 month-old rats were fed with GT since age of 12 Months	Wistar rats	GT treatment protected proteins and lipids against oxidation and prevented the increase of lipofuscin deposition	—
Assunção et al. 2010 [59]	Green tea	Rats fed with GT from 12 to 19 months of age versus controls aged 19 months	Wistar rats	GT increased CREB activation and the levels of BDNF and Bcl-2, but had no effect on activation of NF- κ B subunits	Long-term GT ingestion improves antioxidant systems and activates CREB in the aging rat hippocampal formation, leading to neuroprotection mediated by downstream upregulation of BDNF and Bcl-2

TABLE 1: Continued.

Reference	Polyphenol	Treatment	Model	Effect on hippocampus	Proposed molecular mechanism(s)
Yin et al. 2008 [60]	Green tea/Epigallocatechin-3-gallate	Treatment by EGCG (10–50 μM)	Hippocampal neuronal culture; lead exposure	Lead exposure significantly inhibited the viability of neurons; treatment with EGCG effectively increased cell viability and decreased ROS formation	Free radical scavenging and antioxidative properties of EGCG
Xu et al. 2010 [61]	Green tea/epigallocatechin	GT polyphenols were administered orally to rats from 4 to 8 weeks after experimentally induced cerebral hypoperfusion (400 mg/kg per day or 100 mg/kg)	Wistar rats	Reduced lipid peroxidation and oxidative DNA damage after chronic cerebral hypoperfusion	Free radical scavenging and antioxidative properties of GT polyphenols

a fatty-acid-(F-A) exclusive diet has not been used, there is no conclusive evidence that the effects found are due only to polyphenols. In this sense, the contribution of FA or a synergistic effect of polyphenols and FA should be considered.

This positive effect of polyphenols on hippocampal neurogenesis has also been demonstrated *in vitro*, with low concentrations of curcumin stimulating cell differentiation in cultures of multipotent mouse neural progenitor cells. A similar effect has been demonstrated *in vivo*, with increased AHN in mice administered with this polyphenol [38] (see Section 3.2.2 for further discussion on the effects of curcumin on mental health and possible molecular mechanisms underlying it).

In addition to curcumin, the interaction between polyphenol and chronic stress has also been found with the administration of flavonoids. In this sense, administration of flavonoids extracted from Chinese herb Xiaobuxin-Tang (XBXT-2) significantly increased hippocampal neurogenesis in chronically stressed rats [39]. Additionally, XBXT-2 treatment reversed the stress-induced decrease of hippocampal BDNF and phosphorylated cyclic AMP-response element DNA-binding protein (pCREB) (Ser133) expression, two important factors closely related to hippocampal neurogenesis. Interestingly, as occurred with curcumin, the positive effects of these flavonoids were comparable to those achieved with imipramine treatment.

Dietary polyphenols are thought to be the most abundant antioxidants in foods and beverages [63], with particular potential to inhibit neuroinflammation (reviewed in [64]). Thus, with special regard to inflammation, oxidative stress and microglial activation—all factors known to decrease cell proliferation and neuroplasticity—it has been shown that neural progenitor cell proliferation and spatial memory performance are increased, with decreased microglial activation, in aged rats submitted to 4 weeks of treatment with NT-020—a natural diet based on the combination of polyphenols from blueberry and green tea, as well as antioxidant and anti-inflammatory amino acids like carnosine [65]. It is well established that one of the physiological markers of aging is the increase in circulating factors such as cytokines and chemokines, known to increase proinflammatory factors that exert a negative effect on the progenitor cell pools. The authors then suggest that the positive influence of the NT-020 diet on health promotion could occur via the promotion of proliferation and survival of neurons, as well as by anti-inflammatory actions that influence the stem cell niche of the aged brain [65].

Table 2 summarises the studies discussed before, on the effects of polyphenols on hippocampal cell proliferation and differentiation.

3. Polyphenols and Mental Health

3.1. Effects of Dietary Polyphenols on Depression and Anxiety: Behavioural Aspects and Proposed Mechanisms of Action. There is a growing body of data from animal and human studies supporting the role of a variety of dietary polyphenols in affecting behaviour and mood through anxiolytic

and antidepressant-like properties (see Table 3). The varied mechanisms proposed for the effects of polyphenols on mental health and the mounting evidence for the role of each are suggestive of the complexity of the diverse interactions influencing mood and behaviour. Thus the multiple cellular and molecular mechanisms resulting in antidepressant-like or anxiolytic effects of a particular polyphenol can reveal potential targets at the level of the individual pathways which may collectively contribute to a common behavioural phenotype in the context of the etiologies of anxiety and depressive disorders and expand our understanding of interactions of these pathways.

The proposed mechanisms for polyphenol effects on mental health are not limited to their well-established antioxidant effects and are as varied as the different polyphenols themselves and the sources in which they are found. Chlorogenic acid is a common dietary polyphenol found in fruits such as plums, apples, and cherries and beverages such as tea and coffee which has been shown to have anxiolytic effects in animal studies [67, 76]. Chlorogenic acid has been demonstrated to have a number of effects on a cellular level, leading to several proposed mechanisms for its overall anxiolytic effects. In one study, the anxiolytic effect of chlorogenic acid was blocked *in vivo* by the benzodiazepine receptor antagonist flumazenil, suggesting that anxiety is reduced by activation of the benzodiazepine receptor [67]. *In vitro*, chlorogenic acid protected granulocytes from oxidative stress, which is another proposed important contributor to anxiety [67]. It has also been found to have neurotrophic effects *in vitro* that stimulate neuronal differentiation and neurite growth, supporting neuroplasticity, which also may contribute to its anxiolytic effects [66].

Other polyphenols have been shown to exert anxiolytic effects with proposed mechanisms that overlap those of chlorogenic acid. Like chlorogenic acid, the green tea polyphenol epigallocatechin-3-gallate (EGCG) has also been shown to have anxiolytic properties in animal studies with comparable results to a benzodiazepine anxiolytic drug [68]. *In vitro* work with cultured hippocampal neurons confirmed the specific modulation of the GABA-A receptor benzodiazepine site by EGCG [68].

However, other studies suggest that different pathways might contribute to the anxiolytic effects of other polyphenols. Anthocyanin polyphenols from *Vaccinium* berries (a genus which includes highbush blueberries, rabbiteye blueberries, and bilberries) also show anxiolytic effects in animal studies but *in vitro* studies have elucidated several different mechanisms which may be responsible for the anxiolytic property of this class of polyphenols [69, 77, 78]. The antioxidant properties of anthocyanins from rabbiteye blueberries were shown to reduce oxidative damage to neural DNA and this antioxidant neural protection was proposed as a mechanism for the anxiolytic property of berries [69]. Berry anthocyanins also inhibit monoamine oxidases (MOAs), providing neuroprotective effects and counteracting the MOA activity of lowering neural levels of serotonin, noradrenaline, and dopamine whose low levels have been implicated in the etiology of anxiety disorders [77]. Blueberry polyphenols also have anti-inflammatory

TABLE 2: Effects of different polyphenolic-based diets or treatments on the expression of cell proliferation and differentiation markers, especially in the adult hippocampus.

Reference	Polyphenol	Treatment	Model	Effect on AHN	Proposed molecular mechanism(s)
Valente et al. 2009 [37]	LMN diet (polyphenols and fatty acids)	<i>In vivo</i> : animals fed for 40 days with either a control diet or with LMN diet	<i>In vivo</i> : 129S1/Sv1mJ mice	<i>In vivo</i> : increased proliferation and differentiation in DG and SVZ	—
		<i>In vitro</i> : LMN cream (0.05, 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80, and 1.00 mg/mL) for 24 h	<i>In vitro</i> : neuron-glia cell cultures (hippocampal and cortical) pretreated with H ₂ O ₂	<i>In vitro</i> : cortical cells: antioxidant effect (approximately 80%) Hippocampal cells: antioxidant LMN range concentration restricted to 0.50 and 0.60 mg/mL; antioxidant capacity of approximately 100%	—
So et al. 2008 [38]	Curcumin	<i>In vitro</i> : (0.1, 0.5, 1, 10, 20, and 50 uM)/well	Multipotent NPC; C57BL/6 mice	<i>In vitro</i> : increased proliferation (0.1, 0.5 uM) (BrdU)	Curcumin stimulates the proliferation of embryonic cortical neural stem cells via the MAP kinase pathway
		<i>In vivo</i> : 500 nmol/kg body weight, once daily for 4 days		<i>In vivo</i> : increased proliferation and differentiation (NeuN)	Increased neurogenesis and expression of hippocampal BDNF and pCREB as one of the molecular and cellular mechanisms underlying the antidepressant action of XBXT-2
An et al. 2008 [39]	Flavonoids (XBXT-2)	XBXT-2 (25 or 50 mg/kg), imipramine (10 mg/kg, p.o.)	Sprague Dawley rats submitted to chronic stress	Increased proliferation (BrdU) Increased hippocampal BDNF	
Xu et al. 2007 [40]	Curcumin	Curcumin (5, 10 and 20 mg/kg, p.o.) or imipramine (10 mg/kg, i.p.)	Sprague-Dawley rats submitted to chronic stress	Increased proliferation (BrdU) Increased BDNF levels	Upregulation of 5-HT1A receptor mRNA and of BDNF levels
Fernández-Fernández et al. 2011 [54]	LMN diet (polyphenols and fatty acids)	Control or LMN diet for 5 months	Tg2576 male mice as a model of AD crossing them with 129S1/Sv1mJ females	Increased proliferation in the subventricular zone (SVZ) (BrdU)	—
Acosta et al. 2010 [65]	NT-020 diet (polyphenols, vitamin D3, and carnosine)	Aged: 135 mg/kg per day of NT-020 diet orally administered for 4 weeks versus young and aged controls treated with water by oral gavage	Fischer 344 rats	Increased proliferation (Ki67) Increased differentiation (DCX) Decreased activated microglia	Reduction of proinflammatory compound counteracts age-related decrease of neurogenesis
Ito et al. 2008 [66]	Chlorogenic acid	Polyphenol added to the medium to final concentration of 10 μM	Fetal rat hippocampal neurons	Promoted neuronal differentiation	—

TABLE 3: Effects of different dietary polyphenols on mental-health-related states and behaviour, particularly anxiety and depression. EGC: epigallocatechin; GT: green tea.

Reference	Polyphenol	Treatment	Model	Effect on mental health/behavior	Proposed molecular mechanism(s)
An et al. 2008 [39]	Flavanoids	XBXT-2 (25 or 50 mg/kg), imipramine (10 mg/kg, p.o.)	Sprague Dawley rats submitted to chronic stress	Antidepressant-like effect	Increased neurogenesis and expression of hippocampal BDNF and pCREB as one of the molecular and cellular mechanisms underlying the antidepressant action of XBXT-2
Duffy et al. 2008 [42]	Blueberry	2% blueberry extract versus control diet over 8 weeks	Fischer-344 rats submitted to kainate-induced learning impairment	Blueberry diet reduced memory impairment Less loss of CA1 pyramidal neurons	Possible involvement of MAPK
van Praag et al. 2007 [43]	Flavanoids (-) epicatechin	(-) epicatechin diet ad libitum versus control ad libitum	C57/Bl6 mice (runner versus non-runner)	(-) epicatechin improved memory in Morris water maze especially in combination with exercise	Increase of angiogenesis and spine density
Messaoudi et al. 2008 [48]	Cocoa	Effective doses of cocoa: 24 mg/kg/14 days and 48 mg/kg/14 days	Wistar rats	Antidepressant-like effects measured in the Forced swimming test	Reversal of oxidative damage
Sathyapalan et al. 2010 [49]	Cocoa	High cocoa liquor/polyphenol rich chocolate diet or cocoa liquor free/low polyphenol diet for 8 weeks	Human fatigue syndrome patients	Chalder Fatigue Scale score improved significantly after 8 weeks of the HCL/PR diet	
Xu et al. 2005 [50]	Curcumin	Curcumin (1,2.5, 2.5, 5, 10 mg/kg), or moclobemide (20 mg/kg), imipramine (10 mg/kg)	ICR mice	Curcumin also significantly inhibited immobility in FST	Antidepressant-like effects of curcumin may involve the central monoaminergic neurotransmitter systems
Xu et al. 2010 [51]	Trans-Resveratrol	<i>t trans</i> -Resveratrol (20, 40 and 80 mg/kg, via gavage) moclobemide (20 mg/kg, i.g.), imipramine (10 mg/kg, i.p.), and fluoxetine (10 mg/kg, i.p.)	ICR mice	Decreased the immobility time in mouse models of despair	Antidepressant-like effect of <i>trans</i> -resveratrol might be related to serotonergic and noradrenergic activation
Zhu et al. 2011 [52]	Green tea/epigallocatechin	Orally administered green tea polyphenols (GTP; 5, 10 and 20 mg/kg) for 7 days Forced swimming test (FST) and tail suspension test (TST) 60 min after the last GTP administration	ICR mice	Antidepressive-like effects	May involve inhibition of HPA axis; possibility that chronic GTP treatment can reduce HPA axis hyperactivity in response to stress
Xu et al. 2009 [53]	Curcumin	Curcumin (5, 10, and 20 mg/kg, p.o.) or imipramine (10 mg/kg, i.p.)	Sprague-Dawley rats submitted to chronic stress	Curcumin reversed impaired spatial memory under conditions of chronic stress	Normalizing corticosterone levels and downregulating pCaMKII and glutamate receptor levels
Assunção et al. 2011 [58]	Green tea/epigallocatechin	19-month-old rats were fed with GT since age of 12 months	Wistar rats	Spatial learning abilities of GT-treated rats were significantly improved	Scavenging of free radicals

TABLE 3: Continued.

Reference	Polyphenol	Treatment	Model	Effect on mental health/behavior	Proposed molecular mechanism(s)
Xu et al. 2010 [61]	Green tea/epigallocatechin	GT polyphenols were administered orally to rats from 4 to 8 weeks after experimentally induced cerebral hypoperfusion (400 mg/kg per day or 100 mg/kg)	Wistar rats	Inhibited cognitive impairment Improved spatial learning and memory deficits induced by chronic cerebral hypoperfusion	Free radical scavenging and antioxidative properties of GT polyphenols
Bouayed et al. 2006 [67]	Chlorogenic acid (Mirabelle)	20 mg/kg	Mouse model of anxiety	Decreased in anxiety-related behaviours	Anxiety is reduced by activation of the benzodiazepine receptor
Vignes et al. 2006 [68]	Green tea/epigallocatechin	Acute administration—drugs injected intraperitoneally in a volume of 100 μ L per 20 g of body weight	Swiss OF1 mice	Anxiolytic effect in the elevated plus maze and passive avoidance tests	Anxiolytic effect could result from an interaction of the given polyphenols with GABAA receptors
Barros et al. 2006 [69]	Vaccinium berries	Water with berry extract over 30 days (0.6–1.0 mg/kg/day or 2.6–3.2 mg/kg/day)	Swiss mice	Decreased DNA damage in hippocampal tissue Anxiolytic effect in open-field test	Protective effect against free radical-induced DNA damage in the brain
Hou et al. 2010 [70]	Flavanols (Ginkgo biloba extract)	<i>In vivo</i> : 50 mg/kg per day for 4 months <i>In vitro</i> : 24 h incubation	<i>In vivo</i> : APPswe/P1D9 transgenic mice and wildtype <i>In vitro</i> : primary neuronal cells	<i>In vivo</i> : increased levels of BDNF in hippocampus; anti-depressant effects in wt mice <i>In vitro</i> : flavonols dose-dependently restored BDNF expression compared to vehicle control; increase of pCREB through glutamate-evoked activation	Increase in BDNF and glutamate-evoked activation of pCREB
Chen et al. 2010 [71]	Green tea/epigallocatechin	GTEs and EGCG 0.1 g/d	Wistar rats	Improved the cognitive impairments induced by stress	Involved with changes in plasma levels of catecholamines, 5-hydroxytryptamine, cytokines and expression of metallothioneins
Singal et al. 2004 [72]	Green tea/epigallocatechin	1. 50 μ g i.p. of endotoxin LPS in 250 μ L of pyrogen-freesaline 2. Green Tea Extract (GTE - 10, 25, 50, and 100 mg/kg)	Albino laca mice	Reversal of LPS-induced immobility	COX-2 inhibition by GTE

TABLE 3: Continued.

Reference	Polyphenol	Treatment	Model	Effect on mental health/behavior	Proposed molecular mechanism(s)
Sanmukhani et al. 2011 [73]	Curcumin	Acute study: treatment 24, 5, and 1 h before test: curcumin 50 mg/kg, 100 mg/kg, vehicle, fluoxetine, and imipramine control Chronic study: treatment for 14 days, same doses as in acute	Acute study: Swiss albino mice Chronic study: Wistar rats	Antidepressant-like effects in FST and TST at 100 mg/kg in acute and chronic study	Increases neural levels of serotonin, noradrenaline and dopamine possibly via inhibition of MOA activity
Xu et al. 2006 [74]	Curcumin	Curcumin (2.5, 5, and 10 mg/kg, p.o.) or imipramine (10 mg/kg, i.p.)	Sprague-Dawley rats submitted to chronic stress	Curcumin reversed the effects of chronic stress on behaviour	Effects of curcumin on the behavioural deficits induced by chronic stress may be related to modulating effects on the HPA axis; increased in BDNF and pCREB proteins in specific brain regions may also be related
Wu et al. 2006 [75]	Curcumin	Diet with and w/o curcumin (500 ppm) for 4 weeks	Sprague-Dawley rats submitted to fluid percussion injury	Curcumin-fed injured animals had lower levels of oxidized proteins and counteracted cognitive impairment	Modulation of BDNF-system which acts on CREB and synapsin

properties mediated through inhibition of the expression of inflammatory cytokines interleukin-1 β (IL-1 β) and tumour necrosis factor- α (TNF- α), inhibition of activities of the transcription factor nuclear factor- κ B (NF- κ B), and increased expression of the neurotrophic factor IGF-1 which may increase neural plasticity and neurogenesis [78]. Increases of these inflammatory cytokines and the transcription factor NF- κ B have been associated with the development of mental health disorders and inhibition of these cytokines and NF- κ B has been suggested as a method of treatment [79–82].

A number of polyphenols have been shown to have antidepressant-like effects as well. As was the case with polyphenols mediating anxiolytic effects, a variety of different mechanisms have been implicated for the antidepressant-like effects of different polyphenols. *Ginkgobiloba* extract contains many polyphenols including the flavonols quercetin, kaempferol, and isorhamnetin and has been shown to have antidepressant-like effects that could be due to its properties of increasing BDNF which would increase neuronal survival and plasticity or due its increase of pCREB through glutamate-invoked activation which would enhance synaptic strength and neuronal plasticity [70]. The ginkgo biloba flavonols quercetin and kaempferol also share the property of inhibiting the action of MOA's on serotonin and catecholamines with other polyphenols such as berry anthocyanins, the flavone apigenin in celery and the stilbene *trans*-resveratrol found in red wine [76, 77]. This MOA inhibition may contribute to antidepressant effects as elevated MOA activity is also linked to the etiology of depressive disorders [77]. The polyphenols in cocoa have also been shown to have antidepressant effects and to reduce the symptoms of chronic fatigue syndrome, possibly due to their anti-inflammatory properties mediated by inhibition of proinflammatory cytokines [48, 49, 83].

Green tea contains many polyphenols belonging to several molecular subclasses, including chlorogenic acid, pyrogallol, caffeic acid, (–)-epigallocatechin-3-gallate (EGCG), (–)-epigallocatechin (EGC), epicatechin-3-gallate (ECG), and (–)-epicatechin [71, 76, 84]. Green tea extracts have been shown to have antidepressant-like effects with multiple proposed mechanisms including antioxidant activity, regulation of adrenocorticotrophic hormone (ACTH) serum levels, inhibition of prostaglandins and inflammatory cytokines, increase of anti-inflammatory cytokines, and inhibition of MAO activity [52, 58, 71, 72, 85].

As can be seen in the examples of polyphenols discussed, many mechanisms of action for the antidepressant-like and anxiolytic behavioural effects of polyphenols show overlap between polyphenols and suggest shared cellular pathways that may interact and modulate each other.

A more detailed examination of a case in which the mechanisms of action for the antidepressant effects of the polyphenol have been elucidated may provide a clearer illustration of such modulation and interaction. The mechanisms of action for the polyphenol curcumin have been investigated in detail and provide an illustrative example of how polyphenol molecular and cellular pathways may interact with those established for conditions affecting neurogenesis and mental health such as stress and depression.

3.2. Proposed Curcumin Mechanisms of Antidepressant Action.

The antidepressant effects of curcumin, a polyphenol which is the active ingredient in the spice turmeric, were investigated using the standard testing paradigms used to screen antidepressant drugs. The forced swimming test (FST) and tail suspension test (TST) are two standard animal models of depressive behaviour measurement in which the degree to which the animal ceases to struggle and becomes relatively passively immobile is used to assess depressive behaviour and both have been used as accurate methods for screening antidepressant properties of drugs when used in conjunction with locomotion-screening tests to distinguish any central nervous system stimulant properties [86, 87]. Curcumin was shown to dose-dependently reduce despair immobility behaviour in the TST and FST to a degree comparable to commonly prescribed tricyclic and selective serotonin re-uptake antidepressants [50, 73]. Further in-depth behavioural comparisons combined with *in vitro* studies revealed that curcumin increased neural levels of serotonin, noradrenaline, and dopamine and inhibited MOA activity with molecular mechanisms that appear to differ from typical tricyclic and selective serotonin reuptake antidepressants [50, 73].

However, there were additional cellular mechanisms and antidepressant effects of curcumin revealed by a different animal model of depression which was based on prolonged stress and proved to be more sensitive to these diverse mechanisms. This stress model allowed a more detailed examination of curcumin's multiple mechanisms of action and reflected their complexity, illustrative of the diversity of mechanisms through which a single polyphenol can exert effect. Significantly, several of these pathways also act to upregulate neurogenesis, offering additional context for investigation of the cellular and molecular mechanisms by which other polyphenols exert antidepressant-like and anxiolytic effects.

Prolonged stress has been shown to have a role in the etiology of depression in humans and the chronic unpredictable stress in animal models of depression has been shown to parallel the anatomical, neuroendocrine, and behavioural aspects of depression in humans [74, 88, 89]. Thus the chronic unpredictable stress animal model has been productive in elucidating cellular and molecular mechanisms involved in the behavioural phenotype of depression and shown that antidepressant effects may be related in part to modulating the responses of the hypothalamus-pituitary-adrenal (HPA) axis [74, 89–92] (Figure 2).

Curcumin has been shown to have the ability to block or reverse the stress-induced changes typical of HPA axis dysfunction to a level comparable to a typical tricyclic antidepressant, including behavioural escape-response performance deficits, physiological changes in the adrenal gland, increases in corticosterone levels, reduced glucocorticoid receptor (GR) mRNA expression, decreased levels of BDNF, and reduced levels of phosphorylated CREB [74] (Figure 3).

Curcumin effects on restoring GR mRNA expression are particularly important when viewed in the context of HPA axis function. When functioning normally, activation of the HPA axis begins with the perception of physical or

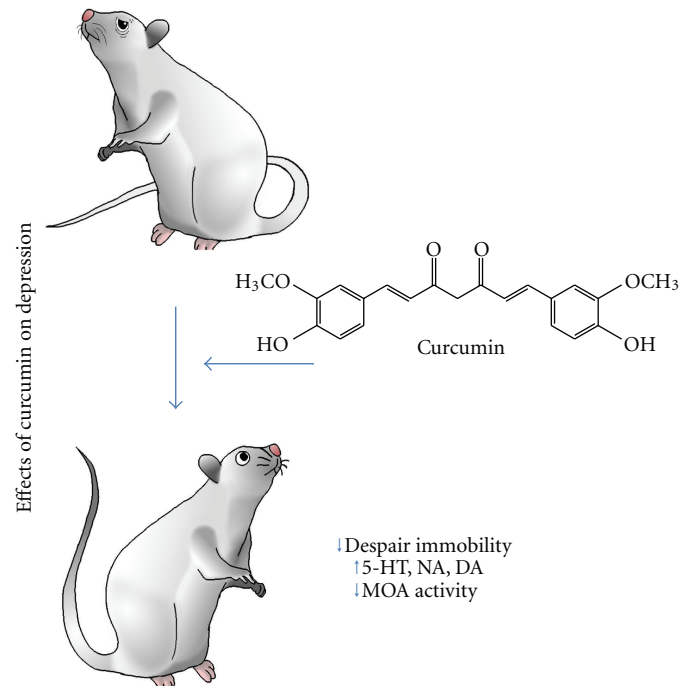


FIGURE 2: *Effects of curcumin on depression.* Administration of curcumin in rodent models of depression has been shown to ameliorate depressive-related behaviours, with decreased despair immobility, associated to increased levels of the neurotransmitters serotonin (5-HT), noradrenaline (NA), and dopamine (DA), and decreased activity of the enzyme monoamine oxidase (MOA).

psychological stress and results in stimulation of the adrenal cortex to release glucocorticoids (corticosterone in rodents and cortisol in humans). Glucocorticoids bind with the GR to regulate a number of systems in the body, including a self-limiting feedback mechanism acting to stop stimulation of glucocorticoid secretion and a GR feedback mechanism which lowers the production of inflammatory cytokines by inhibiting the activity of transcription factor $\text{NF-}\kappa\beta$ [93, 94].

Thus glucocorticoids normally operate their own negative-feedback mechanism to stop HPA axis activation and to inhibit inflammation response; yet this negative feedback effect on both systems has been shown ineffective in depression where high levels of cortisol co-exist with high levels of proinflammatory cytokines [82, 95, 96]. This apparent lack of responsiveness to the feedback mechanism is called glucocorticoid resistance and is attributed to dysfunction of GR signalling rather than to elevated glucocorticoid levels [82, 94, 97, 98].

Curcumin's antidepressant-like effects in increasing levels of stress-reduced GR mRNA expression may be one of the keys in restoring normal levels of GR signalling for GR-modulated feedback mechanisms and, coupled with curcumin's increase of phosphorylated CREB, may also have implications for restoration of neurogenesis. A recent study has shown that antidepressants increase GR expression and induce GR nuclear translocation and transcription activities through pathways involving cyclic AMP and protein kinase

A (PKA) which cumulatively result in increased levels of neurogenesis [90]. This might elucidate the mechanism of antidepressant effects established by earlier works in which antidepressant drugs were shown to restore stress-reduced levels of neurogenesis and GR expression, offering further context for understanding Curcumin's effects on GR expression [19, 29, 98].

Curcumin has also been shown to inhibit $\text{NF-}\kappa\beta$ activation pathways [99, 100]. Activated $\text{NF-}\kappa\beta$ moves into the nucleus where it disrupts GR signalling, preventing proper functioning of GR feedback mechanisms [94, 97]. Activation of $\text{NF-}\kappa\beta$ also upregulates inflammatory cytokines which can have a number of effects also shown in the etiology of depression, including further dysregulation of the HPA axis, metabolism of monoamine neurotransmitters through elevated MOA activity, reduced neuronal plasticity, and reduced neurogenesis [77, 89, 94]. Therefore inhibition of $\text{NF-}\kappa\beta$ activation by curcumin has a number of antidepressant-like effects on the cellular level, preventing the reduced monoamine levels due to the elevated MOA activity, $\text{NF-}\kappa\beta$ disruption of GR signalling, and the upregulation of inflammatory cytokines whose elevated levels would otherwise inhibit neurogenesis and further disrupt GR signalling [89, 90, 101].

Curcumin administration in chronically stressed rats increased hippocampal neurogenesis via modulation of the HPA axis and upregulation of BDNF and 5-HT 1A

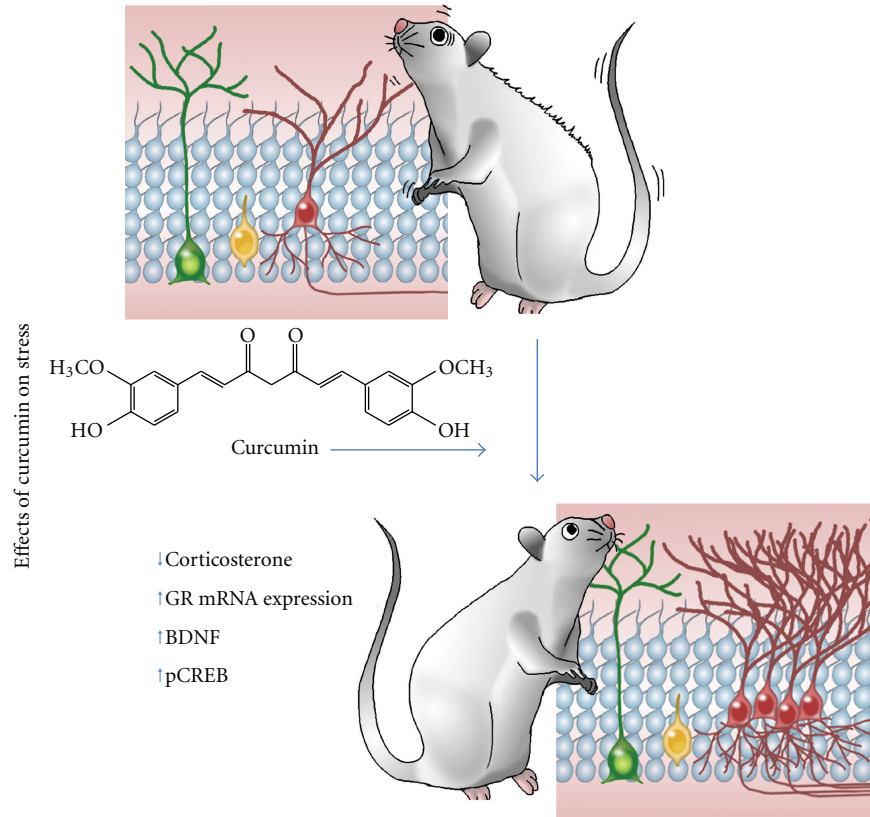


FIGURE 3: *Effects of curcumin on stress.* Administration of curcumin in rodent models of stress has been found to reduce stress-related behaviours, with decreased levels of the stress hormone corticosterone and increased levels of glucocorticoid receptor (GR) mRNA expression, brain-derived neurotrophic factor (BDNF), and phosphorilated cyclic AMP-response element DNA-binding protein (pCREB). Additionally, the decrease in AHN observed after exposure to stress has been found to be reversed following administration of curcumin.

receptors in the hippocampus [40]. Curcumin effects in restoring BDNF protein levels is important in the context of BDNF signalling in adult neurogenesis, shown to increase neuronal differentiation, survival, and dendritic arborisation [29, 102, 103].

However, modulation of serotonergic signalling has proven fundamental to curcumin antidepressant and neurogenic effects. The antidepressant-like effects of curcumin are mediated in part through direct agonistic functions on 5-HT 1A and 5-HT 1B receptors and antagonistic effects on 5-HT 2C receptors [104]. The effects mediated by curcumin upregulation of 5-HT 1A receptors may be even more critical to neurogenesis as 5-HT 1A, 5-HT 1B, and 5-HT 2A receptors have been proven necessary for adult hippocampal neurogenesis and 5-HT 1A receptor antagonists significantly decrease cell proliferation in the hippocampus [105, 106]. The increased serotonin signalling resulting from upregulation of 5-HT 1A receptors and agonist effects on 5-HT 1A and 5-HT 1B receptors is also very pertinent to the antidepressant effects of curcumin as increased serotonin transmission has profound antidepressant effects as well as being associated with an increase in adult neurogenesis [105].

The effect of curcumin on 5-HT receptors also modulates GR signalling through serotonergic signalling activation of PKA. Activated PKA translocates to the nucleus where it can

undergo protein-protein interactions with GR that optimise GR-DNA binding, stimulating GR signalling [94, 107]. In further interpathway modulation, activated PKA can also inhibit $\text{NF-}\kappa\text{B}$ from interfering with GR-DNA binding, thus increasing GR transcription activity through modulation of an additional pathway [94, 108].

Using the chronic unpredictable stress animal model of depression in combination with *in vitro* studies has provided details on many of the mechanisms through which curcumin exerted the antidepressant-like behavioural effects shown in FST and TST studies. As has been the case with many polyphenols, curcumin was shown to have multiple mechanisms of action that affect different cellular and molecular pathways, many of which have been shown to interact and modulate one another. Several of these pathways also act to upregulate neurogenesis both directly and indirectly, which is a further way in which curcumin may exert its antidepressant-like effects as some antidepressant drugs have been shown to exert neurogenesis-dependent behavioural effects [30, 109, 110].

4. Conclusion

Given the high prevalence of depression and anxiety in modern societies, unravelling the neurobiological basis of

these psychiatric conditions is one of the most challenging pursuits of science in the present days. The development of effective treatments for depression is likely to emerge from the identification of the mechanisms underlying its pathophysiological components [111]. In this context, studies on the effects of dietary polyphenols and elucidation of the mechanisms by which they exert these effects may play an important role as promising interventions in the field of mental health.

The present work discussed some recent findings addressing the effects of different dietary polyphenols on models of anxiety and depression and proposed mechanisms underlying these effects with particular focus on those related to AHN. As a whole, there is growing evidence for a positive effect of these plant- and food-derived components on behaviours related to depression and anxiety. The dietary polyphenols tested so far, however, appear to exert their effects through different and specific molecular pathways [112, 113], suggesting that the action of polyphenols is not uniform but highly specific. In addition, it should be noted that generalizing the effects of polyphenols as positive is still nonconsensual. For instance, on the one hand, the administration of 5,7,3'-trihydroxy-3,4-dimethoxyflavone (a flavonoid similar to kaempferol) led to significantly inhibited neurite outgrowth, and on the other hand, the polyphenol chlorogenic acid stimulated it [66].

Indeed, polyphenols are a very heterogeneous group of natural chemical compounds that significantly differ with regard to their chemical properties. Studies have shown that the degree of polymerization and inherent properties such as molecular polarity can determine their potency in a range of actions, including antioxidation and anti-inflammation [83, 114]. These properties also affect the polyphenol level in different tissues, including the brain [36]. This diversity may explain why the same dietary source containing multiple polyphenols may show multiple effects as the effects of a single polyphenol may be either additive or altered when acting in the presence of other polyphenols [76, 78]. This synergistic effect should be considered in future investigations aiming to find effective interventions in the field of mental health.

Some polyphenols have been shown to influence anxiety- and depressive-like behaviours as well as AHN in different *in vivo* and *in vitro* models. However, further studies are necessary to clarify the potential of polyphenols in treating depression and anxiety. It is worth noting that a significant portion of the studies focusing on the effects of polyphenols on the hippocampus did not address AHN and used learning and memory paradigms as primarily models for studying neurodegenerative disorders like Alzheimer's disease. Given that AHN represents one of the most remarkable features of the central nervous system in terms of plasticity, more studies investigating the effects and mechanisms of polyphenols on hippocampal cell proliferation and differentiation may identify additional specific neurobiological targets for psychiatric-related behaviours. In addition, AHN has also been shown to correlate with anxiety [115–118] as well as emotional—and not only cognitive—learning and memory processes [119–121]. Also, it is clear that anxiety disorders

present an important emotional mnemonic component [122]. Given the role of AHN in emotional learning and memory, future investigations that consider the potential effects of dietary polyphenols on depression and anxiety could expand our current understanding of these psychiatric conditions and provide evidence of their potential as tools for effective intervention.

Key Messages

- (i) The adult hippocampus is capable of generating new neurons, but how these newly generated cells affect mental health and the different factors that can regulate AHN are still debated.
- (ii) Polyphenol effects and bioavailability vary greatly due to their differing chemical, physical, and structural properties.
- (iii) Plant- or food-derived polyphenols are widely known for their biological properties in enhancing cognition and neuroprotection in models of neurodegenerative conditions, but some polyphenols can also increase cell proliferation and differentiation in models of anxiety and depression.
- (iv) Different polyphenols exert their effects on AHN via different mechanisms of action, such as by activating the MAP kinase pathway or stimulating the expression and release of neurotrophic factors.
- (v) Dietary polyphenols have been shown to affect mental health, having anxiolytic effects comparable to anxiolytic benzodiazepine drug chlordiazepoxide and antidepressant-like effects comparable to those of the SSRI antidepressant fluoxetine and TCA imipramine.
- (vi) The anxiolytic and antidepressant-like effects of polyphenols are mediated through multiple molecular and cellular pathways, which interact and modulate one another.

Authors' Contribution

Nicole Cavegn and Alina Nix contributed equally to this work.

Conflict of Interests

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in, or financial conflict with, the subject matter or materials discussed in the paper, apart from those disclosed. No writing assistance was utilized in the production of this paper.

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