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Daily Consumption of High-Polyphenol Olive Oil Enhances Hippocampal Neurogenesis in Old Female Rats

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ABSTRACT

Objective: The aim of this study is to evaluate the effect of daily consumption of high-polyphenol (HP) olive oil on neurogenesis by investigating neuronal cell proliferation and maturation in the hippocampus of old rats, and to evaluate the relationship between neurogenesis, spatial memory, and anxiety-like behavior.

Methods: A total of 34 female, 20–22-month-old Sprague Dawley rats were divided into three groups: control group, low-polyphenol (LP) group, and high-polyphenol (HP) group. The animals were fed distilled water, LP olive oil and HP-extra virgin olive oil, respectively for 6 weeks using an oral gavage. At 43 days, animals were tested using the Morris Water Maze to evaluate spatial memory, and the Open-field test to evaluate anxiety-like behavior. Neural cell proliferation in the dentate gyrus (DG) was determined by BrdU labeling and Nestin protein expression. Neuronal maturation was determined by NeuN labeling. Synaptic density in the hippocampus and prefrontal cortex was examined by measuring Synaptophysin (SYN) levels. Hippocampal Calbindin levels were measured to assess cellular calcium metabolism.

Results: Daily consumption of HP olive oil significantly improved cell proliferation and neuronal maturation in the DG of old rats. HP-olive oil significantly increased SYN levels in the prefrontal cortex, and nestin and calbindin levels in the hippocampus ($p < 0.05$). LP olive oil diet has shown no effect on any parameter ($p > 0.05$). We also did not find any statistically significant difference between the groups in terms of spatial memory and anxiety-like behavior ($p > 0.05$).

Conclusion: Our study is first to show that daily consumption of HP-olive oil enhances hippocampal neurogenesis in old rats, which has been confirmed by proliferation and maturation biomarkers. In addition, increased SYN and calbindin levels showed that the generated cells were also functionally developed in the HP group. We suggest that daily consumption of HP olive oil may have beneficial effects on brain aging by triggering neurogenesis.

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Neurogenesis; aging; olive oil; hippocampus

Introduction

Neurogenesis is a concept that has been accepted since the 1960s (1). Currently, it is well known that hippocampal neurogenesis is a process that continues throughout life (2). Adult hippocampal neurogenesis is thought to play a critical role in hippocampal-dependent functions, such as spatial memory and memory formation (3, 4). The correlation between hippocampal neurogenesis and hippocampal-dependent tasks suggests the importance of the maintenance of the hippocampal neurogenic niche. The subgranular zone (SGZ) of the dentate gyrus (DG) is the environment of the adult hippocampus where neural stem cells (NSCs) reside. This unique region allows the proliferation and differentiation of NSCs to provide integration of neurons into the hippocampal circuity. The hippocampal neurogenic niche contains immature and mature NSCs, vascular cells, and ependymal cells; these cells communicate through gap junctions and cell-cell interactions (5). Radial glia-like cells are thought to constitute the NSCs population in the SGZ and the molecular interactions in this environment are determinants of the neural NSCs behavior that forms fully mature neurons through five developmental stages. The proliferation and differentiation ability of NSCs to the adult-born neurons decline during aging (6). Age-related decline in neurogenesis involves several cellular processes that cause a decrease in NSCs renewal and neuronal fate commitment (7). Moreover, altered adult neurogenesis is correlated with a cognitive decline in brain aging and neurodegenerative diseases (8, 9).

Brain aging involves age-related cognitive impairments, which occur together with a decrease in neurogenic capacity, calcium homeostasis, and synaptic density (10–12). Intracellular Ca^{2+} acts as a signaling molecule and Ca^{2+} concentration is important for neuronal excitability, synaptic

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plasticity, cell division, differentiation, and apoptosis (13). During aging, Ca^{2+} influx to cells increases and changes in Ca^{2+} concentration may lead to neuronal degeneration and vulnerability to age-related neurodegenerative diseases (14). Therefore, Ca^{2+} buffering is essential for neuronal functioning, and calbindin, which is one of the calcium buffering proteins, gradually decreases with age and dramatically drops after the age of 65 (10). It was reported that calbindin-expressingneurons are more resistant to neurotoxicity (15). Importantly, Li et al. (16) showed that suppressed calbindin levels in the DG impair spatial memory.

Synaptic density is also altered during aging, and decline in synaptic density is considered to be one of the reasons for brain atrophy during aging (17). In addition, the primary cause of age-related cognitive decline is thought to be a decrease in synaptic density rather than neuronal loss (16). Synaptophysin (SYN) is the most abundant neurotransmission-regulating proteins in synaptic vesicles. It is suggested that a decline in SYN levels underlies age-related cognitive impairment. SYN knockout mice show learning deficits and behavioral alterations (18). In a study by Smith et al. (19), aged rats with spatial memory deficits had reduced SYN immunoreactivity suggesting that age-related changes in cognition are coupled with SYN reactivity.

Diet is a promising approach to slow or even reverse age-related molecular alterations and cognitive impairments. Higher adherence to the Mediterranean diet has been associated with healthy aging and higher psychological resilience (20, 21). The main oil source of the Mediterranean diet is olive, and triacylglycerol is the major component of olive oil constituting 98–99% of its total weight. The remaining minor components of olive oil contain 230 chemical compounds (22). The beneficial properties of polyphenols have been associated with their high antioxidant capacity. The main antioxidant in olive oil is the phenolic compounds which are in the form of glycides (oleuropein), phenols (hydroxytyrosol, tyrosol), alcohols, and flavonoids (23). The total polyphenol content depends on many factors, including agricultural methods, extraction techniques and storage. Reutzel et al (24) demonstrated that consuming polyphenols purified from olive oil for six months increases cognition and brain ATP levels in aged mice. The neuroprotective effect of olive polyphenols against neurodegenerative diseases is also an important research area. In a study by Lauretti et al. (25), feeding mice with extra virgin olive oil ameliorated memory and tau neuropathology in transgenic Alzheimer model mice. Although there are many studies on the beneficial effects of olive oil on brain health, studies investigating its effects on neurogenesis are limited. A study by Zheng et al. (26) demonstrated that the addition of hydroxytyrosol (HT), which is the major phenolic compound in olive oil, to drinking water increases neurogenesis and cognition in prenatally stressed offspring. D'Andrea et al. (27) also showed that HT treatment stimulates neuronal stem and progenitor cell proliferation and survival in aged rats. However, there has been no study investigating the effect of daily consumption of HP olive oil on neurogenesis in association with hippocampal-dependent tasks. So far, studies which demonstrated the neurogenic capacity of olive polyphenols have been performed using purified polyphenols, and studies investigating the consumption of HP extra virgin olive oil on neurogenesis are lacking.

Therefore, we aimed to evaluate the effects of daily consumption of HP extra virgin olive oil and the determinant effects of the polyphenol content on neuronal cell proliferation and maturation. We first analyzed BrdU immune reactivity and nestin protein level to detect proliferation, and then NeuN immune reactivity for maturation. We further examined calbindin and SYN levels and evaluated these proteins in correlation with spatial memory and anxiety-like behaviors in aged rats.

Material and method

Animals

A total of 34 female Sprague-Dawley rats aged 20–22 months were obtained from the Physiology Department of Dokuz Eylul University. The study was approved by the Animal Experiments Local Ethics Committee (TF-HADYEK) of the Faculty of Medicine of Dokuz Eylul University with decision number 69/2019. Animals were housed under standard conditions: 12-hour light/dark cycle, 21–22 °C room, and 40–60% humidity. Animals had free access to food and water.

Preparation of high-polyphenol extra virgin olive oil

Olive oil was obtained from TUAY Co. Ltd. (Turgut Anadolu Yatirim Limited Company). According to the manufacturer, Europaea (Memecik species) were collected from the company's organic gardens in different regions of Mugla and Aydin cities of Turkiye during the maturation stages 1 and 2, and pesticides and fertilizers were not used in the growing period. Olive fruits were pressed using a cold-pressing method (≤27 °C) in a few hours (2–4 hours) after harvest (28). A special squeezing technique designed to increase the polyphenol content of olive oil has been performed by the company (technical information belongs to the company and is not shared). Extra virgin olive oil was stored in bottles between 18–22 °C temperature. The total polyphenol content was analyzed by the company and approved by the Aydin Private Food Control Laboratory of the Ministry of Agriculture and Forestry. The total polyphenol content of the olive oil was analyzed using High-performance Liquid Chromatography, and it was 668 mg/kg for High-polyphenol (HP) olive oil and 77 mg/kg for Low-polyphenol (LP) olive oil.

Experimental design

The rats were randomly divided into three groups and fed by oral gavage for six weeks: (1) Control group (n = 10): 1 ml water/day, (2) Low polyphenol group (n = 12): 1 ml LP olive oil/day, (3) High polyphenol group (n = 12): 1 ml HP extra virgin olive oil/day. The whole experimental timeline is shown in Figure 1.

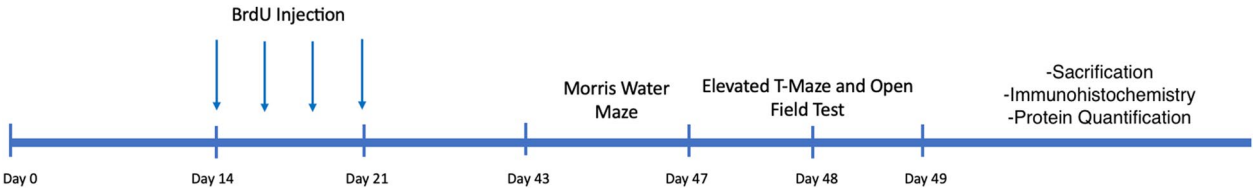


Figure 1. The timeline of the experimental model.

BrdU injection

Three animals (n = 3) from each group were administered daily injections of 5-bromo-2′- deoxyuridine (BrdU 85 mg/kg, i.p., Abcam, Cambridge, UK) for one week starting from the 14th day of the experiment.

Morris water maze

The Morris Water Maze (MWM) test was performed for all rats at the end of the six-week feeding procedure (starting from day 43). The MWM was composed of a circular pool filled with water. The rats were allowed to find the platform that was located 1 cm under the water surface using visual cues with different colors and shapes around the pool. A video camera system was located above the pool to monitor and record the behavior of the rats at a height of about 2 m from the center of the tank. On each test day, rats were put into the water starting from one side of the four tank quadrants and allowed to swim for a maximum of 60 seconds. If a rat couldn't find the platform within 60 seconds, it was guided to the platform to remain there for 15 seconds. Each rat was subjected to four trials per day (a total of 16 trials/per animal), with each rat being put into the water from all four directions of the four quadrants. On the fifth day, a probe trial was applied to each rat. The platform was removed, and the rat was allowed to swim for 60 seconds. Time spent in the target quadrant, thigmotaxic swimming, and swimming speed were recorded using the Noldus Ethovision XT video tracking system.

Open field test

At the end of the six-week feeding period, all rats were subjected to the open field test. A 1 m × 1 m × 1 m open-top box-shaped experimental setup was used for the open field test. Animals were left in the middle of the area and a camera recorded for 5 minutes. After each subject, the test area was cleaned with 70% alcohol to remove the subject's odor. The time spent at the center and the total walking distance were analyzed using the Noldus Ethovision XT software.

Immunohistochemical analysis

A total of 3 rats were used for immunohistochemistry, and each hippocampus dissected to the left and right hemispheres and used separetely for the analysis. Immunohistochemistry were performed on 8 µm-thick hippocampal sections (plate 22, 23 according to Paxinos) fixed on slide glass and air-dried for 20 minutes at room temperature. For permeabilization, slides were fixed with cold acetone for 7 minutes. Then, nonspecific binding was blocked with 4% goat serum for 1 hour. The slides were washed with 1X TBS containing 0.1% Tween-20 and bound with the primary antibodies and incubated at 4 °C overnight (NeuN: Bioss Bs-1613R, BrdU: SantaCruz Sc-51514). Secondary antibodies were incubated for 1 hour at room temperature. After the secondary antibody incubation, tissues were washed 3 times with 1X PBS and then rinsed with dH_2O. Nuclear staining was performed with DAPI. Sections were visualized using a fluorescent microscope (Olympus BX-61, Japan). Images were analyzed with Image-J software (National Institutes of Health, USA). For intensity measurements, at least 5 regions of interest of equal size from each sample were quantified for each experimental group. Following adjustment for standard background across different groups, the average intensity was calculated and given as an arbitrary unit.

Hippocampal nestin, calbindin and synaptophysin levels

On the day after the Morris water maze test, rats were sacrificed by taking all blood from the left cardiac ventricle under carbon dioxide anesthesia. Hippocampus tissues were separated, washed in PBS, and stored at −80 °C until the day of the biochemical analysis.

Nestin (BT-Lab, E1174Ra), calbindin (MyBioSource, MBS454101), and SYN (Cusabio, CSB-E13827r) levels in the hippocampus were determined with ELISA kits according to the manufacturer's instructions. The bicinchoninic acid assay (BCA) analysis was performed to determine the total protein levels in tissues. Specific proteins quantified by ELISA method were divided by the total protein in the tissue.

Statistical analysis

All the data were analyzed by SPSS (Statistical Package for the Social Sciences) program version 24.0. The normal distribution of the data was evaluated with the Shapiro-Wilk test. One-way ANOVA was used for the comparison of normally distributed data. Significant values were analyzed using Bonferroni correction for multiple comparison; the results are presented as mean ± standard deviation (SD). The abnormally distributed data were analyzed with the Kruskal Wallis test followed by Bonferroni correction, and the results are shown as mean ± standard error (SEM). Repeated measures ANOVA test was used in the analysis of repeated measures within the same group, and the results are shown as mean ± standard deviation. $p < 0.05$ was considered statistically significant. Relationships between all parameters were evaluated using the Pearson correlation test.

Results

Morris water maze

In the learning phase, the time spent to find the platform and the distance moved decreased from day 1 in all groups (Figure 2). In the first 4 days, there was no statistical difference between the groups in terms of time to find the platform (Figure 2) and total distance moved (Figure 2) ($p > 0.05$). This result was interpreted as the animals learned the platform's location, so their learning abilities were intact.

In the probe test, the time spent in the quadrant, swimming speed, and thigmotactic swimming time were evaluated. No statistical difference was found in the three evaluated parameters ($p > 0.05$) (Figure 2).

Open field test

The open field test was performed to evaluate anxiety-like behavior. The time spent in the center and the total distance moved were evaluated. According to the results, there was no statistical difference in anxiety-like behavior ($p > 0.05$) (Figure 3).

BrdU labeling

BrdU immune reactivity in the DG was analyzed to evaluate the proliferating cells. BrdU-labeled cells were highest in the HP group (Figure 4). High polyphenol olive oil consumption increased cell proliferation in the hippocampus. BrdU reactivity was higher in the HP group compared to

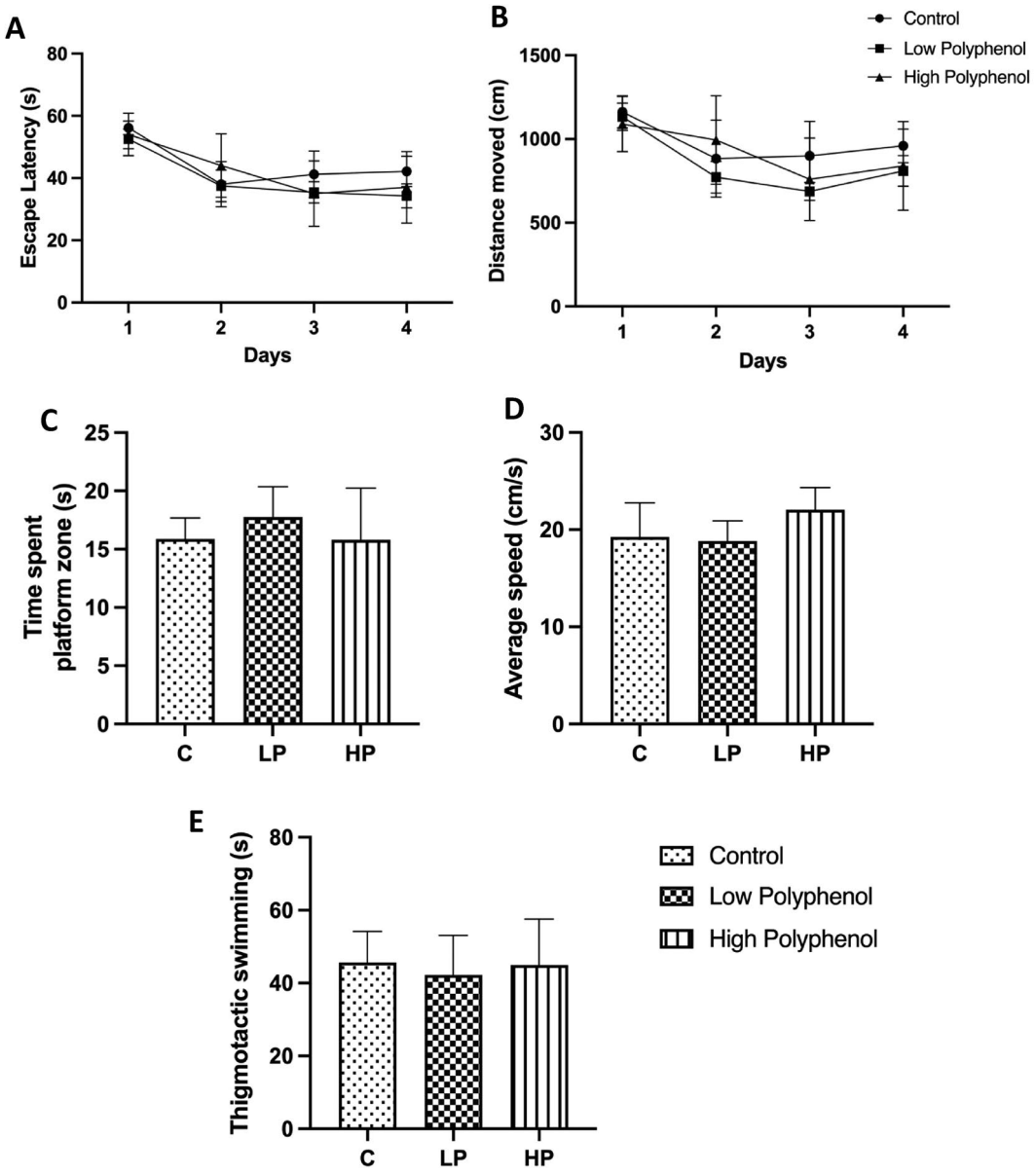


Figure 2. Learning performance of the rats in the Morris water maze. (A) Time to find the platform in the first 4 days of the Morris water maze test. (B) Total distance moved in the first 4 days of the Morris water maze test. (C) The time spent in the quadrant on probe trial. (D) The swimming speed on probe trial. (E) The thigmotactic swimming time on probe trial. Results are given as mean ± standard deviation (SD). No statistical difference was found between the groups for all parameters ($p > 0.05$).

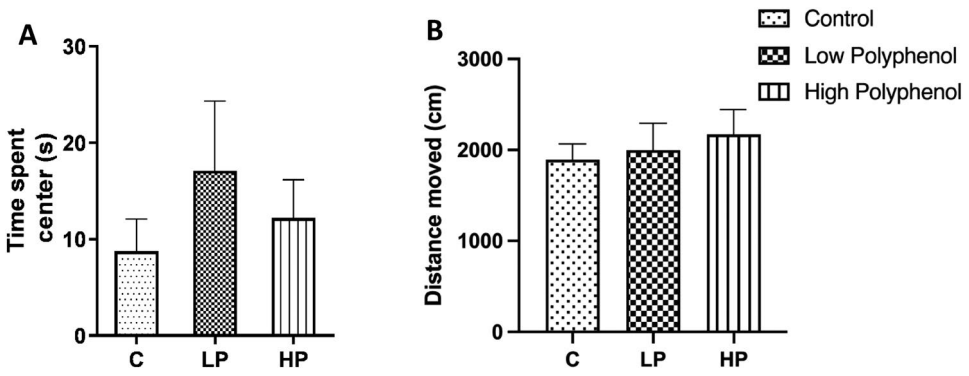


Figure 3. The open field data of the rats to evaluate anxiety-like behavior. (A) The time spent at the center. Results are given as mean ± standard error (SEM). (B) The total distance moved in centimeter. Results are given as mean ± standard deviation (SD). No statistical difference was found between the groups for both parameters ($p > 0.05$).

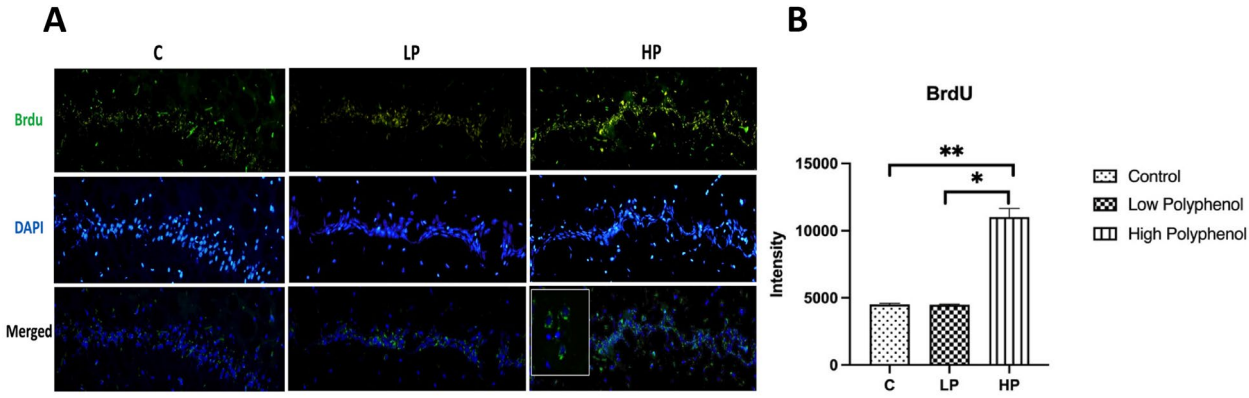


Figure 4. BrdU immunoreactivity in DG. (A) BrdU, DAPI staining and merged images of brain slices (C: control, LP: low polyphenol, HP: high polyphenol). (B) Intensity of each groups. BrdU stained cells were higher in the High-polyphenol group than in the Control and Low-polyphenol groups. Results are given as mean ± standard deviation (SD). *$p < 0.05$ compared to the low-polyphenol group. **$p < 0.01$ compared to the control group.

the control group ($p < 0.01$) and the LP group ($p < 0.05$). Low polyphenol consumption had no effect on cell proliferation ($p > 0.05$).

NeuN labeling

NeuN immunoreactivity was analyzed to evaluate mature cells in the DG. Similar to BrdU staining, NeuN immunoreactivity was highest in the HP group ($p < 0.001$) (Figure 5). Low polyphenol consumption had no effect on cell proliferation ($p > 0.05$).

Hippocampal nestin, calbindin and synaptophysin levels

The proliferation of the hippocampal cells was determined by measuring nestin levels. The highest nestin levels were found in the HP group and it was statistically higher ($p < 0.01$) compared to the control group (Figure 6). Although the nestin level of the LP group was slightly increased compared to the control group, the increase was not statistically significant ($p > 0.05$).

High polyphenol nutrition increased calbindin levels in the hippocampus. Calbindin level was significantly higher in the HP group than in the control group ($p < 0.05$) (Figure 6).

Synaptophysin was chosen as a marker for synaptic density that decreases with age. Although SYN slightly increased in the HP group, this was not statistically significant ($p > 0.05$) (Figure 6).

Correlation analysis

Correlation analysis was performed to examine the relationship between the analyzed markers. No correlation was found between behavioral test parameters and BrdU, NeuN immunoreactivity, nestin, SYN, and calbindin protein levels ($p > 0.05$). In HP group, a positivie correlation was found between nestin and calbindin levels ($r = 0.967$, $p < 0.01$) (Figure 7). A positive correlation in LP group was also found between nestin and calbindin ($r = 0.767$, $p < 0.05$).

Discussion

It is well known that the hippocampal neurogenic niche diminishes with age, and cellular senescence impairs cell functions and cell-cell interactions (27, 28). It has been suggested that aging leads to a reduction in hippocampal

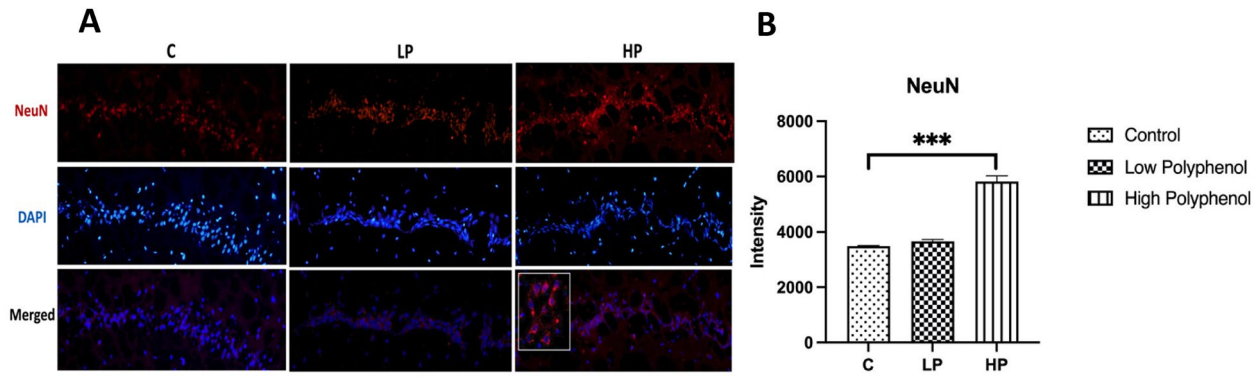


Figure 5. NeuN immunoreactivity in DG. (A) NeuN, DAPI staining merged images of brain slices (C: control, LP: low polyphenol, HP: high polyphenol). (B) Intensity of each groups. The level of NeuN labeled cells was higher in the HP group than in the Control and Low-polyphenol groups. Results are given as mean ± standard deviation (SD). ***$p < 0.001$ compared to the control group.

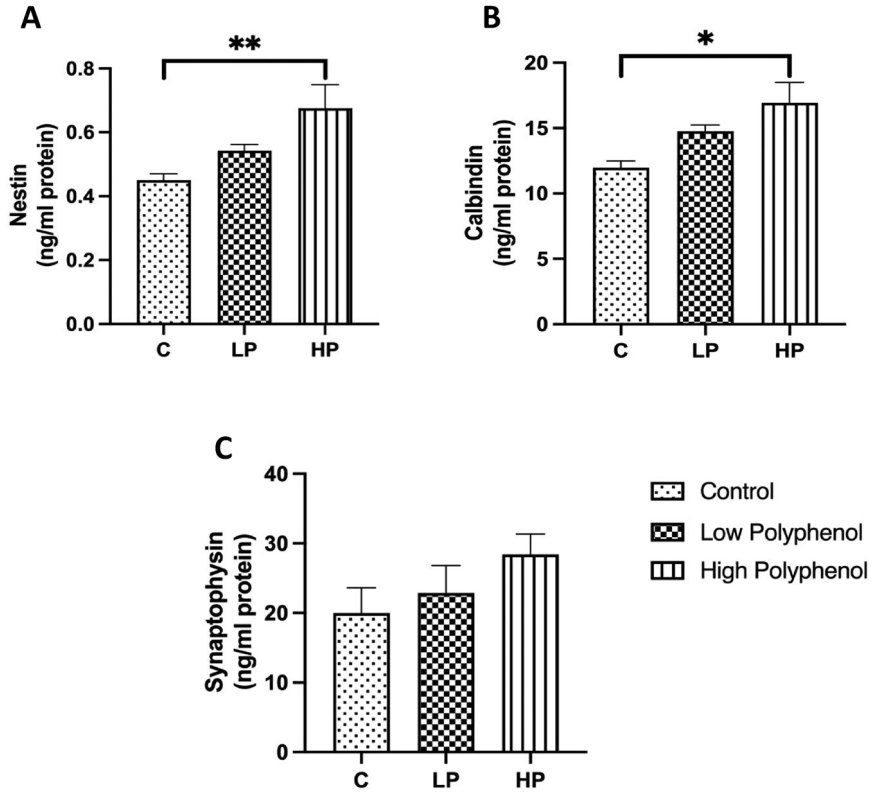


Figure 6. ELISA results of brain tissues (A) Hippocampal nestin levels. The proliferating cells were higher in the HP-group than in control group. **$p < 0.01$ compared to control group. (B) Hippocampal Calbindin level. The HP-Olive oil consumed group had higher calbindin levels. *$p < 0.05$ compared to the control group. (C) Hippocampal SYN levels. There was no difference between the groups in terms of SYN levels. No statistical difference was found between the groups ($p > 0.05$). All results are given as mean ± standard error (SEM).

neurogenesis in both rodents and mammals (29, 30). The alteration in neurogenesis at old age depending on gender differences is an important aspect. However, in vivo studies investigating neurogenesis in the aged brain in terms of sex differences revealed that cell proliferation decreases in middle age (10–12 months) but does not continue to decrease into old age (27 month) in both male and female rats (29–31). In general, we think that our sample represents old age in both males and females.

Changes in daily life habits, such as diet and exercise, have beneficial effects on brain aging (31, 32). These beneficial effects include inhibition of inflammatory pathways, activation of cell survival and maintenance factors, and neurogenesis (26, 33–35). Therefore, to increase hippocampal neurogenesis and/or induce cellular and molecular maintenance in aging, using olive oil polyphenols is a very promising approach (23, 24, 36–38).

Our study showed that daily consumption of olive oil with high polyphenol content increases hippocampal neurogenesis in old female rats (22–24 months). Studies in the literature that examine the effect of olive oil polyphenols on neurogenesis generally use several purified polyphenols, such as

A

	Calbindin	Nestin	BrdU	NeuN
Calbindin	1			
Nestin	.758*	1		
BrdU	.591**	.590**	1	
NeuN	.599**	.739*	.975**	1

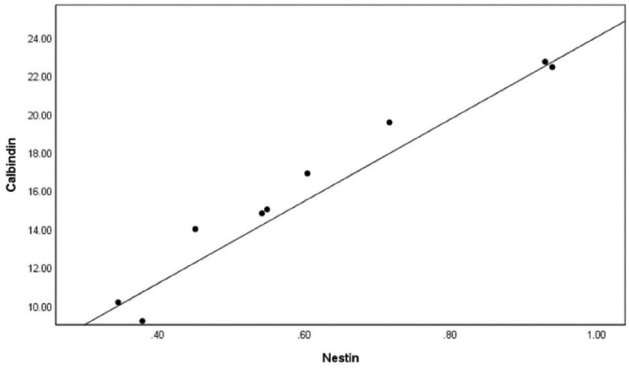
* p<0.05; **p<0.01 (2-tailed). The analysis was done with Pearson's

B

	Calbindin	Nestin	BrdU	NeuN
Calbindin	1			
Nestin	0.967**	1		
BrdU	0.600	0.714	1	
NeuN	0.600	0.486	0.543	1

**p<0.01 (2-tailed). The analysis was done with Spearman's

C



D

	Calbindin	Nestin	BrdU	NeuN
Calbindin	1			
Nestin	0.767*	1		
BrdU	-0.429	-0.771	1	
NeuN	0.943**	0.600	-0.371	1

* p<0.05; **p<0.01 (2-tailed). The analysis was done with Spearman's correlation

E

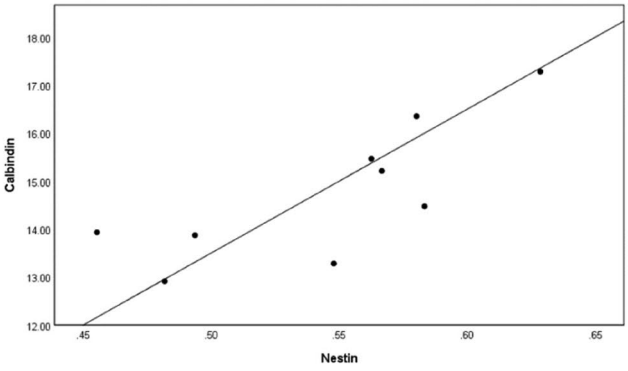


Figure 7. Correlation matrixes and graphs. (A) Correlation matrix for all groups (n = 18), (B) Correlation matrix of markers for HP group (n = 9), (C) Scatterplot of Calbindin and Nestin for HP group, (D) Correlation matrix of markers for LP group (n = 9). (E) Scatterplot of Calbindin and Nestin for HP group.

hydroxytyrosol (HT) or tyrosol, as the major polyphenols in olive oil. Our BrdU and NeuN findings demonstrated that HP-olive oil consumption increases both cell proliferation and cell maturation in old rats. D'Andrea et al. (27) showed that oral HT administration increases both proliferation and survival of DG cells in 15-month-old mice. Mice were fed for 30 days with 100 mg/kg/d HT. At the end of the treatment, BrdU- and NeuN-labeled cells were found to increase. Another study investigating olive polyphenols by Zheng et al. (26) reported that maternal HT administration (10 and 50 mg/kg/d, 2 weeks) increases neurogenesis in prenatally-stressed offspring and improves memory function. Our BrdU labeling and NeuN immunoreactivity results confirmed the neurogenic effect of HP-olive oil despite the fact that the amount of polyphenol (0.65 mg/d, 45 days) in the HP-olive oil was lower than that used in D'Andrea and Zheng's studies. Besides, cell proliferation was also confirmed with the increase of nestin protein expression in our study, which corroborates the previous literature (26, 27). In addition, the strong positive correlation between nestin-calbindin levels in HP group supported our hypothesis and revealed that proliferated cells also matured. Another important finding of our study was that olive oil with LP did not show a neurogenic effect in terms of proliferation and maturation. These results demonstrate that the amount of polyphenol content in olive oil is a determinant of hippocampal neurogenesis.

Since calbindin is the main calcium-buffering protein and buffering of Ca^{2+} is essential for neuronal functioning, we

evaluated the level of calbindin to determine whether olive oil polyphenols have a role in neuronal cell functioning in the hippocampus of aged rats. The high calbindin level in the HP-olive oil group indicates that consumption of the olive oil increased the calcium-buffering capacity of the hippocampus. Many studies investigating the effects of polyphenols on calcium metabolism have focused on calcium concentration changes, but mostly in-vitro. For instance, a study by Carey et al. (35), in which they used primary hippocampal neurons of rats, showed that walnut extract, which is rich in polyphenols and polyunsaturated fatty acids, improves calcium dysregulation in the cells. In one in-vivo study, using the LMN diet (a diet rich in polyphenols and polyunsaturated fatty acids) did not cause an increase in hippocampal calbindin levels in the LMN-fed group (36). In this respect, our study demonstrates a relationship between HP-olive oil and an increase in the calbindin levels in aged rat hippocampus. Considering the fact that calbindin is the main calcium-buffering protein, our calbindin results in the HP and LP groups may make an important contribution to the literature in elucidating the effects of HP olive oil consumption and the calcium regulation capacity of the neuronal cells. Previous studies have shown that an increase in calbindin levels caused an improvement in rats with impaired spatial memory. The reason why we could not find a correlation between the spatial memory and the increase in the levels of calbindin levels may be because the spatial memory of our study group was not impaired when the experiment started. In addition, Calbindin is expressed by mature neurons, and the positive correlation with nestin in our study may indicate that cells expressing nestin may have matured.

Morris water maze was performed to evaluate the effect of HP-olive oil consumption on memory. Neither HP-nor LP-olive oil consumption had a statistically significant impact on memory. This may be related to the amount of polyphenol content of HP olive oil used in the study. Zhang et al. (37) fed rats with three different doses of tea polyphenol (75, 150, 300 mg/kg) and they observed an improvement in spatial memory only in the highest amount of tea polyphenol group (300 mg/kg). The amount of polyphenol content may be a determinant of spatial memory performance, and the polyphenol concentration in our study might not have been sufficient for an improvement in behavior. The other explanation for non-significant MWM results may be the inefficiency of classic spatial memory parameters to reflect the increase in neurogenesis. The view regarding the functional relationship between neurogenesis and spatial memory performance may be that the classical Morris water maze test parameters do not demonstrate the function of newly produced cells in the DG. Kempermann et al. (38) suggested that the "searching strategy" parameter or the experimental setups in which the platform was relocated could yield more accurate results for the pattern separation. Therefore, the parameters that we used to evaluate spatial memory may not have had sufficient sensitivity to reflect the increase in neurogenesis accurately. Additionally, the rats in our study were 24 months of age, which is equivalent to 60 years of human age (39). In the literature, it has been suggested that spatial navigation is impaired after the age of 60, with an acceleration in decline after 70 (40). In a study done by Pitozzi et al. (41), 10 months old rats were fed with high polyphenol olive oil (6 mg/kg), low polyphenol olive oil, and resveratrol (22 mg/kg) for 6 or 12 months. The rats did not show any difference in spatial memory performance in the Morris water maze test. The authors suggest that the memory impairment is not detectable yet at 24 months of age and their suggestions are in line with our findings.

The effect of neurogenesis on anxiety-like behavior is also controversial. In our study, no difference was found in anxiety-like behavior. Some studies argue that a preexisting stress model is required to ameliorate anxiety-like behavior with neurogenesis. Hill et al. (42) used a transgenic animal model to increase hippocampal neurogenesis, but there was no difference in anxiety compared to the control group. However, when a stress model was created in the experiment by administering corticosterone and then neurogenesis was induced by tamoxifen, anxiety-like behavior subsided. It is suggested that neurogenesis may be able to ameliorate anxiety-like behavior only in the presence of stress. Therefore, in our study, the absence of any difference in anxiety parameters despite the increase in neurogenesis may be due to the fact animals were not stressed.

Synaptophysin protein levels are associated with spatial memory and low levels of hippocampal SYN indicate impaired spatial memory (17). We examined SYN levels in the hippocampus to evaluate spatial memory, which is related to synaptic density. Although the level of hippocampal SYN slightly increased in the HP group, this increase was not significant compared to the control and LP groups. In a study by Schmitt et al. (18), they used rats with intact and disrupted spatial memory. They found that while SYN levels decreased in the rats only with impaired spatial memory, they were not altered in the rats with intact spatial memory. The parallelism between SYN and spatial memory in our study is consistent with the study of Smith et al. In addition, the absence of difference in hippocampal SYN levels between the groups may depend on the level of polyphenol content used in this study. In a study by Wang et al. (43), *polygonum multiflorum* plant extract, known for its high antioxidant capacity, was given to 21-month-old rats at low (30 mg/kg) and high (60 mg/kg) doses for 3 months. They observed no difference in the hippocampal SYN levels in rats fed with low doses compared to the control group (rats that didn't receive any treatment). However, a significant increase was detected in the hippocampus of the group fed with high doses compared to both the low-dose and the control group. Therefore, we also consider that higher polyphenol doses may affect hippocampal SYN levels.

Finally, we analyzed the SYN level of the prefrontal cortex. Our results have shown that daily consumption of HP-olive oil increases the synaptic density in the prefrontal cortex. Although there is no study investigating the effect of HP-olive oil on synaptic density or SYN levels of the prefrontal cortex, the effect of tea polyphenols on synaptic density in the frontal cortex was demonstrated in a previous study. In a study by Guo et al. (44), epigallocatechin

gallate (EGCG), a green tea polyphenol, was given to SAMP8 mice at 5 and 15 mg/kg mixed with drinking water for 8 weeks. It was shown that the SYN levels in the frontal cortex increased with both low and high polyphenol consumption. It is argued that the function of the prefrontal cortex, which enables the formation of high cognitive functions, such as attention, information processing speed, and decision making in humans, is only limited to working memory in rodents (45). Therefore, although the prefrontal cortex SYN increased in the HP group in our study, the Morris water maze test and open field test may not be sufficient to measure the functional reflection. As a result, consumption of HP-olive oil increased synaptic density in the prefrontal cortex region, which is necessary for cognitive control behavior.

Conclusion

Our findings show that HP-olive oil consumption increases neuronal proliferation and maturation in the DG of old rats. Hippocampal calbindin levels increased with HP content suggesting that consumption of olive oil with high polyphenol contributes to calcium-buffering capacity, thus, neuronal functioning. Synaptophysin levels in the prefrontal cortex also increased with HP-olive oil. On the other hand, LP-olive oil did not affect cell proliferation, maturation and calbindin, SYN expressions in old rats. In conclusion, the polyphenol content in olive oil is a determinant of the beneficial effect on neurogenesis in female aged rats.

Disclosure statement

No potential conflict of interest was reported by the authors.

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2021 JOURNAL IMPACT FACTOR: **3.571**
View calculation

JOURNAL IMPACT FACTOR WITHOUT SELF CITATIONS: **3.486**
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Journal Impact Factor Trend 2021

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Journal Impact Factor contributing items

Export

Cited Items (JIF) | Citing Sources (SCR)

TITLE	CITATION COUNT
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Does Serum Vitamin D Level Affect COVID-19 Infection and Its Severity? A Case-Control Study	38
Toward the Definition of Personalized Nutrition: A Proposal by The American Nutrition Association	23
Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition?	23
Alzheimer's Disease and Parkinson's Disease: A Nutritional Toxicology Perspective of the Impact of Oxidative Stress,...	19
Vitamin D Deficiency and Low Serum Calcium as Predictors of Poor Prognosis in Patients with Severe COVID-19	17
Can Vitamin D and L-Cysteine Co-Supplementation Reduce 2019-nCoVid Infection?	14
Health Effects of Coconut Oil-A Narrative Review of Current Evidence	14
Cow's Milk Consumption and Health: A Health Professional's Guide	13
Vitamin D in Prevention and Treatment of COVID-19: Current Perspective and Future Prospects.	12

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The Journal Citation Indicator (JCI) is the average Category Normalized Citation Impact (CNCI) of citable items (articles & reviews) published by a journal over a recent three-year period. The average JCI in a category is 1. Journals with a JCI of 1.5 have 50% more citation impact than the average in that category. It may be used alongside other metrics to help you evaluate journals. Learn more



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Export

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Export

The Citation Distribution shows the frequency with which items published in the year or two years prior were cited in the JCR data year (i.e., the component of the calculation of the JIF). The bar graph is most useful functionality as the JIF Trend graph, including hover over data descriptions for each year, and an interactive legend where each data element's legend can be used as a toggle. You can view Articles, Reviews, or Non-Citable (other) items to the JIF numerator. Learn more

ARTICLE CITATION MEDIAN: **2**
REVIEW CITATION MEDIAN: **3**
UNCLASSIFIED ESTIMATE: **55**

TIMES CITED: **0**
ARTICLES: **51**
REVIEWS: **3**
OTHERS: **17**



Open Access (OA)

Export

The data included in this tile summarizes the items published in the journal in the JCR data year and in the previous two years. For example, in the 2020 JCR data, released in June 2021, the Open Access (OA) data show the publication-model (Gold OA or subscription) of materials published in 2018, 2019 and 2020, and citations in 2020 to those items. This three-year view of published items is used to provide descriptive analysis of the content and community of the journal. Learn more



UNLINKED CITATIONS: **61 / 6.59%**

*Citations in 2021 for items published in 2019 - 2021

Items

TOTAL ITEMS: **324** | % OF ITEMS OA: **4.94%**

Citations*

TOTAL CITATIONS: **859** | % OF CITATIONS OA: **8.03%**

Rank by Journal Impact Factor

Journals within a category are sorted in descending order by Journal Impact Factor (JIF) resulting in the Category Ranking below. A separate rank is shown for each category in which the journal is listed in JCR. Data for the most recent year is presented at the top of the list, with other years shown in reverse chronological order. Learn more

EDITION: Science Citation Index Expanded (SCIE)

CATEGORY: **NUTRITION & DIETETICS**

56/90

JCR YEAR	JIF RANK	JIF QUARTILE	JIF PERCENTILE
2021	56/90	Q3	38.05
2020	54/90	Q3	39.28
2019	61/89	Q3	32.02
2018	59/87	Q3	32.76
2017	56/83	Q3	33.13

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CATEGORY: **NUTRITION & DIETETICS**

57/109

JCR YEAR	JCI RANK	JCI QUARTILE	JCI PERCENTILE
2021	57/109	Q3	48.17
2020	56/106	Q3	47.64
2019	61/106	Q3	42.92
2018	67/104	Q3	36.06
2017	62/101	Q3	39.11

Citation network

Cited Half-life

13.2 years

The Cited Half-Life is the median age of the items in this journal that were cited in the JCR year. Half of a journal's cited items were published more recently than the cited half-life.

TOTAL NUMBER OF CITES: **6,294**
HALF-LIFE CITATIONS: **6,252**
NON-CITATIONS: **42**

Cited Half-life Data



Citing Half-life

8.0 years

The Citing Half-Life is the median age of items in other publications cited by this journal in the JCR year.

TOTAL NUMBER OF CITES: **4,449**
HALF-LIFE CITATIONS: **4,407**
NON-CITATIONS: **42**

Citing Half-life Data

Export

CITING YEAR	# CITING ITEMS (NON-SELF)	CUMULATIVE %	CITATIONS TO ITEMS
All years	**4,294 citations**	**100.00%**	**6,798 sources**
2021	51 citations	0.81%	39 sources
2020	581 citations	10.04%	320 sources
2019	294 citations	14.71%	179 sources
2018	256 citations	18.78%	154 sources
2017	356 citations	24.44%	218 sources
2016	264 citations	28.63%	168 sources
2015	211 citations	31.98%	141 sources
2014	167 citations	34.63%	123 sources
2013	131 citations	36.71%	91 sources
2012	110 citations	38.58%	79 sources
Older	1,881 citations		

Journal Citation Relationships

Cited Data | Citing Data

Top 20 journals citing J AM COLL NUTR by number of citations



Content metrics

Source data

This tile shows the breakdown of document types published by the journal. Citable Items are Articles and Reviews. For the purposes of calculating JIF, a JCR year considers the publications of that journal in the two prior years. Learn more

79 total citable items

	ARTICLES	REVIEWS	COMMERCIALS	OTHER DOCUMENT TYPES	PERCENTAGE
NUMBER OF JCR YEAR 2021 ITEMS	66	13	79	5	99%
NUMBER OF CITATIONS	5,255	1,186	6,435	14	100%
RATIO (C/I)	80.1	90.8	56.2	14.0	

Average JIF Percentile

Export

The Average Journal Impact Factor Percentile takes the sum of the JIF Percentile rank for each category under consideration, then calculates the average of those values. Learn more

5-YEAR JIF AVERAGE	SOURCE
38.33	Science Citation Index Expanded
	AVERAGE JIF PERCENTILE: **38.33**

Contributions by organizations

Export

Organizations that have contributed the most papers to the journal in the most recent three-year period. Learn more

RANK	ORGANIZATION	COUNT
1	CALIFORNIA STATE UNIVERSITY SYSTEM	12
2	UNIVERSIDADE DE SAO PAULO	10
3	ISFAHAN UNIVERSITY MEDICAL SCIENCES	9
4	UNIVERSIDAD FEDERAL DE RIOJA	9
5	LOMA LINDA UNIVERSITY	8
6	TUFTS UNIVERSITY	8
7	GEORGETOWN UNIVERSITY	7
8	OHIO STATE UNIVERSITY	7
9	GEORGE MASON UNIVERSITY	6
10	INTEGRAX NETA TECHNOL	6

Contributions by country/region

Export

Countries or Regions that have contributed the most papers to the journal in the most recent three-year period. Learn more

RANK	COUNTRY / REGION	COUNT
1	USA	127
2	Brazil	42
3	India	36
4	CHINA MAINLAND	33
5	Turkey	23
6	Iran	18
7	England	17
8	Italy	16
9	Canada	15
10	South Korea	10

Additional metrics

Eigenfactor Score

0.00294

The Eigenfactor Score is a reflection of the density of the network of citations around the journal using 5 years of cited content as cited by the Current Year. It considers both the number of citations and the source of those citations, so that highly cited sources will contribute more weight than those with few citations. The Eigenfactor calculation does not include journal self citations. Learn more

Normalized Eigenfactor

0.63393

The Normalized Eigenfactor Score is the Eigenfactor score normalized, by equating the median value of journals in the JCR each year, so that the average journal has a score of 1. Journals can then be compared and influence measured by their score relative to 1. Learn more



Article influence score

0.633

The Article Influence Score normalizes the Eigenfactor Score according to the cumulative size of the cited journal across the prior five years. The mean Article Influence Score for each article is 1.00. A score greater than 1.00 indicates that each article in the journal has above average influence. Learn more



5 Year Impact Factor

3.566

View Calculation

The 5 year Impact Factor is the average number of times articles from the journal published in the past five years have been cited in the JCR year. It is calculated by dividing the number of citations in the JCR year by the total number of articles published in the five previous years.

Immediacy Index

0.646

View Calculation

The immediacy index is the count of citations in the current year to the journal that reference content in this same year. Journals that have a consistently high immediacy index attract citations rapidly. Learn more