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Review Paper

Olive Oil and Its Extracts in Alzheimer's Disease: A Systematic Review in Animal Models

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ABSTRACT

Background: The prevalence of Alzheimer disease (AD) is expected to increase, especially in Indonesia. Despite lacking a cure, extra-virgin olive oil, abundant in neuroprotective compounds, offers promise in delaying cognitive decline by opposing oxidative stress in the aging brain. Research indicates its capacity to bolster long-term cognitive function and memory.

Objectives: We examined the impact of olive oil and its derivatives on AD through a comprehensive analysis of experimental studies in mouse and worm models.

Materials & Methods: Thirteen relevant articles were selected from the initial pool based on specific inclusion criteria. Data were extracted regarding study design, intervention types, model species used, cognitive outcomes, and findings. The reliability of the selected studies was ensured by evaluating their methodological quality and risk of bias.

Results: Our systematic review of 13 selected experimental studies involving mice and worm models provides insights into the potential impact of olive oil and its extracts on AD. Findings suggest that these interventions may exhibit neuroprotective properties, positively influencing cognitive function and mitigating AD-related outcomes in the experimental models studied.

Conclusion: Experimental studies on mice and worm models suggest that olive oil and its extracts may present neuroprotective benefits and positively influence cognitive function in AD contexts. Further research involving human subjects is essential to validate these findings and explore their practical implications in AD prevention and management.

Keywords: Experimental animal models, Alzheimer disease, Dementia, Olive oil, Systematic review

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Highlights

- Olive oil interventions show neuroprotective potential against Alzheimer disease in animal models.
- Cognitive function improvements are observed in mice and worm models with olive oil supplementation.
- Olive-derived compounds mitigate Alzheimer-related outcomes, suggesting therapeutic promise.

Introduction

Dementia stands out as a significant burden worldwide; it is one of the causes of life loss and functional limitations. There are about 47 million dementia cases worldwide nowadays, and 10 million new cases are expected to be added each year. In Indonesia, about 1.2 million people had dementia in 2016, and this is likely to rise to 4 million by 2050. This condition can significantly interfere with a person's daily functioning and independence, thus severely affecting one's social and occupational functions [1, 2]. Dementia is a group of symptoms presenting as a decline of cognitive function, such as memory, language comprehension, and problem-solving, that may extend to other brain domains. Dementia results from either degenerative or non-degenerative etiology [3]. The early detectable phase of dementia is called mild cognitive impairment (MCI), where affected individuals exhibit impairment in cognitive functions with little or no interference with their ability to perform essential daily tasks [4].

The neurodegenerative process is the primary cause, especially Alzheimer disease (AD), comprising up to 70% of total dementia cases worldwide. AD commonly, but not limited to, affects the elderly, especially those older than 65. AD presents with progressing amnestic condition affected non-memory cognitive domains to the point where these alterations have an impact on everyday functioning. Other cognitive domains are affected as the illness worsens, and behavioral changes often appear [5]. There are some hypotheses of AD pathophysiology. Neuritic/senile plaques, due to β-amyloid peptides (Aβ) accumulation and neurofibrillary tangles (NFTs) from the phosphorylated tau protein, are the two most common ones [5]. Aβ plaques, which have neurotoxic feature, result from the biosynthesis of amyloid precursor protein (APP) by β-secretase and γ-secretase, proteolytic cleavage enzymes. Tau protein in AD, meanwhile, presents as a paired helical filament, which disturbs the cytoskeletal microtubules and tubulin-associated proteins. Furthermore, the plaque will hinder the reception of stimuli and the NFTs prevent the transmission of stimuli within a neuron cell, which later becomes a neuronal death. Another hypothesis is the cholinergic theory, which highlights the acetylcholine esterase (AchE) and acetylcholine deficits in AD patients, essential substances in human memory function. At last, synaptic loss theory refers to synaptic damage in the neocortex and limbic system during the early AD stage [6, 7]. However, there is still no definitive cure for AD and other dementia. Various possible treatments are continuously being studied to increase and maintain the patients› and caregivers› quality of life.

Extra-virgin olive oil (EVOO) is one example of a non-pharmacological approach to delay AD, as it is clinically approved to lower the risk of vascular disease, stroke, and age-related cognitive disorders. Olive oil contains neuroprotective agents called phenolic compounds with strong antioxidant properties, mainly affecting memory and behavior. The EFSA has emphasized the relevance of active compounds found in olives. The EFSA provided health approval, affirming the effectiveness of olive oil phenolics at a dosage of 5 mg per day within 20 g of EVOO [8]. Long-term consumption of EVOO is associated with lower cell oxidative stress and cell apoptosis [9, 10]. Aging brains, in particular, show increased nuclear and mitochondrial DNA oxidation, which changes the body's activity of enzymes and antioxidants. According to this statement, age-related brain disorders can be prevented by decreasing oxidative damage and balancing the disrupted equilibrium. EVOO composition includes hydroxytyrosol (3,4-dihydroxyphenylethanol), elenolic acid, and glucose [11]. The distribution of phenolic components is intricately linked to geographical origin, cultivar type, and tree age [12, 13]. Additionally, the extraction method significantly influences the polyphenol yield in extracts from olive leaves [14]. Beyond phenolic compounds, simple phenols (tyrosol and hydroxytyrosol) and secoiridoids (specifically oleocanthal and oleacein) are recognized for their efficacy in neutralizing reactive nitrogen and oxygen species (RNS and ROS), respectively. These compounds are essential for reducing the biochemical consequence of reactive spe-

Table 1. Search method in databases

Source	Keyword	Filter	Record
Web of Science	(Extra virgin olive oil OR olive oil) AND (dementia OR mild cognitive impairment OR Alzheimer OR parkinson OR major neurocognitive disorder) NOT (review OR Meta-analysis)	2018-2023, English	122
PubMed	("Extra-virgin olive oil*" OR "olive oil*") AND ("dementia" OR "Alzheimer" OR "Parkinson" OR "mild cognitive impairment*" OR "major neurocognitive disorder*")	2018-2023, English, free full text	62
ProQuest	("Randomized controlled trial" OR "experimental study") AND (["extra virgin olive oil" OR "olive oil"] AND ["mild cognitive impairment" OR "Alzheimer" OR "Parkinson" OR "dementia" OR "major neurocognitive disorder"])	2018-2023, scholarly journals, English, full text	810
Science Direct	("Randomized controlled trial" OR "experimental study" (["Extra virgin olive oil" OR "olive oil"] AND ["mild cognitive impairment" OR "Alzheimer" OR "Parkinson" OR "dementia" OR "major neurocognitive disorder"])	2018-2023, research article, open access and open archive	225
EBSCO	(SU [neurology OR psychiatry]) AND (TX [extra virgin olive oil OR olive oil]) AND (TX [dementia OR mild cognitive impairment OR Alzheimer OR Parkinson OR major neurocognitive disorder])	2018-2023	12
SCOPUS	("Randomized controlled trial" OR "experimental study" (["extra virgin olive oil" OR "olive oil"] AND ["mild cognitive impairment" OR "Alzheimer" OR "Parkinson" OR "dementia" OR "major neurocognitive disorder"])	2018-2023, English	28
Taylor & Francis	("Randomized Controlled Trial" OR "Experimental Study" (("Extra virgin olive oil" OR "Olive oil") AND ("mild cognitive impairment" OR "alzheimer" OR "Parkinson" OR "dementia" OR "major neurocognitive disorder")))	2018-2023, only show open access	11
SAGE	(["olive oil"] AND ["dementia" OR "Alzheimer"])	2018-2023, English, open access research article	24

cies to prevent oxidative stress. Notably, oleocanthal, a nutraceutical component found in EVOO, exhibits various health properties, including anti-inflammatory, neuroprotective, and anticancer effects [15]. Hydroxytyrosol (HT), an antioxidant in olive oil, has demonstrated greater potency than vitamin E. Additionally, HT can cross the blood-brain barrier due to its amphipathic nature [16]. This review explores the potential impacts of olive oil and olive-derived extracts on animal experimental models such as mice and worms with AD.

Materials and Methods

Search method

The present study followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines, ensuring a comprehensive and standardized approach to the review and analysis process [17]. The database search encompassed multiple sources, including Science Direct, PubMed, ProQuest, Web of Science, EBSCO, SAGE, Scopus and Taylor & Francis, conducted in August 2023. Screening incorporated all relevant literature published from 2018 to 2023. The strategy employed utilizing synonyms for several keywords, such as a randomized controlled trial, Alzheimer, EVOO, Parkinson, dementia, major neurocognitive disorder, and MCI. We collected all search results and removed the duplicate and screen. The identified papers' titles and abstracts were meticulously scrutinized to identify eligible literature, followed by screening of the full texts. Any disagreements among the six researchers were deliberated until a consensus was reached. The detailed search methods for various sources are meticulously delineated in Table 1.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) Experimental studies that assess the effects of olive or its components in AD, 2) Animal studies, 3) Use of olive or its components as primary intervention, 4) Studies assessing the effects of olive or its components on neurological symptoms, disease progression, neuroprotective effects,

Table 2. The research quality of studies

Authors (y)	Items									
	1	2	3	4	5	6	7	8	9	10
Basuny et al. (2022) [20]	Unclear	Yes	Unclear	Yes	Unclear	No	Unclear	Yes	Yes	Yes
Kandiş et al. 2022 [21]	Unclear	Yes	Unclear	Unclear	Unclear	No	Unclear	Yes	Yes	Yes
Abdallah et al. 2022 [22]	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes
Kumar et al. 2019 [23]	Unclear	Yes	Unclear	Unclear	Unclear	No	Unclear	Yes	Yes	Yes
Qin et al. 2020 [24]	Unclear	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Romero-Márquez et al. 2022 [25]	Unclear	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Gea-González. 2021 [26]	Unclear	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Lauretti et al. 2019 [27]	Unclear	No	Unclear	Unclear	Unclear	No	Unclear	Yes	Yes	Yes
Al Rihani. 2019 [28]	Unclear	Yes	Unclear	Unclear	Unclear	No	Unclear	Yes	Yes	Yes
Romero-Márquez et al. 2022 [29]	Unclear	Yes	Unclear	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes
Kokras et al. 2020 [30]	Unclear	Yes	Unclear	No	Unclear	No	Unclear	Yes	Yes	Yes
Abdallah et al. 2023 [31]	Unclear	Yes	Unclear	No	Unclear	No	Unclear	Yes	Yes	Yes
Afsana et al. 2021 [32]	Unclear	Yes	Unclear	Yes	Unclear	No	unclear	Yes	Yes	Yes

cognitive function, motor function, quality of life, biochemical markers, or any relevant clinical outcomes, 5) Articles published in English, 6) Studies published within the last 5 years (2018-2023) and 7) Studies whose full texts were open access. We included articles that are freely available and accessible without any subscription or paywall restrictions. This criterion ensures the review can incorporate a wider range of accessible studies to a broader audience.

The exclusion criteria encompassed: 1) Non-experimental studies such as review articles, case reports, case series, and observational studies, 2) Human or in vitro studies, 3) Other non-English studies will be excluded unless relevant resources are available for translation, and 4) Studies published more than 5 years ago. When multiple publications reported on the same study, the most comprehensive or the latest study was selected to avoid data duplication.

Data extraction

Four reviewers (Alexander Tikara Sugondo, Qorina Nadya Salfi, Maura Tuzzahrah Ramadhani and Vania Ayu Puspamaniar) independently extracted data using a standard form. Discrepancies were deliberated upon and resolved under the supervision of senior researchers (Yudha Haryono and Abdulloh Machin). The following information was systematically collected from each paper: 1) Author(s), 2) Year of publication, 3) Number of samples, 4) Sex, 5) Types of olive oil, 6) Dose, 7) Duration and 8) Analysis/results.

Quality of the studies

We evaluated all the articles in our analysis for potential biases using Systematic Review Centre for Laboratory Animal Experimentation (SYRCLE)'s 10-item checklist designed for animal studies [18, 19]. We made some adjustments to align with the protocols used in our present study. However, it is important to note that some aspects like "sequence generation" (which assesses selection bias), "allocation concealment" (related to selection bias) and "blinding" (which addresses both performance and detection bias) were not following the protocols employed in our current study.

The quality rating for this review was assessed based on ten criteria: Sequence generation, baseline characteristics, allocation concealment, random housing, blinding, random outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of

bias. Two reviewers were responsible for data extraction and quality evaluation for all studies, with additional reviewers conducting a thorough re-evaluation of the process to ensure accuracy and thoroughness (Table 2).

Results

Reporting results and study selection

We conducted an extensive literature search and retrieved 1294 records from various databases: 62 from PubMed, 225 from ScienceDirect, 122 from Web of Science, 810 from ProQuest, 12 from EBSCO, 24 from SAGE, 11 from Taylor & Francis, and 28 from Scopus. After removing duplicate records, we had records remaining for the initial screening based on titles and abstracts. Subsequently, records were subjected to exclusion, resulting in 100 studies that met the criteria for a full-text review. After a thorough assessment using the study's defined criteria, 87 records were subsequently excluded. Ultimately, 13 studies were carefully selected (Figure 1) [20-32].

Study characteristics

All 13 studies were experimental, with 10 mice and 3 worm studies. Table 3 lists the overall features of selected studies with additional data, such as types of olive intervention, dose, duration, and study findings. Several studies have provided interventions using olive or its derivatives on animals, with varying dosages and durations.

Discussion

Exploring the mechanisms sheds light on olive efficacy in AD. Synaptic improvement, anti-inflammatory pathways, amyloid aggregation inhibition, and antioxidant effects collectively contribute to their therapeutic potential.

In a study by Lauretti et al. (2019), compelling evidence is presented for the EVOO's synaptic function and plasticity-positive effects in a tauopathy model. Elevated levels of presynaptic complexin-I following EVOO treatment suggest a potential link to enhanced synaptic activity, complementing observed improvements in cognition associated with AD [27]. EVOO consumption has been associated with cognitive improvements, synaptic integrity, and mitochondrial health in AD mouse models [33, 34, 35]. Cognitive function, crucial in daily activities, is enhanced alongside synaptic integrity, facilitating neuronal communication. Mitochondrial health, essential for cellular energy production, is also bolstered. The upregulation of synaptic proteins may mediate these effects, as well as increased autophagy. This cellular process removes damaged components and enhances mitochondrial function, which may play a vital role in EVOO's neuroprotective effects.

Furthermore, neuroinflammation, a chronic inflammatory process implicated in AD progression, may be mitigated by EVOO consumption [22, 31, 36]. This reduction in neuroinflammation could be attributed to EVOO's ability to suppress the activation of NLRP3 inflammasomes, inhibit NF-κB pathways and modulate MAPK signaling pathways. Abdallah et al. (2023) also highlighted suppressing the RAGE/HMGB1 pathway and NLRP3 inflammasome activation as key neuroprotective effects of EVOO and its constituent, oleocanthal (OC) [22, 31]. The observed reduction in astrocyte activation and pro-inflammatory cytokine levels suggests a potential role for EVOO and OC in alleviating neuroinflammation, a key pathological feature of AD.

Investigating the effects of olive leaf extract compounds, Oleuropein aglycone (OleA) and HT, on Aβ1-42 aggregation, a hallmark of AD condition, Leri et al. (2019) revealed distinct mechanisms underlying amyloid aggregation inhibition. While OleA stabilizes oligomeric intermediates, preventing fibril formation, HT accelerates fibrillation, generating less toxic fibrils. Both compounds reduce cytotoxicity and interfere with Aβ seeding ability, offering potential therapeutic avenues in AD [37]. Several studies have indicated that EVOO consumption reduces brains' Aβ levels in AD mouse models. EVOO's mechanisms for reducing Aβ levels include facilitating Aβ clearance in the brain, encouraging the enzymatic breakdown of Aβ, and directing APP processing towards the non-amyloidogenic pathway. APP is cleaved to generate Aβ, making this pathway crucial in Aβ accumulation [22, 34, 38].

Conclusion

This systematic review of experimental studies in mice and worm models indicates that olive oil and olive-derived extracts hold promise as potential interventions for addressing AD. The observed neuroprotective effects and improvements in cognitive function suggest a valuable avenue for further research in understanding the mechanisms underlying these benefits. However, additional research, including clinical trials, is essential to determine the translational relevance of these findings to human AD prevention and management. These results emphasize the importance of investigating natural com-

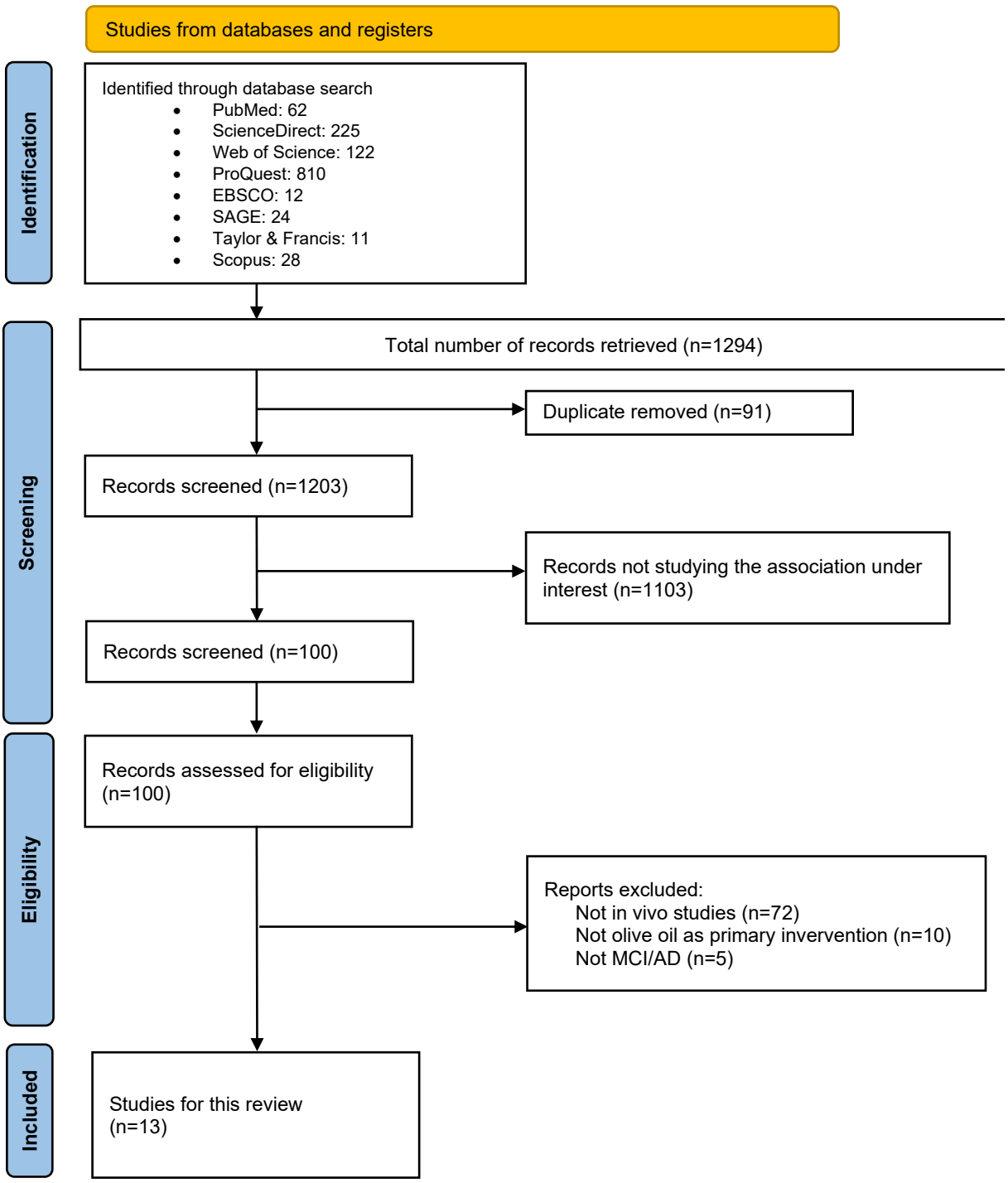

Figure 1. Flow diagram following PRISMA guideline

Table 3. Olive interventions in various studies and their main findings

No.	Authors (y)	Species	n	Sex	Types of Olive Oil	Dose	Duration	Analysis/Results
1	Basuny et al. (2022) [20]	Albino Wistar	24	Male	Koroneiki (K) and Coratina (C) Olive Oil	0.3 mg/kg/d	60 days	↓ Brain antioxidant markers (MDA and LDH) ↓ Neuroinflammation: Pro-inflammatory cytokines (iNOS) ↓AChE levels ↓ Aβ production: ↓ APP gene expression
2	Kandiş et al. (2022) [21]	Sprague Dawley	35	Male	Extra-virgin olive oil (EVOO)	1 mL/d	21 days	↑ Spatial learning and memory ability: ↑ time in the hidden platform area ↓ thymus weight
3	Abdallah et al. (2022) [22]	5xFAD Mice	20	Male	Glycosylated oleuropein (OLG)-rich olive leaf extract (OLE)	695 µg/kg/d	3 months	↓ Total Aβ loads and plaque: ↓ soluble Aβ40 levels, ↑ Aβ clearance proteins (P-gp and LRP1), ↑ expression of both sAPPα and αsecretase, ↓ expression of sAPPβ ↓ Neuroinflammation:↓ astrocyte activation, ↓ astrocyte shape, ↓ GFAP, ↓ Iba1 in cortex and hippocampus, ↓ IL-1β and IL6, ↓ NLRP3, pro-caspase-1, pro-caspase-8, ↓ RAGE and HMGB1, v ↓ p-IKKβ, ↓ p-IκBα, ↑ IκBα ↑ BBB function: ↑ tight junction proteins (claudin-5, occludin, ZO1) and adherence junction protein (VE-cadherin) ↑ presynaptic markers: SNAP-25, synapsin-1, PSD-95 ↑ Spatial learning and memory ability: Found the platform faster and longer time in the target quadrant
4	Kumar et al. (2019) [23]	Wistar Rats	30	Male	Dietary olive oil	3.1 mL/kg/d	37 days	↑ Spatial learning and memory ability: ↑ D latency values, ↑ time spent in D quadrant, ↓ time reached to escape area ↓ AChE in the frontal cortex ↑ Antioxidant markers: ↑ catalase in the frontal cortex, ↓ nitrite in the frontal cortex, ↓ MDA
5	Qin et al. (2020) [24]	C57BL/6J mice; APP/PS1 transgenic mice	19	Female	Hydroxytyrosol acetate	50 mg/kg/d	12 weeks	↑ Spatial learning and memory ability: ↓ time reached to escape the area, ↑ mean number of platform crossings, ↑ mean spontaneous alternation ↓ Neuronal apoptosis level in cortex and hippocampus: ↓ expression of Bad and Bak protein, ↓ caspase-3 and caspase-9 ↑ expression of ERβ
6	Romero-Márquez et al. (2022) [25]	*Caenorhabditis elegans*	10-180/test	NA	Diluted OLE	100 µg/mL	24-72 hours	↓ Total Aβ Loads and Plaque ↑ Antioxidant markers: ↑ SOD-3:GFP, ↑ HSP-16.2:GFP, ↓ GST-4:GFP ↑ locomotive parameters, speed, wavelength, ↓ stretching effort

No.	Authors (y)	Species	n	Sex	Types of Olive Oil	Dose	Duration	Analysis/Results
7	Gea-González et al. (2021) [26]	*Caenorhabditis elegans*	75-180/ test	NA	Hydroxytyrosol and hydroxytyrosol acetate	IC_{50}: 0.57 mM (HT) and 0.62 mM (HT-ac)	60 hours	↓ Total Aβ Loads and Plaque ↑ chemotaxis index (CI), neuroprotective agent ↑ lifespan of neuron-impaired nematodes
8	Lauretti et al. (2019) [27]	hTau mice	31	Male and Female	chow diet supplemented with EVOO (polyphenols (253 mg/kg), α-tocopherol (381 mg/kg), and γ-tocopherol (23 mg/kg))	diet: 50 mg/kg/d	6 months	↑ Spatial learning and memory ability: ↑ percentage of spontaneous alternation, ↑ time with the novel object, ↑ number of platform zone entries ↑ Hippocampal synaptic activity (basal, STP, and LTP) in the CA1 area ↑ Synaptic vesicle: Complexin-1 ↓ phosphorylated tau ↑ GSK3-β
9	Al Rihani et al. (2019) [28]	TgSwDI mice	14	Female	Powdered diet supplemented with EVOO (315 mg/kg oleacein, 389 mg/kg hydroxytyrosol, 994 mg/kg tyrosol, and 72 mg/kg oleuropein aglycon)	Diet: 0.714 (g/kg)/d, contains 476 (µg/kg)/d oleocanthal	3 months	↑ BBB function: ↓ IgG extravasation ↓ total Aβ Load and Plaques: ↑ sAPPα, ↓ sAPPβ, and BACE1 expressions ↓ total tau ↓ Neuroinflammation: ↓ astrocyte activation, ↑ astrocyte shape, ↑ Iba1, MMP9, microglial activation-FEPPA levels, TRPA1 activation, IL-1β, ↑ IL-10, ↓ NLRP3 protein expression, procaspase-1 and cleaved caspase-1 p20 and p10, procaspase-8, and cleaved caspase-8 p18 ↓ Oxidative Stress Markers: ↓ protein carbonyl, ↑ SOD ↑ Autophagy ↑ AMPK, ULK1, ATG7, ATG3, LC3-II, ↓ LC3-I and ubiquitin-binding protein p62 ↑ Neurosynaptic markers: PSD-95, synapsin-1, and SNAP-25 ↑ Spatial learning and memory ability: found the platform faster and ↓ mouse swimming distance
10	Romero-Márquez et al. (2022) [29]	*Caenorhabditis elegans*	10-200/ test	NA	Hydroxytyrosol-rich olive fruit extract (HOFE)	100 µg/mL	24-48 hours	↓ AAPH-Induced Oxidative Stress ↓ Aβ-Induced Paralysis: ↑ Aβ deposits ↑ Improve swimming speed and waviness ↑ Antioxidant markers: ↑ DAF-16:GFP, SKN1:GFP, SOD3:GFP, HSP-16:GFP, GST-4:GFP)
11	Kokras et al. (2020) [30]	C57BL/6 mice	7-9 group	Female	Total phenolic content (TPC) from koroneiki EVOO	10 mg/kg (TPC LOW dose) and 30 mg/kg (TPC HIGH dose)	7 days	↑ Spatial learning and memory ability: ↑ Object Field Test (center entries, horizontal, vertical, and stereotypic counts), ↑ Tail Suspension Test (↓ immobility time) ↑ aspartate levels in the hippocampus ↓ taurine, aspartate, glutamate levels in the prefrontal cortex

No.	Authors (y)	Species	n	Sex	Types of Olive Oil	Dose	Duration	Analysis/Results
12	Abdallah et al. (2023) [31]	5xFAD mice	30	Male	Oleocanthal (OC)-low EVOO and OC (540 mg/kg in olive oil)	0.5 mg/kg/d	3 months	↓ Total Aβ Load and Plaque: ↓ soluble Aβ40 and Aβ42 level, ↑ Aβ clearance proteins (P-gp and LRP1), ↑ sAPPα and ADAM10 ↓ expression of sAPPβ ↑ BBB function: ↑ tight junction proteins (claudin-5, occludin) and adherence junction protein (VE-cadherin) ↑ Presynaptic markers: SNAP-25, synapsin-1, PSD-95 ↓ Neuroinflammation: IL-1β and IL-6, ↓ NLRP3 protein expression, procaspase-1 and procaspase-8, ↓ RAGE and HMGB1, ↓ p-IKKβ, ↓ p-IκBα, ↑ IκBα
13	Afsana et al. (2021) [32]	5xFAD mice	18	Female	OC	10 mg/kg/day	120 days	↑ Spatial learning and memory ability: ↓ latency time, ↑ mice swimming distance ↓ Total Aβ Load and Plaques in cortex and hippocampus ↓ phosphorylated tau ↓ Neuroinflammation: ↓ C3AR1 and p-STAT3

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Abbreviations: MDA: Malondialdehyde; LDH: Lactate dehydrogenase; iNOS: Inducible nitric oxide synthase; AChE: Acetylcholinesterase; Aβ: Amyloid -β; APP: Amyloid precursor protein; P-gp: P-glycoprotein; LRP1: Low-density lipoprotein receptor-related protein 1; sAPPα: Soluble amyloid precursor protein-α; GFAP: Glial fibrillary acidic protein; Iba1: Ionized calcium-binding adapter molecule 1; IL-1β: Interleukin-1 β; RAGE: Receptor for advanced glycation end products; HMGB1: High mobility group box 1; NLRP3: NLR family pyrin domain containing 3; p-IKKβ: Phosphorylated inhibitor of nuclear factor kappa-B kinase subunit-β; p-IκBα: Phosphorylated nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor α; IκBα: Nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-α; BBB: Blood-brain barrier; SNAP-25: Synaptosomal-associated protein 25; PSD: Postsynaptic density; Erβ: Estrogen receptor β; SOD-3: Superoxide dismutase 3: Green fluorescent protein; HSP: Heat shock protein; GST-4: Glutathione S-transferase 4: Green fluorescent protein; STP: short-term potentiation; LTP: Long-term potentiation; CA1: Cornu ammonis 1; GSK3-β: Glycogen synthase kinase 3-β; BACE1: β-site amyloid precursor protein cleaving enzyme 1; MMP9: Matrix metallopeptidase 9; FEPPA: N-[2-(2-fluoroethoxy)benzyl]-N-(4-phenoxyphenyl)acetamide; TRPA1: Transient receptor potential ankyrin 1; AMPK: AMP-activated protein kinase; ULK1: Unc-51 like autophagy activating kinase 1; ATG7: Autophagy related 7; ATG3: Autophagy related 3; LC3: Microtubule-associated protein 1A/1B-light chain 3; AAPH: 2,2'-azobis(2-amidinopropane) dihydrochloride; DAF-16: Forkhead box O transcription factor: Green fluorescent protein; SKN1: SKN-1 transcription factor: Green fluorescent protein; HSP-16: Heat shock protein 16: Green fluorescent protein.

pounds like those derived from olives in the context of neurodegenerative diseases.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors contributions

Conceptualization: Abdulloh Machin, Yudha Haryono, and Alexander Tikara Sugondo; Writing the original draft: Qorina Nadya Salfi and Vania Ayu Puspamaniar; Visualization: Maura Tuzzahrah Ramadhani, Data collection: Alexander Tikara Sugondo, Qorina Nadya Salfi, Maura Tuzzahrah Ramadhani, and Vania Ayu Puspamaniar; Resources: Abdulloh Machin and Yudha Haryono; Formal analysis: Alexander Tikara Sugondo and Qorina Nadya Salfi; Methodology: Abdulloh Machin, Alexander Tikara Sugondo, and Vania Ayu Puspamaniar; Validation: Abdulloh Machin and Yudha Haryono; Investigation: Qorina Nadya Salfi, Maura Tuzzahrah Ramadhani, and Vania Ayu Puspamaniar; Review and editing: Alexander Tikara Sugondo and Qorina Nadya Salfi; Supervision: Abdulloh Machin and Yudha Haryono; Funding administration: Abdulloh Machin; Final approval: All authors.

Conflict of interest

The authors declared no conflict of interest.

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