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Role of Dietary Polyphenols on Adult Neurogenesis and Cognition during Aging

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ABSTRACT

The formation of new neurons in adults is an important function that occurs only in specific brain regions. Adult neurogenesis plays an important role in maintaining normal brain homeostasis, replacing damaged neurons, neuronal plasticity, and cognitive functions. The generation of new neurons from Neuronal Stem Cells (NSCs) occurs throughout postnatal stages; however, the process is affected during aging. The decline of the Neuronal Progenitor Cell (NPC) population and the rate of differentiation of NPCs into neurons leads to decreased adult neurogenesis and cognitive functions during aging. Several factors that contribute to the age-associated decline of adult neurogenesis are changes in hormonal and neurotransmitter levels, formation of Amyloid β (Aβ) protein plaque aggregates, oxidative stress, and neuroinflammation. Due to anti-apoptotic, antioxidant, anti-inflammatory properties and other health benefits, plant polyphenols have been widely used to recover cognitive functions in animal models as well as in human subjects. Several studies show that intake of dietary polyphenols such as resveratrol, curcumin, grapeseed, blueberry extract, etc., induces adult neurogenesis and improves learning and memory in different animal models. The present article discussed the significance of dietary polyphenols and their effects on adult neurogenesis and cognition during aging.

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Introduction

Neurogenesis is the process of generating functional neurons from NSCs and NPCs. Neurogenesis mostly occurs during embryonic stage (embryonic neurogenesis) and postnatal stage (adult neurogenesis). At the start of 20th century, neurogenesis was thought to exclusively occur during the embryonic stages. With the development of [H3]-thymidine cell labeling and autoradiography techniques in the 1950s and 1960s, it was discovered that neurons are also generated during the postnatal stages called adult neurogenesis [1]. Adult neurogenesis is reported both in non-mammalian and mammalian species. In fishes, adult neurogenesis is well studied in teleosts, where neurogenesis occurs in many brain regions such as dorsal and ventral telencephalon, hypothalamus, optic tectum, and cerebellum. Adult neurogenesis in teleosts is regulated by environmental factors, social interaction, rearing conditions, etc [2]. The songbird system is a well-studied adult neurogenesis system where new neurons are generated in a region called the High Vocal Center (HVC) in birds. Adult neurogenesis in birds depends on the genders and seasons [3]. In mammals, adult neurogenesis is confined to specific regions in the brain, i.e., the neocortex, Sub-Ventricular Zone (SVZ), and Sub-Granular Zone (SGZ) in the Dentate Gyrus (DG) of the hippocampus and Olfactory Bulb (OB). Using the rostral migratory route, neurons generated from the SVZ region migrated to the OB, becoming granule and periglomerular neurons. On the other hand, the neurons generated in the SGZ region undergo differentiation and integrated as granule cells in the DG [4].

Adult neurogenesis takes place throughout life. Studies in fishes, birds, and mammals showed that a decrease in the number of neuronal stem cell population that generates neurons and their microenvironment leads to a decline in adult neurogenesis during aging [5]. Several factors that reduce the neuronal stem cell population in these brain regions during aging are lowered expression of mitogens such as Epidermal Growth Factor (EGF) and Fibroblast Growth Factor (FGF) and notch signaling that promotes neurogenesis, decreased cerebral blood volume in the DG, lowering of blood vasculature due to decrease of Vascular Endothelial Growth Factor (VEGF) level, accumulation of protein aggregates due to decrease in lysosomal degradation pathways, neuroinflammation, mitochondrial dysfunction and oxidative stress [6].

Polyphenols are secondary metabolites synthesized by plants through the shikimate/polyketide pathway and present in fruits, vegetables, seeds, and nuts. Earlier studies suggested that intake of plant-derived polyphenols (i.e., genistein, curcumin, resveratrol) shows neuroprotection and improves cognition in different animal models [7]. Due to their antioxidant and anti-inflammatory properties, plant polyphenols ameliorate neuronal damage caused by age-associated mitochondrial dysfunctions, oxidative stress, and inflammation and thus prevent and improve cognition [8]. Recent studies showed that polyphenols also improve the decline

of adult neurogenesis and memory during aging [9,10].

Adult Neurogenesis

The NSCs in adult brain are mostly in the quiescent stage except in the SVZ and SGZ of DG of the hippocampus. Self-renewal NSCs in the SVZ and SGZ undergo proliferation and differentiation to give rise to NPCs, neurons, and glial cells. Newly formed neurons from the SVZ and SGZ regions are integrated into the preexisting neuronal network and execute their functions. The newly generated neurons play an important role in regulating olfaction and hippocampal-dependent memory, sexual behavior, offspring recognition, etc.

The proliferative cell layer of the SVZ region contains four different types of cells. are ependymal cells, migrating neuroblast cells (type A cells), astrocytes (type B cells), and immature Transitory Amplifying Progenitor (TAP) cells (type C cells) [11]. The NSCs population of the SVZ region is Glial Fibrillar Acidic Protein (GFAP) positive cells and show properties similar to astrocytes or type B cells. After differentiation, the type B cell gives rise to GFAP-negative TAP or type C cells. These type C cells undergo differentiation to form doublecortin-positive neuroblast cells or type A cells. Using the rostral migratory system, these type A neuroblast cells move towards the OB [5]. In the OB, the type A cells differentiated into mature granule and periglomerular cells. These mature neuronal cells, after reaching the OB, show expression of glutamate and Gamma-Aminobutyric Acid (GABA) receptors, dendritic and axonal synaptic connection, and voltage-dependent electrophysiological activities [12]. The newly generated neurons make connections with the preexisting neurons of OB such as mitral and tufted cells as well as pyramidal cells of olfactory cortex. It takes around 10 days from the generation of new neurons to the incorporation of neuronal circuits to synapse formation in OB [13]. These neuronal cells are important in regulating olfaction-mediated behavioral functions [14].

Adult neurogenesis in the SGZ region of the hippocampus starts due to the proliferation of neuronal progenitor cells. It later differentiates into Dentate Granule Cells (DGCs) and glial cells [4]. It takes about 6-8 weeks from the generation of a neuron to integrate into the preexisting neuronal network to make functional synaptic connections [15]. In the first week, the newborn DGCs undergo differentiation and migrate into the granule cell layer of the DG, where DGCs start forming cellular processes [16]. In the second week, the DGCs look more like neurons. The dendritic and axonal processes extend towards the molecular layer and the CA3 region of the hippocampus. At this point, immature neurons start getting synaptic inputs from surrounding interneurons [17,18]. DGCs start forming synaptic connections in the third week with the preexisting neuronal network. At 4 to 6 weeks, DGCs show stronger synaptic connectivity with the surrounding neurons, NR2B subunit containing N-Methyl-D-Aspartate (NMDA) receptor expression, and increased long-term potentiation. Adult neurogenesis plays an important role in maintaining cellular homeostasis and the cell population of the brain as well as regulating olfactory bulb and hippocampal-dependent learning and memory.

OB-Dependent Behavior and Adult Neurogenesis

Animals use their olfactory system to detect and analyze chemical signals from surroundings through the receptors present in sensory neurons of the OB. The granule cells and periglomerular cells are glutamatergic and GABAergic and receive inputs from the mitral and tufted cells and glomeruli, [19]. Several reports showed that the rate of NSC proliferation and differentiation in the SVZ region depends on olfactory input received by the OB [14,20,21]. Further, deprivation of olfactory inputs decreased the number and length of dendrites and the spine density of granule cells in the OB [22,23]. On the other hand, anti-mitotic drugs, stress, and irradiation affect NSC proliferation, decrease neurogenesis, and impair olfaction-dependent behavior [24,25].

Adult neurogenesis in OB is regulated by different factors such as social behavior, maternal behavior, pups recognition and reproductive behavior in animal models [26]. Earlier reports showed that the adult neurogenesis is increased during the gestation period as well as during lactation and play a significant role in recognizing odors of the pups. [27,28].

Hippocampal Dependent Behavior and Adult Neurogenesis

The hippocampus is an important brain region that helps to form different types of memory, i.e., spatial memory, fear memory, recognition memory, and episodic memory [29-31]. Studies in animal models show that new neurons generated and integrated in the hippocampus influence hippocampal-dependent learning and memory [15]. Adult neurogenesis is regulated by several factors, including the behavioral and cognitive states of the animals. Several behavioral paradigms influencing hippocampal-dependent cognitive function are environmental enrichment, social interaction, exposure to hippocampal-dependent spatial and recognition memory tasks, and exercise. This behavioral experience is encoded in the hippocampus as memory by altering the neuronal network of the hippocampus. Similarly, anti-mitotic drugs, stress, and irradiation also decrease neurogenesis and impair hippocampal-dependent learning and memory [32].

Hippocampal-dependent memory tasks such as spatial memory tests increase the generation and promote the survival of new neurons. Previous studies have shown that newly generated neurons are integrated into the preexisting neuronal network and regulate hippocampal-dependent memory [33]. The Morris Water Maze (MWM) test evaluates hippocampal-dependent spatial memory in rodents. MWM training increased the survival of new neurons generated seven days earlier than the water maze training. These newly generated neurons are in the excitable stage and form synapses with preexisting neuronal networks [31]. Environmental enrichment plays an important role in improving cognitive functions in animal models. Kempermann et al. reported that enriched environment increased the survival of DGCs in the hippocampus and thus promotes adult neurogenesis as compared to standard housing condition in mice [34]. The enriched environment exposed mice showed a thick granule cell layer with 15% more cells in the hippocampus as compared to control mice and associated with better spatial memory in MWM test. Apart from survival, enriched environmental conditions also help in the maturation of newly born neurons. Tashiro et al. reported that neurons that were generated within three weeks showed more activation when re-exposed to the same environmentally enriched condition and not on a new condition [35].

Adult Neurogenesis during Brain Aging

Neurogenesis occurs in specific regions in the adult brain that can form new neurons from their precursors, like NSCs. New neurons are necessary for learning and memory and maintain the brain's structural integrity and regeneration [36]. NSCs microenvironment is known as niche of stem cells viz all cells present in niches of stem cells affect the process of neurogenesis. This microenvironment is necessary for the normal functioning of stem cells and the coordination of their behavior and interaction with organisms' environment [36]. The neurogenic niche comprises precursor

cells and their progeny, such as glia and endothelial cells, which play an important role in the process of neurogenesis such as cell-cell contacts, involving gap junctions, paracrine effects of neurotransmitters, neurotrophic factors, and growth factors as well as synaptic contacts' control [37]. Moreover, NSC niches are present in SVZ of the lateral ventricles and SGZ of DG in the hippocampus of the adult mammalian brain [38]. In the SVZ niche, the neurogenic ability of stem cells is retained throughout adult life, but in humans, after 2 years of birth, it is greatly reduced [39]. In the adult brain, the NSC pool is comprised of quiescent and has distinct roles with activated populations.

Aging remains one of the most common modifiers of neurogenesis in the adult brain. It is associated with the reduction of the mechanisms involved in the maintenance of organisms and organ homeostasis. The aging brain has been characterized by cognitive impairments, which lead to a high risk of pathologies. Further, it negatively affects neurogenesis by decreasing cell production in both neurogenic niches of the hippocampal brain and SVZ [40]. Several studies have reported aging as a risk factor that declines the ability of the brain to produce new neurons throughout the entire life and affects hippocampal NSC activity, reducing the number of progenitors that affect the fate of newly formed cells [41].

The brain contains several distinctive features and age-related mechanisms leading to decreased neurogenesis. Moreover, aging causes structural changes in DG and SVZ neurogenic niches [42]. Moreover the SVZ gets thinner during aging, and several other significant changes have occurred ependymal and astrocytic cell morphology, and RMS tends to disappear [43]. These changes may be responsible for progressive loss of new neurons and correlate with the impairment of olfactory discrimination abilities [44]. In the hippocampus, a dependent significant increase in the quiescent to active NSCs ratio suggests a loss of NSC activity. Further, dendritic spine densities of new neurons in young and old animals were similar, whereas neurogenesis was low in the hippocampus of old mice [45]. During the formation of DGCs, synapses have been formed by the middle and inner molecular layers of the hippocampal DG; however, during aging, the density of these synapses has decreased [45,46].

Neurogenesis in OB has been involved in olfactory memory, maintenance of the structure of OB, and behavioral responses to pheromones. During aging, loss of function has been shown in OB due to a reduction in the capacity of cells to proliferate as well as a decrease in the number of Olfactory Receptor Neurons (ORNs) in the niche, which causes decreased expression of extracellular matrix genes, which involve in insulin growth factor and EGF signaling and leads to olfactory impairments [40,47]. During aging, several changes have occurred in the microenvironment of the neurogenic niche. These extrinsic and intrinsic molecular signalling regulate neurogenesis. Growth factor is important for cellular proliferation and neuronal differentiation, and useful for cellular plasticity during aging. Epidermal Growth Factor Receptor (EGFR) plays an important role in proliferation of SVZ NSPCs by activating Extracellular Signal Regulated Kinase (ERK) transduction pathways. Reports showed that both EGFR and ERK/p-ERK signaling pathways are decreased in the SVZ region during aging [44,48]. Further, defects in the NSCs lysosomes activity led to the increased formation of protein aggregates that affect the proliferation and activation of NSCs decreased with age [36].

Physical activity and an enriched environment might potentially regulate hippocampal adult neurogenesis and OB neurogenesis. Exercise maintains the level of cognitive functions and loss of physical activity due to aging [49]. During aging, NSCs lose their ability to proliferate and become quiescent; however, they can be reactivated by certain stimulations like exercise. Recently, it has been demonstrated that High Mobility Group B2 (HMGB) family protein is important for the transition of NSCs from quiescence to proliferation. Aging negatively regulates these cell populations while running exercise and stimulates the proliferation of HMGB2+ cells. It can be a novel marker for identifying NSC activation in the adult hippocampus [50]. The regulation of hormones is also an important aspect of aging. Estrogen has neuroprotective properties. Its deficiency during menopause may cause cognitive impairments. In the adult female, high levels of estrogen lead to increased hippocampal cell proliferation [51].

Acute stress may reduce NSC proliferation in the adult brain. Corticosteroids that are important for maintaining the homeostasis of the Hypothalamic-Pituitary-Adrenal Axis (HPA-axis). HPA-axis dysregulation involves several psychiatric disorders with high levels of Glucocorticoids (GCs). Corticosteroids are involved in declining of adult hippocampal neurogenesis with age. It has been demonstrated that adrenalectomy restored neurogenesis in adults like younger animals [37]. Chronically increased GC levels might be one of the reasons behind the reduced neurogenesis during aging and age-related memory decline. Mifepristone, a GC receptor antagonist, up-regulated the neurogenesis in the hippocampus and improved cognitive function in old rats. Similarly, inhibition of GC-mediated singling increased adult neurogenesis in aging rats. During aging, microglia get activated in the SVZ niche and secrete proinflammatory cytokines, resulting in an unfriendly environment for NSCs and, subsequently, reduce neurogenesis.

Oxidative Stress and Adult Neurogenesis during Aging

Reactive Oxygen Species (ROS) are generated from normal cellular processes. These important metabolic products have beneficial functions and deleterious effects on cells or tissues. In the cell, oxygen free radicals are generated in the electron transport chain during oxidative phosphorylation. These oxygen free radicals include singlet oxygen (1O2), superoxide (O2•–), hydroxyl free radicals (HO•), peroxides (O22–), etc. Apart from normal cellular processes, ROS are also generated due to irradiation, pollution, metal toxicity, smoking, radiation, etc [52]. Aging is one of the important factors associated with an imbalance in the production and elimination of free radicals, which results in accumulation of ROS. Age-associated increase in ROS levels leads to damage of cellular and mitochondrial membrane damage, protein oxidation, and DNA damage that affects cellular homeostasis, neurodegeneration, and cognitive dysfunction [53].

Mitochondrial dysfunction and the accumulation of oxidative free radicals are important cellular and biochemical factors that affect the NSC population during aging. Due to high energy demand, NSCs accumulate high oxidative free radicals. Previous studies showed that oxidative stress has positive and deleterious effects on the NSC population. During normal physiological conditions, oxidative free radicals play an important role in regulating NSC proliferation, differentiation, synapse formation, and neurotransmission. In vitro and in vivo studies showed that activation of NADPH oxidase is important for ROS generation and NSCs proliferation through protein kinase B (PI3K)/Akt signaling pathway. Further, with an increase in ROS level, the proliferation of NSCs decreased, and differentiation increased [54-56]. On the other hand, high oxidative free radicals generated due to an imbalance of its production and elimination show harmful effects and lead to neuronal cell death.

Antioxidant enzyme systems are crucial for scavenging oxidative free radicals and protecting cells from oxidative damage. SOD is one of the antioxidant enzymes that protect cells from oxidative stress by breaking down superoxide ions into O2 and H2O2. Earlier reports showed that the activity of SOD decreased in the brain during aging [57,58]. Analysis of genetic knockout models showed that SOD plays an important role in the proliferation and differentiation of NSCs during adult neurogenesis. CuZnSOD and MnSOD heterozygous knockout mice showed impaired adult neurogenesis with reduced BrdU+/NeuN+ positive cells in the SGZ region of the hippocampus [59]. Similarly, Rola et al. reported that EC-SOD mutant mice showed a 40% reduction in the BrdU+/NeuN+ positive neuronal cells in the hippocampus [60]. Therapeutic irradiation is one of the major factors affecting adult neurogenesis through ROS generation. Due to reduced antioxidant enzyme activities, aging is more susceptible to radiation-mediated oxidative stress and cognitive dysfunction. Casciati et al. reported that radiation damaged hippocampal mitochondria, induced apoptosis, and decreased NSCs population and adult neurogenesis (NeuN+ positive cells) and effects of radiation increased with aging [61]. Nuclear factor erythroid 2-related factor 2 (NRF2) is a transcription factor that induces expression of genes involved in the scavenging of ROS and cytoprotection. NRF2 is also plays an important role in adult neurogenesis and associated learning and memory function. However, the expression of NRF2 at both mRNA protein levels decreased in the brain during aging [62,63]. Robledinos-Antón et al. analyzed the role of NRF2 in a genetic mutant mouse model. They reported that NRF2 knockout mice showed impaired NSC proliferation, altered neuronal to glial cell differentiation in the SGZ region of the hippocampus, and cognitive dysfunction. This shows a decrease in the activities of the antioxidant enzyme system and proteins involved in various pathways that affect adult neurogenesis and cognitive function during aging [64].

Inflammation and Adult Neurogenesis During Aging

Inflammation is a complex cellular and molecular response that attempts to respond to injury, clear pathogens, and destroy or damage host cells. Cellular and molecular changes due to immune response in the neurogenic niche affect adult neurogenesis [40]. In the brain, microglia, astrocytes, and circulatory macrophages play an important role in maintaining the production of inflammatory cytokines in the form of either pro-inflammatory cytokines or anti-inflammatory cytokines and chemokines. These mediators may alter the NSC's niche. During inflammation, microglial cells activate and produce proinflammatory cytokines and chemokines such as Interleukins (ILs), Tumor Necrosis Factor-A (TNF- α), Transforming Growth Factor-β (TGF- β), interferon-ϒ (INF- ϒ) [65].

Proinflammatory cytokines affect neurogenesis by several pathways. IL-6 proinflammatory cytokines decrease neurogenesis and responsible for the initiation of the JAK/ STAT3 pathway, which activates astrocyte differentiation [66]. Further, RAF/MEK/ ERK pathway modulates the JAK/STAT3 pathway by regulating gp130 expression in NSCs henceforth, switching the process of NSCs neurogenesis to astrocytogenesis. Jia et al. suggested that gp130 is a therapeutic target for increasing neurogenesis [67]. Briefly, treated with recombinant TNF- α on cultured NSCs causes decreased expression of a neuron-specific cytoskeletal protein, microtubule-associated protein (MAP)-2, suggesting that TNF-α might have inhibitory effects on neuronal survival and differentiation. Further, in vitro and in vivo studies have shown that the administration of IL-1β decreases the rate of hippocampal NSC proliferation, attributed to the nuclear factor-kappa B (NF-κB) pathway [68]. During aging Sub Ependymal Zone (SEZ) is mediated with proinflammatory cytokines [69,70].

Chemokines are secreted signaling proteins that can guide migrating cells by increasing the concentration of chemokine receptors in attracting cells. Chemokines in the Central Nervous System (CNS) and their associated receptors are widely expressed in NSCs, such as Stromal Cell-Derived Factor-1 alpha (SDF- 1α)/ C-X-C chemokine receptor type 4 (CXCR4). Moreover, activated SDF- 1α gave single to NSCs for migration from neuronal damage site and enhanced NSCs proliferation by activating Akt1 and Forkhead box O (FOXO3a) singling [71,72]. FOXO3a is a transcription factor that leads to the downstream target of Akt-1, and is important for regulating NPCs proliferation and cell cycle control. Several studies have shown that microglia have dual roles according to their situation, regulating adult neurogenesis by either activating or inhibiting in both intact or injured brains. Microglial activation and inflammation can be dangerous for adult neurogenesis despite some other studies have shown that microglial is beneficial for neurogenesis under certain conditions [73,74].

Adult neurogenesis is also regulated by immune cells. CD4 T cells promote adult neurogenesis by regulating insulin growth factor 1 (IGF-1), which is involved in the production of BDNF in the DG of the hippocampus. IGF-1 helps in NSC proliferation and increases the number of granule cells in DG [75]. Th1 cells are mostly detrimental via the release and action of cytokine IFN-γ. On the other hand, Th2 cells are neuroprotective via the release and action of its main anti-inflammatory cytokine, IL-4. IL-4-stimulated microglia in the presence of IGF-1 and IFN-γ and induced neurogenesis [76]. TGF-β involved in cell growth, differentiation, migration, and apoptosis. TGF-β ligands bind to the TGF-β receptor kinase and activate Smads (R-Smads). In mammals, TGF- β has three isomers β1, β2, and β3. Studies have shown that in Smad3 null mice, these play an important role in neurogenesis and colocalization with mature neuron marker neuronal nuclei (NeuN) in the DG of the hippocampus. Moreover, deficiency of Smad3 showed disrupted neuronal proliferation and migration and decreased DG neurons compared to wild-type mice [77,78]. Further, CD8 T cells release granzyme B (GrB), which inhibits neurogenesis via activation of the Giα/Go-coupled receptor. Stimulation in these receptors causes a decreased level of cyclic AMP, which increases Kv1.3 channels on NSCs [77]. Kv1.3 is also responsible for neurotoxicity. Studies have suggested that blocking of Kv1.3 channels increased the NSCs level of differentiation [77,79,80]. In aged mice T cell infiltration in neurogenic niches decreased the NSCs proliferation [70].

Inflammation also has been caused by bacterial components, e.g., lipopolysaccharide (LPS). LPS is a constituent of gram-negative bacterial cell walls and binds with toll-like receptor 4 (TLR-4), mainly expressed in the brain by microglia, astrocytes, and neural precursor cells. TLRs activate NF-κB, a transcription factor that induces the production of main proinflammatory mediators IL-1β, IL-6, and TNF-α [81]. Moreover, LPS decreased neural precursor cell proliferation through activation of TLR-4. Several studies have shown that LPS negatively regulates neurogenesis by affecting type 2 progenitor cells, decreasing the number of newborn cells in DG, and is responsible for hippocampal memory impairment [82-84]. Seong et al. suggested that injection of LPS to 7-week-old mice activates TLR4-NF-κB signaling in the hippocampus and induces proinflammatory cytokines. Thereafter, treated with Epigallocatechin-3-Gallate (EGCG), a polyphenolic flavonoid found in green tea, it restores the proliferation of NSCs in DG and ameliorates NSCs apoptosis [85].

Histamine, a biogenic amine associated with allergic and inflammatory reactions, is also involved in inflammation and regulates adult neurogenesis. Histamine receptor 1 (HR1) and (HR4) promote the production of proinflammatory cytokines TNF-α and IL-6. HR1, HR2, and HR3 express in NSCs niche and spatially induced NSCs differentiation and proliferation through the HR2 and HR3 singling pathways. Histamine induces some SVZ neuroblasts, which can migrate towards the OB and differentiate into mature neurons [86]. Proinflammatory cytokines also indirectly regulate neurogenesis via the HPA axis. Stimulation in the HPA-axis rises to a high level of GCs. Studies have shown that GCs inhibit cell proliferation and neurogenesis in DG. It also stimulates glutamate from the hippocampus, which decreases cell proliferation in DG [49].

Antioxidative and Anti-Inflammatory Effects of Plant Polyphenols and Cognition

The importance of diet in healthful aging is well acknowledged, leading to increased studies into the scientifically supported functional qualities of common foods. Polyphenols are bioactive secondary plant metabolites naturally produced and classified under nutraceuticals based on their chemical structure [8]. Fruits, vegetables, grains, and other dietary sources, such as spices, dry fruits, legumes, and herbs, contain polyphenols. Polyphenols are classified into the following groups based on the number of phenol rings and attached elements: stilbenes (e.g., resveratrol) present mainly in red fruit, grapes, peanuts, and wine, among others; flavonoids (e.g., quercetin, catechins, and kaempferol) present in red wine, onions, curly kale, leeks, broccoli, and blueberries; phenolic acids (e.g., Benzoic acids, cinnamic acid) abundant in red fruit such as strawberries, raspberries, and blackberries. More precisely, polyphenols can be found up to 200-300mg per 100g fresh weight in fruits like apples, grapes, pears, cherries, and other berries [87]. Consuming diets rich in polyphenols reduces the risk of cognitive impairments, a slower rate of cognitive decline, and better local memory performance [88,89].

Several studies showed that dietary polyphenols are neuroprotective due to their antioxidant and anti-inflammatory properties. These properties protect brain cells by reducing the oxidative and inflammatory-mediated damage to neuronal cells. Dietary polyphenols possess one or more aromatic rings bonded to a hydroxyl group. This feature makes them good electron or hydrogen atom donors, neutralizing ROS [90]. Oxidative damage to cell constituents, DNA, proteins, and lipids accumulates with age and leads to the degeneration of neuronal cells [91]. At a cellular level, phenolic compounds are observed to be the largest group of natural antioxidants in the human diet and anti-inflammatory factors elevated by modulating signal transductions [92]. Presence of bioactive compounds confers major function to neutralize free radicals also preventing the deterioration of aging, decreasing oxidative injury and showing anti-inflammatory effects. Antioxidant capabilities of plant-derived bioactive substances have been researched in human subjects and animal models to improve cognitive health throughout aging and neurodegenerative illnesses. Their anti-inflammatory properties, such as radical scavenging and cellular activity modulation occur in inflammatory cells.

Polyphenols are important plant derived secondary metabolites that have the potential to increase cognitive performance including learning and memory. Research on different animal models suggest that blueberries [93,94] and strawberries are helpful at restoring age-related deficits in spatial working memory, enhancing object recognition memory, and regulating inhibitory fear conditioning. It has also been found that flavonoid-rich food and beverages improve psychomotor performance in elderly animals. In addition to berries, pure flavanols like quercetin [95] and rutin [96] as well as *Ginkgo biloba* [40] have been found to reverse neural and behavioral aging. The antioxidant effects of resveratrol on the cognitive function of aged rats were investigated by Navarro-et al. [97]. Chronic resveratrol administration lowered nitrite and malondialdehyde levels in brain and improved hippocampal-dependent recognition memory throughout aging. Polyphenols may modify chronic inflammatory processes during cytokine production, amplify NF-kβ mediated inflammatory gene expression, and release the anti-inflammatory cytokine, transforming growth factor-beta.

Inflammatory responses against various inflammatory stimuli (oxidative stress, cytokines, excess corticosterone) are characteristic of senescent tissues and organs. In a stress-induced brain, where activation of the inflammasome and another proinflammatory signaling cascade, such as the NF-κβ signaling pathways, leads to neuroinflammation [98]. Neuroinflammation connected with aging can occur from many causes like accumulation of cell damage, including oxidative damage, failure of responses of the immune system, the natural tendency of senescent cells to secrete proinflammatory cytokines and deregulation of the autophagy system [99-101]. Once neuroinflammation occurs, deleterious effects on memory, synaptic formation, impaired synthesis of catecholamines and serotonin, and impaired adult neurogenesis [9,102]. Further, increasing attention is being paid to novel anti-aging strategies oriented toward the attenuation of the molecular mechanisms that regulate this proinflammatory state, which seem to be related to the modulation of the NF-κB signaling pathway and the antiaging protein SIRT1 for maintaining cognitive health.

Role of Plant Polyphenols on Adult Neurogenesis during Aging

Adult neurogenesis is a largely preserved phenomenon that includes variations in adult-born neurons compelling spatial and associative memory impairments. Several pieces of evidence suggest that complete diets could be an adaptable factor of adult neurogenesis and cognitive health. In this context, effect of polyphenols in reducing cognitive abnormalities in aged adults and protecting against common degenerative and chronic illness that are known to be caused by oxidative stress has attracted substantial attention [103]. Polyphenols may protect brain in a variety of ways, such as by protecting susceptible neurons and improving existing neurogenesis. With age, decline in cognitive behavior has been characterized by compromised neuronal plasticity, aberrant neurogenesis, and neural death. Polyphenols are characterized by lipophilic nature and can cross the blood brain barrier. It functions as an exogenous molecule for adult neurogenesis regulation. Hayashi et al. examined that supplementation of diet enriched in polyphenols induced neurogenesis in SVZ and hippocampus of adult mice [104].

The aged brain can be characterized by an imbalance in metabolic function, changes in brain vasculature, and a decline in adult neurogenesis, which reduces the number and function of NSCs and NPCs [105,106]. These lead to a decline in cognitive health, loss of working and episodic memory, impaired learning capacity, and motor coordination, not only in the context of human neurodegenerative disorders but also during normal aging. Polyphenols also help in the prevention of the age-dependent decrease of monoaminergic neurotransmitters (e.g., serotonin, dopamine, and noradrenaline) in old rats (20 months) after chronic treatment with the polyphenols resveratrol, silymarin, quercetin and naringenin [9,107]. This is important for synaptic plasticity, memory, and the modulation of other aging-related processes, such as neuroinflammation [108]. Polyphenols may possibly lower cognitive deterioration rates in aged rats, ameliorating working

memory, learning, and motor functions [9]. Similarly, Shukitt et al. observed that old rats of 19 to 21 months showed improved motor and cognitive performance after a 2% strawberry-supplemented diet [109]. Further, these rats showed enhanced hippocampal neurogenesis. Reports also suggested that polyphenols can prevent or delay age-associated neurodegenerative changes, at least in animal models of Alzheimer's disease [110]. Polyphenols have been pointed out as exogenous molecules that modulate adult neurogenesis [111]. Adult mice's SVZ and hippocampus have been demonstrated to stimulate neurogenesis after 40 days of treatment with a diet rich in polyphenols and polyunsaturated fatty acids [112]. Several adult neurogenesis indicators, including several newly produced SGZ and SVZ cells, were shown to be up-regulated compared to the control diet, with considerably more cells expressing neuroblast markers. This is consistent with a polyphenolic diet that positively affects the proliferation and differentiation of neuronal populations.

Sarubbo et al. reported that rats given polyphenols had higher co-localization of cell proliferation marker 5-bromo-2′-deoxyuridine (BrDU) and NeuN in mature neurons-in the granule layer, indicating greater production of new neurons [9]. Further, low concentrations of curcumin stimulate neuronal differentiation of multipotent mouse neural progenitor cells in vitro, and increased adult neurogenesis has been documented in vivo in mice fed with polyphenols. Increase hippocampal adult neurogenesis in a dose-dependent and time-dependent manner and positively affect memory. Furthermore, Flowers et al. showed that NT-020, a natural supplement based on the combination of polyphenols from blueberry and green tea, increases the proliferation of neural progenitors and improves cognitive function in aged rats, likely through the attenuation of hippocampal inflammation and the enhancement of proneurogenic signaling pathways in the same region [113].

Polyphenols have a wide range of neuroprotective effects on the brain, including the control of immune cells and adaptive stress responses, as evidenced by multiple studies [114]. Polyphenols may also have an effect on supporting cells such as astrocytes or microglia and have a direct influence on brain progenitor cells [115]. These findings highlighted the use of polyphenols in stem cell-based neurodegenerative disease therapy. In aged rats given NT-020 for four weeks, neural progenitor proliferation and spatial memory performance can improve, with lower microglial activation [113]. In adult rats, resveratrol (20mg/kg body weight) substantially enhanced the number of newly produced cells in the hippocampus, accompanied by overexpression of phosphorylated CREB and SIRT1, proteins involved in neuronal survival [116]. According to the findings, resveratrol's effects on neurogenesis are dose and context-dependent; however, lower concentrations have a positive impact on adult NPC proliferation and survival, as well as hippocampal neurogenesis in aged rats, indicating its potential as a compound for restorative therapies against age-related brain disorders [116].

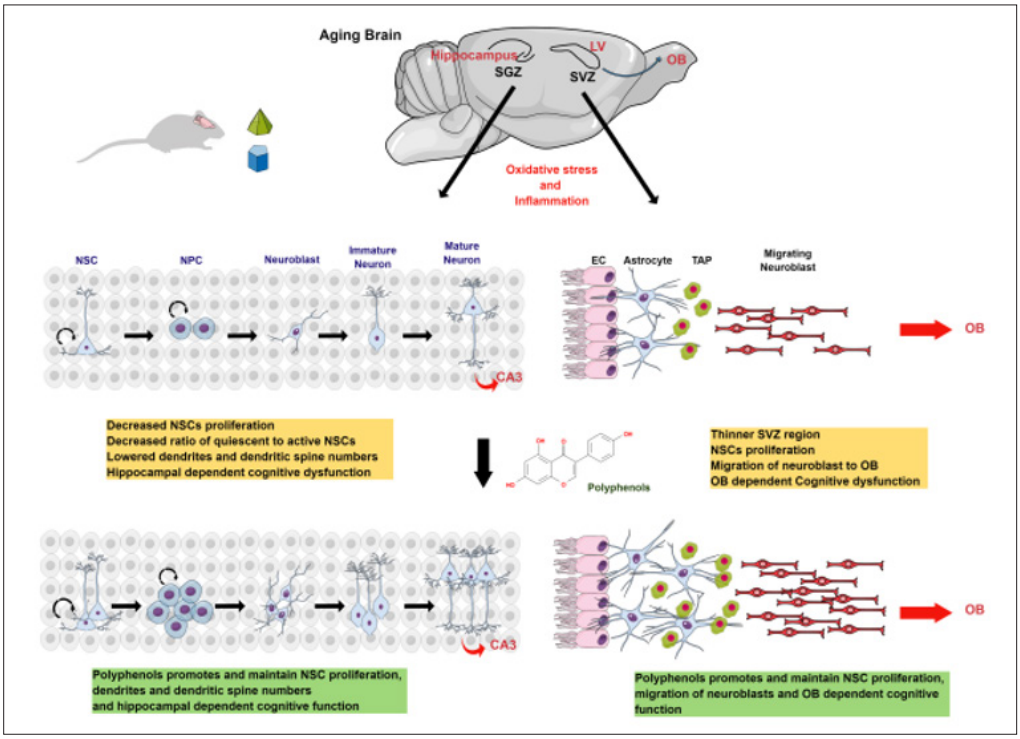

Figure 1: Schematic Diagram Representing the Role of Polyphenols on Age-Associated Changes in Adult Neurogenesis and Cognition

Oxidative stress and inflammation decreased the proliferation and differentiation of NSCs in the hippocampus and the SVZ region and their migration to OB. These age-associated changes affect hippocampal and OB-dependent cognitive functions. Further, dietary supplementation of plant polyphenols during aging promotes and maintains NSC proliferation, differentiation, and migration and thus improves cognitive functions.

Conclusion

The neurogenic niches of SVZ and SGZ regions in the brain constantly produce neurons in the postnatal stage and play an important role in maintaining brain homeostasis and cognitive function. However, biochemical and physiological changes such as oxidative stress and inflammation show harmful effects on these neurogenic niches during aging, affecting the proliferation and differentiation of NSCs and associated cognitive functions. Studies in different animal models show that dietary supplementation of polyphenols is neuroprotective due to their antioxidant and anti-inflammatory properties. Further, polyphenols activate NSCs proliferation, survival, and differentiation as well as improve cognitive and motor functions in aged animals (Figure 1). Though polyphenols show promising results in improving adult neurogenesis during aging, more research is needed to understand the details of molecular mechanisms. Understanding different molecular pathways may be beneficial to identifying new targets and designing new molecules to recover or improve adult neurogenesis during aging and age-associated neurodegenerative disorders.

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