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Effects of Ferulic Acid on Cognitive Function: A Systematic Review

*Yesim Karademir, Alan Mackie, Kieran Tuohy, and Louise Dye**

Scope: Plant (poly) phenolic compounds have been reported to decrease the risk of developing dementia and have been associated with maintenance of cognitive performance in normal ageing. Ferulic acid (FA) is a phenolic acid, present in a wide variety of foods including cereals, fruits, vegetables, and coffee. The aim of this systematic review is to examine the effect of FA on cognitive function in humans and animals.

Methods and results: The search terms "Ferulic acid AND cognit*" and "Ferulic acid OR feruloyl OR ferula AND (memory OR attention OR learning OR recognition)" are used in Web of Science, Scopus, PubMED, OVID (Medline/PsycInfo), and CINAHL through October 2023. No human studies are identified that matched the inclusion criteria. Twenty-six animal studies are identified. A small number ($n = 5$) of these studies examined FA in healthy animals whilst the remainder examined animal models of dementia. Alzheimer's disease ($n = 11$) is the most prevalent model.

Conclusion: Overall, results from studies employing disease models suggest that FA ameliorates induced cognitive decline in a time and dose-dependent manner. Similarly, studies in healthy animals show a beneficial effect of FA. However, further studies are required to determine the effects of FA on human cognitive function.

1. Introduction

The dietary habits of modern society such as increased consumption of fat and sugar, coupled with a reduced intake of fiber, polyphenols and whole plant foods are associated with cognitive decline including mild cognitive impairment and some forms of dementia.[1–3] Phenolic compounds have been reported to decrease the risk of developing dementia[4,5] and shown to be associated with better cognitive performance or maintenance of cognitive function in normal ageing.[6,7] Among the phenolics, ferulic acid, chlorogenic acid, caffeic acid, curcumin, catechin, quercetin, myricetin, taxifolin, and resveratrol in particular have been reported to play a role in improved cognitive performance in different experimental models of neurological diseases.[8–16] The neuroprotective effects of some polyphenols have been attributed to their ability to cross the blood-brain barrier and accumulate in the brain following long term intervention.[17] Some polyphenols have been shown to affect neuronal signaling pathways, protect neurons against oxidative or inflammatory stress, and lead to changes in peripheral and cerebrovascular responses, such as improved blood pressure and cerebral blood flow.[18–20]

FA (4-hydroxy-3-methoxycinnamic acid) is commonly present in the trans form in a wide variety of foods from cereals (e.g., wheat and brown rice) to fruits, vegetables and coffee. Despite the high FA content of cereals, only 0.1%–0.5% of this content is free FA, the remaining fraction is covalently bound to cell wall polysaccharides and thus cannot be released from the food matrix during digestion in the upper gastrointestinal tract.[21] However, a range of processing methods (particle size reduction, microfluidization, fermentation, and enzyme applications) can improve bioavailability and subsequent health effects of bioactive components.[22–26] FA is an antioxidant to which some therapeutic properties such as anti-inflammatory, antiaging, anticancer, antidiabetic, antihypertensive, and neuroprotective effects have been ascribed.[18,27–37] Long-term consumption of FA in animals has been reported to be neuroprotective in relation to Alzheimer's disease and other cognitive deficits.[18,38–41] Free FA is highly bioavailable as a result of its low molecular weight (194.18 g mol^{-1}), rapid absorption to plasma[42,43] and longer persistence in circulation compared with other similar bioactive compounds. However, the bioavailability of FA is limited by its chemical form, which is related to whether it is free or covalently bound to lignins or other biopolymers in plant fibers. The high abundance of FA in cereals and its potential for increased bioavailability using different processing methods, highlights the importance of investigating its cognitive effects. Therefore, this

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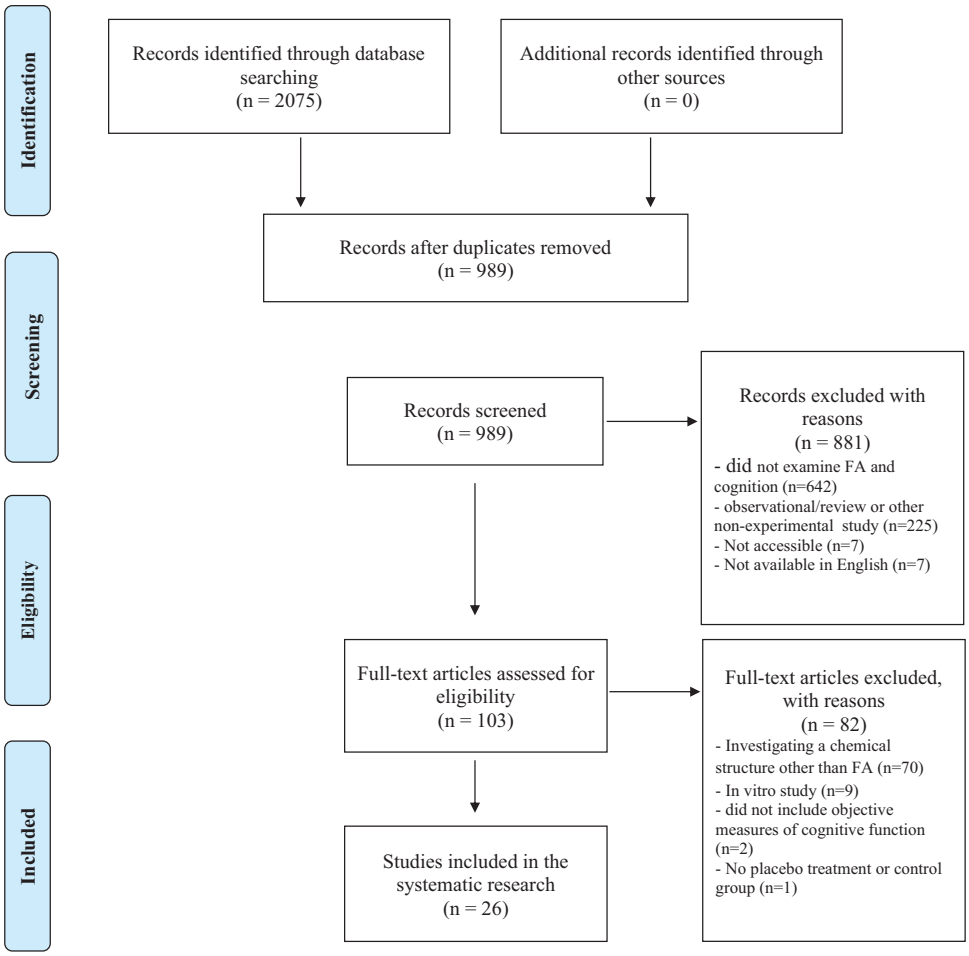

Figure 1. PRISMA flow diagram of the study selection process.

systematic review aimed to examine the effect of FA administration on objectively measured cognitive function in human and animal studies.

2. Methods

An electronic search of articles published up to October 2023 was conducted using the Web of Science (1900–2023), Scopus (1960–2023), PubMED (1966–2023), OVID (Medline [1946–2023]/PsycInfo [1806–2023]), and CINAHL (1937–2023) databases. Search terms were "Ferulic acid OR feruloyl OR ferula AND cognit*" and "Ferulic acid AND (memory OR attention OR learning OR recognition)." A total of 2075 results were returned from the initial searches. The PRISMA flow diagram (**Figure 1**) shows the study selection methodology. After removal of duplicates, 989 articles were retrieved and subjected to further screening using the inclusion criteria. Studies were excluded if the article: did not examine FA and objectively measured cognitive function ($n = 642$); was a review, book chapter, or meeting abstract ($n = 225$); did not include pure FA (e.g., administered herbal extracts) or included an FA derivative with a complex chemical structure not similar to FA (e.g., pharmaceutical preparations) ($n = 70$); was in vitro ($n = 9$); was not accessible ($n = 7$); was not in English ($n = 7$); did not include objective measures of cognitive function ($n = 2$); did not have a placebo or control group ($n = 1$). Finally, 26 articles were selected and included in the review.

3. Results

The results are summarized in **Tables 1** and **2**. Of the 26 articles extracted, there were no studies in humans which met the inclusion criteria. Only five studies investigated healthy animals. Twenty-two studies examined FA in animal models of neurodegenerative disease, with Alzheimer's disease ($n = 11$) being the most commonly employed, followed by ischemia ($n = 3$), epilepsy ($n = 2$), diabetes ($n = 1$), sclerosis ($n = 1$), and aging ($n = 1$). Three animal studies induced impairment using scopolamine ($n = 1$), lipopolysaccharide ($n = 1$), or lead acetate ($n = 1$). The applied dose of FA across all these studies ranged between 0.3 and 2000 mg kg^{-1} with duration from single dose to daily doses over 6 months. The most frequently administered tests used to measure cognitive function were novel object recognition test, passive avoidance test, Morris water maze (MWM) and Y-maze test. MWM and Y-maze tests are used to measure exploratory activity and spatial working memory to assess spatially related forms of learning and memory while episodic memory is assessed by

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Table 1. The effect of ferulic acid (FA) on cognitive function in healthy animals.

Reference	Animal (species, *n*)	Experimental design	Cognitive test (outcome measures)	Results	Key findings
Michels et al. (2010)	– Flies – 4 groups (n = 16, 17, 18, 19 per different groups)	– FA eicosyl ester (FAE-20) – 0.071, 0.71, 7.1 μM – Control	– Odor-learning task with subsequent preference for learned odors – T maze task where the flies chose between previously rewarded and unrewarded odors	– Higher memory scores in larval Drosophila in dose dependent manner compared to control – Partial attenuation of age-related memory decline in adult flies and memory function loss in young flies	– FAE-20 partially compensated for age-related memory decline in adult flies and genetically induced early onset loss of memory function in young flies
Georgieva et al. (2015)	– Rats – 8 groups (n = 10 per group)	– FA – 20 mg kg^{-1} for 7, 14, 21, and 30 days (4 treatment groups) – 4 Control groups (Saline) for each treatment duration – Retention tests were performed 3 and 24 h after the acquisition trial	– Passive avoidance test (one-way, step through, latency time, s; learning criterion, a latency of at least 180 s) – Active avoidance test (two way shuttle box, Number of avoidances)	– 7 and 14 day administration of FA showed no significant effect on either passive or active avoidance tests – FA for 21 or 30 days resulted in longer latency time in retention tests (learning) and increased number of avoidances (memory) compared to control group	– FA improved learning and memory function in healthy rats
Mhillaj et al. (2018)	– Rats – 2 groups (n = 7 for control, n = 8 for treatments)	– FA – 150 mg kg^{-1} for 7 days – Control (vehicle: 0.9% NaCl/NaOH 0.5 M)	– Novel object recognition (Exploration time, s, total exploratory activity, discrimination index)	– Better long-term retention memory in unhabituated rats – No significant effect on exploration time and total exploratory activity in habituated rats, – increased discrimination index and decreased exploration time of familiar objects compared to control in unhabituated rats	– FA treatment in unhabituated rats induced significant improvement of long-term retention memory as indicated by novel object recognition test but there were no effects on habituated rats
Michels et al. (2010)	– Mice – (n = 11 to 18 per condition)	– FA eicosyl ester (FAE-20) – 6, 12 mg kg^{-1} – Control (vehicle: 80% ethanol)	– Contextual fear conditioning tests	– Improved memory scores in old (>2-years-old) mice	– FAE-20 showed memory enhancement probably because long chain esterification might increase the bioavailability or membrane accumulation of FA
Xia et al. (2019)	– Mice (n = 12 per group) for SmartCube, forced swim and open field tests – Rats (n = 15 per group) for Novel object recognition test	– FA – 0, 0.3, 1, 3, 10, 30 mg kg^{-1} for 7 days (Smart cube test) – FA – 0.3, 3 mg kg^{-1} and saline control for 8 days (forced swim and open field tests) – FA – 0.3, 3 mg kg^{-1}, saline control and Galantamine as a positive control for 7 days (Novel object recognition test) at a dose volume of 10 mL kg^{-1} body weight for all tests	– SmartCube test (multiple behavioral measures) – Forced swim (measures stress coping ability) and open field test (Distance traveled, cm; Rearing frequency, count) – Novel object recognition test (RI: Recognition Index, %; Exploration time, s)	– FA showed behaviors indicative of cognitive enhancement resembling acetylcholinesterase inhibition on the Smartcube test – FA reduced immobility time at 0.3 mg kg^{-1} with no effect over the whole test period FA had no effect on the open field test – Enhanced RI at 0.3 mg kg^{-1} for the first 1 min but had no effect when the first 3 and entire 5 min of the test was analyzed – No effect of FA at any dose on total exploration time – Significant memory improvement at 3 mg kg^{-1} for the first 3 min analysis of RI	– FA showed nootropic effects which authors suggest FA augments cholinergic activity and so enhances cognitive effects – No effect of FA on forced swim or open field which are stress measures rather than learning or memory outcomes. – Better performance (RI) in Novel object recognition test followed FA administration with higher dose producing better and more enduring effects

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Table 2. The effect of ferulic acid (FA) on cognitive function in disease models.

Reference	Impairment agent/disease model	Animal (species, *n*)	Experimental design	Cognitive test (outcome measures)	Results	Key findings
Alzheimer's Disease						
Jung et al. (2016)	– Aß1-42 induced memory damage and APP/PS1 mutant transgenic mice/Alzheimer model	– Mice – 4 groups ($n = 7$ per group)	– Dimeric derivative of FA (KMS4001) Control (Water) – Aß1-42 and APP/PS1 mice treated with 2 doses of FA – 3 and 30 mg kg^{-1} per day for 5 days	– Passive avoidance test and Y Maze test, 1.5 and 3 months in Novel object recognition test – Passive Avoidance test (Step through latency) – Y Maze test (alteration behavior, %) – Novel object recognition test (exploratory preference, %)	– 30 mg kg^{-1} of KMS4001 enhanced Aß1-42 induced memory damage in both passive avoidance and Y maze test No effect of 10 mg kg^{-1} dose – Better memory in Novel object recognition test with the maximum effect at 3 mg kg^{-1} per day, same effect observed for 30 mg kg^{-1} per day on 45th day in APP/PS1 Tg mice	– KMS4001 (30 mg kg^{-1}) counteracted Aß1-42 induced memory damage – 3 mg kg^{-1} per day for 1.5 and 3 months KMS4001 treatment had considerable effect in APP/PS1 Tg mice FA (16 mg kg^{-1} per day) for 6 months – improved novel object recognition
Mori et al. (2013)	– Transgenic mice (PSAPP)/Alzheimer model	– Mice – 4 groups ($n = 12$ per group)	– FA – 30 mg kg^{-1} per day for 6 months – Control: PSAPP-V, PSAPP mice treated with vehicle	– Novel object recognition test (Recognition index, %) – Y-maze test (Number of arms entered, Alternation, %) – Morris water maze test (Escape latency, s-Time spent in the quadrant, s)	– Compared to control (PSAPP-V), PSAPP-FA treated mice had better novel object exploration frequencies, significantly higher alternation behaviors and shorter latencies with longer swimming time in goal quadrant	– FA attenuated novel object recognition deficit induced by PSAPP – 6 month FA intervention totally compensated the PSAPP associated spatial memory injury
Mori et al. (2017)	– Transgenic mice (PSAPP)/Alzheimer model or wild type	– Mice – 4 PSAPP transgenic mice + 4 Wild type mice (8 groups, $n = 8$ per group)	– FA (30 mg kg^{-1} per day for 3 months) – Octyl gallate, OG (30 mg kg^{-1} per day for 3 months) – Combined (OG+FA) (30 mg kg^{-1} for both per day for 3 months) – Control: PSAPP-V, PSAPP mice treated with V (vehicle)	– Novel object recognition test (Recognition index, %) – Y-maze test (number of arms entered, alternation, %) – Radial arm water maze test (errors, escape latency, s)	– Higher novel object exploration frequency after treatment with OG+FA or OG or FA alone compared to control (PSAPP-V) – FA + OG significantly enhanced alternation behavior compared to OG or FA alone making the PSAPP mice indistinguishable from the healthy WT – Less errors and shorter latencies in FA, OG and OG+FA treatments compared to control group	– Combined treatment of FA and OG for 3 months completely reversed episodic memory injury and attenuated cognitive impairments associated with PSAPP trans gene, particularly episodic and spatial working memory were most ameliorated by combination therapy There were no effects of FA on WT

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Table 2. (Continued)

Reference	Impairment agent/disease model	Animal (species, *n*)	Experimental design	Cognitive test (outcome measures)	Results	Key findings
Mori et al. (2019)	– Transgenic mice (APP/PS1)/Alzheimer model	– Mice – 8 groups ($n = 8$ per group) 4 (APP/PS1) transgenic mice + 4 Wild type mice	– FA (30 mg kg^{-1} per day for 3 months) – Epigallocatechin-3-gallate EGCG (30 mg kg^{-1} per day for 3 months) – Control (APP/PS1V) (Vehicle: 0.2% dimethyl sulfoxide in distilled water)	– Novel object recognition test (Recognition index, %) – Y-maze test (Number of arms entered, Alternation, %) – Radial arm water maze test (Errors, Escape latency, s)	– Improved novel object exploration frequency by 60.8–71.6% compared to control (50%) after combined or single treatments of FA or EGCG – Less errors and shorter latencies in both single and combined treatments compared to control group No effects of FA alone or in combination on WT	– Mitigating effect of combined treatment of FA and EGCG on episodic memory damage – Restored spatial working memory by greater alternation in Y-maze test – EGCG and/or FA completely reversed spatial reference learning and induced memory impairment
Okuda et al. (2019)	APPswe/PS1dE9 Transgenic Mice/Alzheimer Model	– Mice – 6 groups ($n = 5$, 6, 7, and 12 per group)	– Control (MF basal diet alone) ($n = 6$); – FA, 0.2%, ($n = 5$); – PS, 0.2%, ($n = 5$); – Cur, 0.2%, ($n = 12$); – FA(0.05%) + PS (0.05%), ($n = 6$); – FA(0.05%) + PS (0.05%)+Cur (0.01%), ($n = 7$); – 0, 4, 8, and 12 weeks	– Y-Maze test (spontaneous alternation, %) (total arm entry, times)	– Decreased spontaneous alternation frequency by 3 months intervention in control group while no such decrease was observed in double and triple groups – Significant difference between control and triple group in alternation frequency after 3 months – When FA was administered alone for 3 months, spontaneous alternation frequency declined from 61.0% ± 4.4% to 46.5% ± 7.9% (poorer performance)	– FA + PS + Cur significantly ameliorated cognitive impairment while FA treatment alone did not

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Table 2. (Continued)

Reference	Impairment agent/disease model	Animal (species, *n*)	Experimental design	Cognitive test (outcome measures)	Results	Key findings
Yan et al. (2001)	– Aβ1-42/Alzheimer model	– Mice – 9 groups (n = 10 per group)	– FA – 0%, 0.002%, 0.004%, 0.006% FA in drinking water – 14–19 mg kg^{-1} per day – 1, 2, 3, 4 weeks – Control	– Passive avoidance test (step through latency, s) – Y maze test (alternation behavior, %, number of arm entries) – Morris water maze test (escape latency, s, percentage time in platform quadrant)	– With Aβ1-42, 35% decrease in step-through latency (passive avoidance test), 19% less alternation behavior (Y-maze test) and 32% shorter percentage time in platform quadrant (water maze test) were observed – FA pretreatment resulted in 9% decline in step-through latency, no change in alternation behavior, 14% less percentage time in platform quadrant	– Improved performance in passive avoidance test in a dose dependent manner with maximum effect at 0.006% FA dose against Aβ1-42 related deficits – Protective effect of 4 weeks FA pretreatment on Aβ1-42 associated cognitive deficits – No significant change in number of arm entries between different groups indicating no effect of Aβ1-42 on locomotor activity –No statistically significant change by post treatment with FA in Aβ1-42 induced performance decline in passive avoidance test – Long-term intervention of FA has protective effect against Aβ1-42 toxicity, learning, and memory impairment
Yan et al. (2013)	– Presenilin-1 Transgenic Mouse, APP/PS1 (Amyloid precursor protein-presenilin 1)/Alzheimer model	– Mice – 4 groups (n = 5 per group)	– FA – 5.3 and 16 mg kg^{-1} per day for 6 months – Controls (non-Tg, APP/PS1 Tg)	–Y maze test (alternation behavior, %) – Novel object recognition test (exploratory preference, %)	– No significant difference in spontaneous alternation behavior in Y-maze test – Improved performance in novel object recognition test by 5.3 mg kg^{-1} per day FA for 6 months – No effect at a dose of 16 mg kg^{-1} per day of FA	– Ameliorating effect of FA was only observable at 5.3 mg kg^{-1} d^{-1} for 6 months

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Table 2. (Continued)

Reference	Impairment agent/disease model	Animal (species, *n*)	Experimental design	Cognitive test (outcome measures)	Results	Key findings
Kim et al. (2007)	– Trimethyltin (TMT)/Alzheimer model	– Mice – 5 groups ($n = 8$ per group)	– FA – 0.002%, 0.005% w/v in water for up to 28 days before TMT administration – Normal control (vehicle: saline), TMT treated control	– Passive avoidance test (Step through latencies) – Y maze test (Alternative behavior, %- Number of arm entries, times)	– No significant difference in number of arm entries in Y-maze test in FA treated groups – 0.002% and 0.005% of FA resulted in 14% and 28% decline, respectively in TMT induced reducing alternation behavior compared to TMT control – Shortened step-through latency by nearly 33% and 43% with 0.002% and 0.005% w/v FA, respectively. while TMT control had 52% decrease compared to normal control group	– 28 days of FA pretreatment prohibited TMT induced injury in passive avoidance and ameliorated memory impairment – TMT has no effect on general locomotor activity of the mice
Mamiya et al. (2008)	– DL-Buthionine-(S,R)-sulfoximine (BSO)/Alzheimer model	– Mice – 6 groups ($n = 10$ per treatment, $n = 15$ per control group)	– FA (0.5, 1, 5 mg kg^{-1} for 6 days) – Vitamin E (300 mg kg^{-1}) – Control SAL (vehicle: 0.9% saline), control BSO	– Novel object recognition test (exploratory preference, %) – Y maze test (alternation behavior, %-number of arm entries)	– Improved memory after FA pretreatment (5 mg kg^{-1} per day for 6 days), – Improvement in decreased exploratory preference induced by BSO in dose dependent manner in novel object recognition test – Reduced impairments of spontaneous alternation behavior with 5 mg kg^{-1} of FA – No significant difference in the number of arm entries between 6 groups	– Ameliorating effect of FA pretreatment (5 mg kg^{-1} for 6 days) on memory impairment induced by BSO
Zafeer et al. (2019)	– Streptozocin (STZ)/Alzheimer Model	– Mice – 4 groups ($n = 6$ per group)	– FA – 100 mg kg^{-1} for 14 days – Sham + FA – Lesion + FA – Controls (sham: saline with corn oil, lesion: ICV-STZ, 3 mg kg^{-1})	– Morris water maze test (escape latency, s; time spent in the target quadrant, s)	– Decreased escape latency – Increased time spent in the target quadrant along the probe trial test	– Better retention and recall of memory after FA treatment

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Table 2. (Continued)

Reference	Impairment agent/disease model	Animal (species, *n*)	Experimental design	Cognitive test (outcome measures)	Results	Key findings
Wang et al. (2021)	– APP/PS1 transgenic mice/Alzheimer model	– Mice – 4 groups (n = 12, 13 per groups)	– WT (Age-matched negative littermates – AD (Alzheimer's disease) – AD + FA (Alzheimer's disease + FA) – 20 mg kg^{-1} day^{-1}, 30 days – Vehicle Control (Drinking water)	– Morris water maze test (latency to platform, s; time spent in the target quadrant, s; Velocity, cm s^{-1})	– Shorter latency time in the AD mice with the 30-day FA treatment (7 months old) compared to the vehicle group – Spatial memory, as indicated by the time spent in the target quadrant (s) increased by the FA treatment (FA-AD) compared to the AD	– 30 days FA treatment ameliorated spatial memory deficit completely – FA only partially affected Aβ plaque deposition and aggregative microglial cells
Ischemia						
Chen et al. (2010)	Ischemia	– Mice – 5 groups (n = 6 per group)	– Sodium ferulate (100 mg kg^{-1}; 400 mg kg^{-1} per day for 4 days), Borneol (10 mg kg^{-1}) – Control, sham-treated (10% ethanol), I/R treated	– Morris water maze test (escape latency, s)	– No significant effect of sodium ferulate (100 mg kg^{-1}) on memory damage – Combination of sodium ferulate (400 mg kg^{-1}) with borneol (10 mg kg^{-1}) resulted in significantly shorter escape latency compared to I/R group	– Combined treatment of sodium ferulate and borneol showed counteracting effect against brain injury induced by ischemia
Ren et al. (2017)	– Ischemia/reperfusion	– Mice – 5 groups (n = 10 per group)	– FA – 28, 56, and 112 mg kg^{-1} after ischemia for 5 days – Control (sham-operated group (saline), untreated ischemia group)	– Morris water maze test (escape latency, s) – Passive avoidance test (escape latency, s)	– Lower escape latency times after FA treatment in a dose dependent manner in Morris water maze test compared with ischemia group – Higher escape latency times by FA treatment in a dose dependent manner in passive avoidance test compared with Ischemia group	– Ameliorated spatial cognitive and memory dysfunction associated with I/R
Zhang et al. (2017)	Ischemia/middle cerebral artery occlusion (MCAO)	– Mice – 4 groups (n = 10–13 per group)	– FA, 100 mg kg^{-1} for 5 and 28 days (before ischemia) – Danshen-Chuanxiong Honghua (DCH); 5, 10, and 20 g kg^{-1} for 5 and 28 days – Control (sham and vehicle: saline)	– Morris water maze test (escape latency, s)	– No statistically significant (p > 0.05) difference in escape latencies	– Enhanced spatial learning with DCH pretreatment for 5 days

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Table 2. (Continued)

Reference	Impairment agent/disease model	Animal (species, *n*)	Experimental design	Cognitive test (outcome measures)	Results	Key findings
Epilepsy						
Hassanzadeh et al. (2017)	Pentylenetetrazole (PTZ)/epilepsy	– Rats – 7 groups ($n = 15$ per treatment; $n = 8$ per control)	– FA – 25, 50, 75, and 100 mg kg^{-1} in 0.5% dimethyl sulfoxide – Control (Vehicle: 0.9% Saline) and PTZ group	– Elevated plus maze test (Initial transfer latency, Retention transfer latency) – Passive avoidance test (initial transfer latency, retention transfer latency)	– FA treatment (75 and 100 mg kg^{-1}) attenuated increased retention transfer latency induced by PTZ compared to PTZ group in elevated plus-maze test – Pretreatment of FA (75 and 100 mg kg^{-1}) prohibited shortening of retention latency in passive avoidance test	– FA exhibited protective role on kindling induced cognitive damage
Zhang et al. (2019)	Pentylenetetrazol (PTZ)/epilepsy	– Rats – 3 groups ($n = 12$ per group)	– FA – 60 mg kg^{-1} for 28 days – Control (saline) – PTZ group treated with pentylenetetrazol only	– Morris water maze test (escape latency, s)	– Shorter escape latency in PTZ + FA group at days of 2, 3 and 4 compared to PTZ group only – Higher numbers of platform crossings in PTZ + FA pretreatment than that of PTZ group	– Improved spatial cognition and memory in rats with PTZ-associated seizures
DRUG/diet induced impairment						
Wang et al. (2017)	– High-glucose-fat (HGF) diet, low dose of streptozotocin (STZ)/diabetes model	– Rats – 5 groups ($n = 8$ per group)	– FA (15, 30 mg kg^{-1} for 4 weeks) + DM (diabetic group) – Rosiglitazone (4 mg kg^{-1} for 4 weeks) + DM – Control (vehicle: distilled water), DM	– Morris water maze test (escape latency, s)	– No statistical difference between treatment groups within the first 3 days – On 4th and 5th days, shorter escape latency and longer stay in the target quadrant (probe trial test) in FA and rosiglitazone treated groups compared to the untreated diabetes model group	– Ameliorating effect of FA and rosiglitazone on learning and memory impairment associated with diabetes – FA reversed diabetes related inflammatory response in the brain
Antony et al. (2004)	Syncytin/multiple sclerosis model	– Mice – 4 Groups ($n = 6$ per group)	– FA – 20 mg kg^{-1} per day for 14 days – Syncytin + FA – Control: mock ($n = 6$, mock implanted, conditioned medium from mock-infected cultures as a control for virus implanted cells) syncytin (SINrep5-Syncytin), EGFP (SINrep5-enhanced green fluorescent protein)	– Static rod test (a test of coordination) – Horizontal bar test (a test of coordination and forelimb strength) – Modified screen test (as a measure of curiosity and seeking behavior) – Beam test (motor activity and exploratory behavior)	– No difference between any??? groups at days of 3 and 7 – Intervention of FA in addition to SINrep5-syncytin for 14 days revealed improved performance on the horizontal bar test (longer time to hold horizontal rod), modified screen test (shorter time to reach the screen edge), beam test (shorter time to cross a beam)	– Improved coordination skills (horizontal bar test) – Ameliorated curiosity and seeking behavior (modified screen test) – Enhanced motor activity and exploratory behavior (beam test)

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Table 2. (Continued)

Reference	Impairment agent/disease model	Animal (species, *n*)	Experimental design	Cognitive test (outcome measures)	Results	Key findings
Yang et al. (2016)	D-Galactose/aging	– Mice – 5 groups ($n = 12$ per group)	– FA – 50 and 100 mg kg^{-1} for 8 weeks – D-gal + DON (donepezil hydrochloride); D-gal + 50 mg kg^{-1}; D-gal + 100 mg kg^{-1} – Control (0.9% saline); D-gal group	– Morris water maze test (escape latency, s)	– Shorter escape latency and higher number of crossings over the platform (in probe test) in FA treatment group compared to D-gal group	– Protective role of FA on brain was reported against oxidative stress, neuroinflammation, neurodegeneration, AChE (acetylcholinesterase) activity and associated memory damage via aging process
Boultadakis et al. (2010)	Scopolamine (delay dependent recognition memory impairments)	– Rats – Experiment 1, 6 groups ($n = 10$ per group) – Experiment 2, 4 groups ($n = 10$ per group) – Experiment 3, 6 groups ($n = 10$ per group)	– Experiment 1 nitric oxide releasing derivative of FA (NCX 2057) (1, 3, 10, and 30 mg kg^{-1}); molsidomine (4 mg kg^{-1}), vehicle as control – Experiment 2 FA (1.9, 6.2, and 18.7 mg kg^{-1}) + molsidomine (4 mg kg^{-1}), vehicle as control – Experiment 3 (NCX 2057) (3, 10 mg kg^{-1}) + scopolamine (0.2 mg kg^{-1}), vehicle as control – Control (saline or vehicle, dimethyl sulfoxide 8%, castor oil 16% and serum-free culture media 76%) used instead of both FA, NCX 2057 or molsidomine and scopolamine in all experiments	– Object recognition test (times spent by rats in exploring each object (N: new or F: familiar), T1, ITI: 24 h, T2, D)	– No difference in T2 for different groups in Experiment 1 and Experiment 2 – FA treatment in Experiment 2 resulted no difference in discrimination of N and F – Nonsignificant three way interactions between scopolamine x NCX 2057 x trials in motor activity and total exploration times in Experiment 3 – Significantly enhanced ($p < 0.05$) N than F in all NCX 2057 + scopolamine treated groups compared to scopolamine + vehicle treated group in Experiment 3 – NCX 2057 (10 mg kg^{-1}) administered rats showed the ability to discriminate N and F	– No effect of FA in motor activity and total exploration levels in delay dependent cognitive impairments – Attenuated effect of NCX 2057 at 3 and 10 mg kg^{-1} compared to scopolamine induced recognition or memory impairments – No relation between motility and exploratory behaviors, T1 and T2 and cognition in NCX 2057 + scopolamine treatments

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Table 2. (Continued)

Reference	Impairment agent/disease model	Animal (species, *n*)	Experimental design	Cognitive test (outcome measures)	Results	Key findings
Rehman et al. (2019)	Lipopolysacchari-de (LPS)	– Mice – 4 groups ($n = 15$ per group)	– FA – 20 mg kg^{-1} for 4 days (prior LPS) + 7 days (after LPS) – LPS (0.33 mg kg^{-1}) +FA (20 mg kg^{-1}) – FA (20 mg kg^{-1}) alone – Control (vehicle: saline), mice treated with LPS	– Morris water maze test (escape latency, s)	– Enhanced spatial learning impairment with shorter escape latency in LPS + FA compared to FA alone – FA treatment resulted in better spatial learning and memory with higher number of crossings and time spent in the target quadrants in probe trial	– FA treatment improved memory performance in LPS treated mice – FA attenuated the inflammation derived neuronal degeneration and memory injury in brains of LPS-treated mouse
Yu et al. (2021)	Lead acetate (PbAc) (prenatal administration)	– Mice – 4 groups ($n = 10$ per group)	– Control – FA (50 mg kg^{-1} for 31 days) – Pb (250 ppm) – Pb + FA	– Morris water maze Test Escape latency, s; virtual platform crossing times, s; swim speed, s	– FA treatment significantly decreased the escape latency of the PbAc-treated mice in days of 3–5 – No significant effects of FA on the escape latency in normal mice – The virtual-platform crossing times of the PbAc/FA-treated mice were significantly increased compared to the PbAc-exposed mice – Virtual-platform crossing times remained unchanged in the FA treated normal mice – No significant differences in the swimming speeds of the mice between the four groups	– FA protects against Pb-induced offspring's cognitive deficits no significant effect was observed in the normal mice

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novel object recognition test. Passive avoidance tests are measure of emotional memory based on the contextual fear conditioning.

3.1. Healthy Animals

Healthy rodents were used in four studies[18,44–46] whilst one study investigated effect of FA in mice and drosophila.[47] This study reported improved memory scores in larval drosophila and aged mice following FA eicosyl ester (6, 12 mg kg^{-1}) treatment, demonstrating the effect of FA on cognitive function in different species. Georgieva et al. reported higher scores on passive and active avoidance tests after 21 and 30 day administration of FA (20 mg kg^{-1}) with no effect on day 7 or 14.[18] Mhillaj et al. reported that 7 days of FA (150 mg kg^{-1}) treatment resulted in significant improvement of long-term memory in nonhabituated rats with no effect in habituated rats.[44] Better performance on the novel object recognition test was also reported after 7 days of FA (3 mg kg^{-1}) in another study.[45] However, Yu et al. found no significant effect of FA (50 mg kg^{-1}) treatment for 31 days in healthy mice.[46] Taken together, this small number of rodent studies suggest enhanced memory or learning skills after longer term FA treatments.

3.2. Disease Models

Alzheimer disease models were employed in 11 studies mainly using transgenic mice. Jung et al. investigated the dimeric derivative of FA in Aß1-42 and APP/PS1 transgenic mice and reported enhanced memory scores in both passive avoidance and Y maze tests after an acute dose of 30 mg kg^{-1} while 10 mg kg^{-1} had no significant effect. Interestingly, 3 mg kg^{-1} was found to be effective after 1.5 and 3 months of treatment.[48] Mori et al. showed total compensation of spatial memory injury in PSAPP-transgenic mice after 30 mg kg^{-1} of FA intervention for 6 months.[49] Similarly, positive effects of FA in Alzheimer models were reported in 11 studies (Table 2). Furthermore, different synergistic effects of other bioactive compounds (borneol, octyl gallate, epigallocatechin-3-gallate, curcumin, phosphatidylserine) when administered in combination with FA were also reported in four studies.[8,50–52] On the other hand, several studies showed no significant effect on locomotor activity after FA treatment.[53–55] Overall results from these models revealed ameliorating role of FA on cognitive damage induced by Alzheimer disease in a time and dose-dependent manner (Table 2).

Contradictory results were reported from three studies investigating cerebral ischemia model.[19,36,50] According to Chen et al., combination treatment of sodium ferulate (400 mg kg^{-1}) with borneol (10 mg kg^{-1}) resulted in the amelioration of memory damage while the sodium ferulate (100 mg kg^{-1}) treatment alone was found not to have an effect.[50] Similarly, no significant difference in cognitive function was reported in a different study as a result of FA treatment (100 mg kg^{-1}) for 5 and 28 days.[19] However, Ren et al. found decreased cognitive dysfunction in a dose-dependent manner after 5 days of FA (28, 56, and 112 mg kg^{-1}) administrations.[56] In epilepsy model studies, FA (60, 75, and 100 mg kg^{-1}) was reported to improve induced cognitive impairments.[10,57]

Protective and attenuating effects of FA on cognitive impairments were also observed in studies employing other models (Multiple sclerosis; Neuronal degeneration and Memory Injury; Diabetes; Aging; Lead acetate).[34,46,58–61] In a study conducted by Boultadakis et al., no significant effect of FA treatment (1.9, 6.2, and 18.7 mg kg^{-1}) on the molsidomine induced cognitive deficits was reported.[62]

4. Discussion

The potential of FA to improve cognitive function is generally attributed to its antioxidant and antiinflammatory properties. However, phenolic compounds might also have vasodilatory effects through increasing cerebral/peripheral blood flow in addition to their protective and ameliorating role in the neurons and neuronal functions.[37,63] Neuroprotective effects can also be derived from interactions between phenolic compounds and specific proteins involved in intracellular signaling pathways (protein and lipid kinase signaling).[64–66] Reactive oxygen species (ROS) (superoxide anion [$^{\cdot}O_2^-$], hydroxyl radical [$^{\cdot}OH$], alkoxyl radical [RO·] and peroxyl radical [ROO·], hydrogen peroxide [H_2O_2], and singlet oxygen [$^1O_2$]) and reactive nitrogen species (RNS) (nitric oxide [NO·], nitric dioxide [NO_2·], and peroxynitrite [OONO–]) produced in the brain can lead to protein, DNA, RNA, lipid oxidation and conclude with neuronal dysfunction or death.[67,68] Accumulated damage originating from reactive species along with declining antioxidant functions upon aging is associated with Alzheimer's disease and other neurodegenerative disorders. FA has been shown to have scavenger activity against ROS and RNS and prevent oxidative modification of proteins.[69] Decreased choline acetyltransferase, β-secretase (declined Aβ aggregation), and NADPH oxidase activity reduced accumulation of glial fibrillary acidic protein and interleukin-1 beta in the hippocampus (reversed neuroinflammation) and increased activity of cytoprotective systems (ERK1/2, Akt) were also suggested as possible mechanisms of action of FA in Alzheimer's disease.[20,29,62,65,70]

Overall, the results of the studies conducted in the healthy animals suggest a role for FA in improving cognitive function. The therapeutic effect of any functional compound is dependent on intervention dose and duration. In this context, Georgieva et al. observed significant improving effects of FA (20 mg kg^{-1}) on cognition in passive and active avoidance tests when the intervention duration was raised from 7–14 to 21–30 days, respectively.[18] However, Xia et al. were able to show a positive effect of FA at both the lower dose (3 mg kg^{-1}) and short duration (7 days) in the novel object recognition test.[45] These differences in the results likely result from the different tests and doses of FA applied in these experiments. Given the very limited number of studies conducted in healthy animals, further evidence is required to establish any beneficial role for FA on cognition in healthy animals.

The effect of FA on cognitive function was studied in various models of neurological disease and neurodegeneration (n = 21), with Alzheimer's disease being the most commonly studied model (n = 11). Dose and duration of the FA intervention were also significant for these models. While 30 mg kg^{-1} of FA was shown to have a positive effect, 3 mg kg^{-1} was effective for only the longer dose durations (1.5 and 3 months).[48] It is also noteworthy that the combination of other bioactives (borneol, octyl gallate, epigallocatechin-3-gallate, curcumin,

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phosphatidylserine) with FA was also demonstrated to enhance ameliorating effect of FA in Alzheimer's models.[8,50–52] The finding that a lower dose of FA was effective over longer periods of time and the observed synergistic effect with other bioactives could be relevant to develop dietary approaches to reduce Alzheimer's disease risk. That some of these ingredients are antioxidants and some are not suggests that the mechanism of effect extends beyond an antioxidant effect and the effect of FA, alone and in combination with other bioactives, on cognitive function in ageing and neurodegenerative diseases in humans merits investigation.

No significant effect of FA on cognition was reported in the two of three ischemia and molsidomine model studies. On the contrary, the two epilepsy and all other chemical model studies demonstrated a positive role for FA on cognition. This lack of effect is surprising and may indicate that these models are not as effective at mimicking ROS damage if indeed ROS activity is mechanistically involved in the disease process.

In order to comprehensively evaluate the effect of FA on cognition, several factors should be considered simultaneously. The physiological importance of FA is determined by its pharmacokinetic properties (absorption, metabolism, distribution, elimination) and subsequent interaction with the target tissues.[67] Compared to other phenolic compounds due to its low molecular weight (194.18 g mol^{-1}), FA has high bioavailability and can be easily absorbed through stomach, jejunum and to a significantly lesser extent from ileum mucosal cells.[33] It is conjugated with glucuronide and/or sulfate in the hepatic portal vein. 56.1% of the perfused FA has been recovered from the plasma mesenteric vein as conjugated forms.[67] FA-glucuronide, FA-sulfate, and FA-sulfoglucuronide are the main conjugated metabolites of FA detected in the plasma and urine.[43] Free and conjugated FA enter the systemic circulation and are distributed in peripheral tissues and brain. Approximately, 4%, 10%, and 53% of the orally administered FA were estimated to be distributed in the gastric mucosa, blood and other tissues (including liver and kidney), respectively.[37,38] Moreover, FA has been shown to be able to cross blood–brain barrier which is important to exert neuroprotective effect.[31,71] 30 min after oral administration of 521 µmol kg^{-1} BW of FA, 2.6 µg g^{-1} tissue (approximately 13.39 nmol L^{-1}) was detected in the rat brain.[72,73] Plasma concentrations of FA was detected to reach maximum levels at 24 min after oral administration, with a half-life of 42 min.[21,71] The urinary excretion of FA was reported to reach maximum at 7–9 h after administration in humans.[74,75]

A low bioavailability (3%) of FA in humans has been observed after the consumption of cereal products, particularly the bran portion.[21,76,77] The absorption of FA in whole grains is limited because it is mainly esterified to arabinoxylans (5-*O*-feruloyl-L-arabinofuranose and 5-*O*-feruloyl-arabinoxylane) and other cell wall polysaccharides which are able to resist to digestion in the upper GI tract.[75] Therefore, the releasing degree of FA from the food matrix is one of the primary factors determining its absorption. In cases of being free or bound to simple sugars rather than complex carbohydrate polymers, higher absorption rates of FA can be observed.[21] In a human study, after administration of wheat bran cereals (22.5 µmol kg^{-1} BW FA), FA concentrations in the plasma were determined to reach 150–210 nM (mainly in the glucuronidated form) between 1 and 3 h postingestion, decreasing rapidly between 3 and 6 h and then more slowly up to 24 h. In a different study, plasma concentrations of FA were reported to increase from 2.2 mg L^{-1} (baseline) to 5.70 mg L^{-1} after whole grain breakfast cereal consumption.[78] Similar to absorption rate and plasma concentration, urinary excretion of FA is also affected by its chemical structure. After bran consumption, FA elimination rate was found to be 15-fold slower than after intake of the free form.[75,79,80]

The dose or dietary intake of FA is another important factor to consider to determine whether it is able to generate a biological effect. Estimated daily intake of FA was reported to range between 150 and 250 mg day^{-1} through consumption of cereals, vegetables, fruits, coffee, and juices. Whole grains may contribute to this extent up to 167 mg day^{-1}.[21] Daily intake of FA was reported to vary between 45 and 159.3 mg day^{-1} in another study.[81] Regarding these reports, estimated FA intake per kg body weight might be up to 2–3 mg kg^{-1} via whole grains. The concentration of FA can range between 25 and 3300 mg/100 g in grains while the range in the wheat bran can be 1351–1456 mg/100 g.[21] However, although whole grains are the major dietary source of FA, free FA accounts for only 1%–4% of total FA which is quite a lot below the dose generally used in vivo animal experiments. In this context, different processing methods might be a promising approach to increase bioaccessibility/bioavailability of FA and hence to observe potential cognitive enhancing effect.[82]

5. Conclusion

Although this review has identified a number of studies investigating effect of FA on cognition, most of them have focused on experimental models of cognitive deficits in animal models. Overall, depending on the dose and duration of the study, an ameliorating role of FA has been reported in those which employed disease models. However, only four articles were identified which reported a cognitive enhancement effect of FA in animals without any induced cognitive damage. Critically, no human studies were found. In the light of its marked neuroprotective effects in animals, there is a knowledge gap in the scientific literature related to the effect of dietary FA on cognitive function in healthy animals and more importantly, a complete lack of data on the cognitive effects of FA in humans. Regular consumption of FA via cereals, vegetables, fruits, coffee, and juices could potentially confer cognitive enhancing effects in humans. The evidence reviewed here suggests that there may be good reason to hypothesize particular benefits in people with age related cognitive impairment or early stage neurodegenerative disease. However, the bioaccessible FA content in the cereals, the major source of FA in human daily diet, will need to be substantially increased to confer any beneficial effect of cereals on cognitive function in the healthy individuals.

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Conflict of Interest

The authors declare no conflict of interest.

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Author Contributions

Y.K. was involved in design, search strategy development, database searching, study selection, data extraction, analysis and writing of the manuscript. L.D., A.M. and K.T. were involved in design, search strategy development, secondary study selection, quality appraisal and critical review of the manuscript.

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cognition, dementia, ferulic acid, in vivo, phenolics

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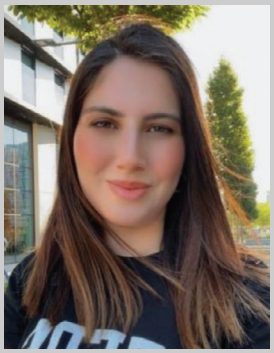

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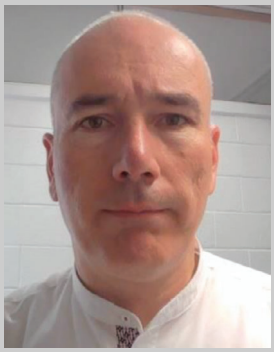

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