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Original Article

THE ROLE OF *CITRUS RETICULATE ETHANOLIC LEAF EXTRACT* IN RESTORING MEMORY IN MICE WITH HIGH-FAT DIET-INDUCED DEMENTIA

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ABSTRACT

Objective: To evaluate *Citrus reticulate* ethanolic leaf extract in restoring memory in mice with high-fat diet-induced dementia.

Methods: The experimental animals were divided into five groups, including the Naive Animal group, High Fat Diet (HFD) group, Piracetam+HFD group, HFD+Citrus reticulata, a low dose of 250 mg/kg was given orally, while a high dose of 500 mg/kg was administered via the same route. The factors used involve the Morris water maze (MWZ), elevated plus maze (EPZ), T maze delayed alteration task, and measurement of serum total cholesterol levels.

Results: This study examined the effects of Citrus reticulata ethanolic leaf extract on dementia. Two doses, a high dose (500 mg/kg; orally) and a low dose (250 mg/kg; orally), were chosen based on prior research, aiming to induce behavioral changes, particularly in learning and memory. The findings from the morris water maze, elevated plus maze, and t-maze tests suggest that the high dose (500 mg/kg; orally) of Citrus reticulata ethanolic leaf extract produced results comparable to the standard drug piracetam. However, the low dose (250 mg/kg; orally) did not exhibit any significant positive effects.

Conclusion: The study found that HFD impairs learning and memory, while Citrus reticulata extract treatment significantly improved cognitive functions in HFD-treated mice. The entire study suggests that Citrus reticulata leaves may have a memory-restorative role in HFD-induced dementia, and that Pregnane X receptors may be implicated.

Keywords: Dementia, Citrus reticulata, Morris water maze (MWZ) test, Elevated plus maze (EPZ) test, T maze delayed alteration task, High fat diet, Piracetam

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INTRODUCTION

A progressive cognitive decline that substantially hinders activities of daily living is the hallmark of dementia, a serious worldwide health concern. This disorder affects several cognitive abilities, such as recall, problem-solving, spatial awareness, understanding, mathematical skills, learning capacity, communication, and decision-making. It is commonly caused by various neurological conditions, including Alzheimer's disorder, blood vessel-related cognitive decline, Lewy body-related dementia, and frontal lobe degeneration [1].

Amyloid beta plaques and tau tangles interfere with neuron function and communication, resulting in cognitive deterioration and memory impairment [2]. The NF-kB family plays a significant part in controlling oxidative stress. *In vitro* experiments revealed that NF-kB caused increased oxidative stress in nerve cells subjected to amyloid beta (Aβ). Heightened oxidative pressure led to the build-up of lipid peroxides and nerve cell damage.

Furthermore, numerous investigations verify that Aβ peptides promote the production of the NF-κB gene quality and its development to the core. Acetylcholinesterase inhibitors (AChEI) and glutamate are two sorts of solutions utilized to protect patients' cognitive capacities [3]. There are various methods for managing the disease's symptoms, including using antioxidants and anti-inflammatory medications.

Heme, a large iron-containing molecule, has been linked to the development of Alzheimer's disease. A crucial molecule in many physiological and pathological processes is heme. It has been proposed that, in comparison to normal aging controls, AD patients have smaller cell volumes and lower hemoglobin levels. The electron transport chain's complexes II, III, and IV need heme to assemble the cytochromes that are necessary for proper operation. Oxidative stress and cell death can result from disruptions in heme metabolism. Heme can lessen the neuroinflammation caused by Aβ 42 that is triggered by astrocytes. Additionally, heme can attach to Aβ, and this complex possesses peroxidase activity that may harm serotonin and DOPA. This implies a fascinating connection between heme and oxidative push in Alzheimer's infection.

Thus, OS is caused by a lack of heme, which also that leads to the formation from APP polymers as well as a breakdown in Complex IV of the mitochondrial respiratory chain. Results suggested that heme deficiency could be the only source of the iron accumulation observed in AD [4]. Several citrus species can improve cognition through their anti-cholinesterase antioxidant activities. Based on these factors, The purpose of this think about was to examine the anti-cholinesterase movement and the antioxidant impacts of Citrus reticulata leaf extricates [5]. The 'Neuro-Protective' benefits of citrus reticulata leaf extract in a rat model of vascular dementia were done and observed improvements in cognitive function, along with reductions in neuronal damage and inflammation markers, highlighting the potential of citrus reticulata leaves as a therapeutic agent for dementia [6, 7].

Moreover, natural compounds derived from plants often possess favorable safety profiles and may offer complementary benefits alongside conventional dementia treatments. Citrus reticulata, commonly known as mandarin or tangerine, is renowned not only for its delicious fruits but also for the numerous benefits derived from its leaves. Products derived from Citrus reticulata leaves possess a diverse chemical composition, offering various advantages, including pleiotropic effects and relatively low toxicity. Citrus reticulata leaves are rich in bioactive compounds, including flavonoids, alkaloids, essential oils, and phenolic compounds. These constituents contribute to the therapeutic properties of products derived from the leaves. For example, flavonoids exhibit antioxidant properties, alkaloids may have antimicrobial effects, and essential oils often possess anti-inflammatory and analgesic properties [8].

Products derived from Citrus reticulata leaves demonstrate pleiotropic effects that can include antioxidant, antimicrobial, anti-inflammatory, anticancer, and neuroprotective properties. HFD-Induced Cognitive Impairment Model: High-fat diet (HFD) consumption has emerged as a significant risk factor for neuroinflammation and oxidative damage, both of which play a part in the advancement of dementia and cognitive weakening. Researchers conducted recent research aimed at elucidating the mechanisms underlying HFD-induced metabolic dysfunction and its subsequent effects on neuroinflammatory responses and neuronal damage [9]. Their findings shed light on the intricate interplay between HFD consumption, metabolic dysregulation, and neuroinflammation. HFD-induced metabolic dysfunction, characterized by insulin resistance, dyslipidemia, and obesity, triggers a cascade of inflammatory processes within the CNS. These activities activate the 'Microglia, the brain's resident defense cells, and increase pro-inflammatory cytokines and chemokines'.

Citrus reticulata as PXR agent: Citrus juices include a flavonoid called hesperetin, which may reduce cholesterol. Hesperetin has demonstrated its efficacy as an anti-inflammatory and antioxidant in the past. This study examined hesperetin'sneuroprotective properties against LPS-induced brain inflammation, oxidative injury, neuronal cell death, and memory loss in both *in vivo* and *in vitro* settings [10]. LPS treatment activated microglia and astrocytosis, leading to increased generation of provocative go betweens within the cortex, hippocampal areas, and BV2 cells. The mediators include "Phosphorylated NF-κB, tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β)". Improving the activation of Iba-1/GFAP and ionized calcium-binding adapter molecule 1/Toll-like receptor-4 (TLR4) can lead to improved outcomes. Hesperetin treatment significantly decreased Cytokine markers of inflammation. Similarly, the mouse brain, hesperetin increased the expression of antioxidant proteins like HO-1 (Haemoxygenase) and Nrf2 (atomic calculate erythroid 2-related figure) [11]. It repressed the era of ROS/lPO caused by LPS. Hesperetin also reduced the Cellular harm and reactive oxygen species (ROS)/lipid peroxidation that lipopolysaccharide produced in hippocampal neuronal cell line. It inhibited neuronal death induced by LPS via increasing Bcl-2 protein levels and decreasing Caspase-3, p-JNK, and Bax expression. Hesperetin enhances 'synaptic preservation, thinking skills, and recollection by upregulating Syntaxin, Post-Synaptic Density protein 95,and p-CREB. Based on our preclinical finding research shows that bioactive compound, hesperetin protects neurons by impacting the Toll-Like Receptor 4 and uclear Factor kappa-light-chain-enhancer of actuated B cell signaling cascade, counteracting negative impact of lipopolysaccharide.

MATERIALS AND METHODS

Analytical-grade chemicals were procured from Sigma Chemical, USA, and S. D. Fine Chem. Ltd., India. The citrus reticulata leaf extract was ordered from ShreedhaPhyto Extracts in Sodala, Jaipur, India.

Drugs

This study used Piracetam (the standard drug) 12 and Citrus reticulate Ethanolic Leaves Extract (Test drug). The drugs were dissolved in 1% Carboxymethylcellulose (biocompatible and biodegradable) and administered orally to the mice [12].

Animals required

During the current study, mature Swiss albino mice, regardless of sex, with weights extending from 25 to 30 g, were employed. While psychological investigations began, they were given two weeks in order to become acclimated to their new lab environment. Once cognitive investigations began, they were given an entire week to grow accustomed to the lab environment. Mice were housed in conditions that provided them with an unlimited supply of nourishment and water, in addition to 12 h of illumination as well as 12 h of twilight.

Nootropic activity

The complete studies were carried out at the Animal House, St. Soldier Institute of Pharmacy, Jalandhar, Punjab, India (CPCSEA Reg. Number 2011/PO/Re/S/18/CPCSEA) following IACE approval.

Studies on acute toxicity

These investigations were carried out in compliance with OECD guideline [13]. Animals were given free access to water for 5 h. Following the administration of 0.1 mg/kg of C. reticulate Ethanolic leaves extract orally, the death rate was monitored for three days. In the absence of mortality, additional procedures were taken.

Experimental parameters

Morris water maze (MWM)

This is a standard tool for evaluating spatial learning and memory in experimental settings. A round pool filled with cloudy water, with a covered-up stage underneath the surface that mice must find order to escape, are both part of the process. The experiment begins with a habituation phase, where the mice are familiarized with the pool and water. This phase usually involves placing the mouse in the pool without the platform for a short period to reduce stress. Next, the training phase begins when the platform is positioned slightly below the level of the water on an established spot. Mice are placed in the pool at various beginning locations for every trial, and given a predetermined amount of time (often 60 seconds) to locate the platform. If a mouse is unable to find the platform inside this time, it is gently guided to it. Over 5-7 d, the mouse undergoes multiple sessions per day with a typical range of 3 to 4 repetitions, allowing it to familiarize themselves with the platform's position based on visual cues around the room. During these trials, parameters such as swim distance, path efficiency, and latency (time it takes to locate the platform) are noted. Following the training stage, a probing trial is carried out in which the platform is taken down, and the mouse has a predetermined amount of time—typically 60 seconds—to investigate the pool. The length of time went through within the target quadrant (where the stage was put) is measured.

Mice with better spatial memory will spend more time in this area. The MWM is useful for assessing hippocampal-dependent spatial memory in mice [14, 15].

Elevated plus maze

This "External sensory-driven behavior" paradigm, in which conditions where the stimulus was external to the mice body, was used to analyze memory as well as learning in mouse subjects. The setup included two open arms (16 cm x 5 cm) and two encased arms (16 cm x 5 cm x 12 cm). The labyrinth was raised to a tallness of 25 cm situated over the ground level with arms expanding from a central stage measuring 5 cm by Five centimeters. On day one, each mouse was set at the terminal conclusion of one of the open arms, confronting inverse the central stage. The time went through by the mouse to move all four feet interior any of the encased arms was captured as well as recorded as exchange idleness (TL). In the event the mouse did not enter any enclosed arms before 90 seconds had passed. The TL set to this value. After spending ten seconds exploring the maze, the mouse was returned to its cage. On the second day, 24 h after the initial trial, the mouse's memory retention was evaluated [16].

T-maze

The T-maze represent as a straightforward action-oriented assessment commonly used to evaluate skill development, memory, as well as decision-making abilities in mice. The maze is shaped like the letter "T," with a starting arm and two goal arms, one of which is usually identified as the "correct" arm. The test starts by placing the mouse in the starting arm, facing the open end. The mouse is given the opportunity to explore the maze and must select one of the two goal arms. In many versions of the task, one arm contains a reward (such as food or water) while the other does not. The goal is for the mouse to learn which arm consistently leads to the reward. Typically, the mouse undergoes a series of trials, with the researcher recording. The amount of valid choices the animal makes, the response time to reach goal along with the total count of arm entries.

A forced-choice trial, the animal is carefully guided into one of the goal arms to guarantee it learns the correct response, while in a free-choice trial, the mouse can choose which arm to enter based on prior

learning. To assess memory, the delayed alternation version of the T-maze is used, where a delay (e. g., 10-30 seconds) is introduced before the animal is allowed to choose the goal arm again. The number of correct responses is measured across trials, and a high rate of correct choices indicates good memory and decision-making ability. The T-maze is frequently utilized in neuroscience research to evaluate cognitive abilities, including working memory and learning.

Assessment of learning and memory

Extraction of serum total cholesterol

The extraction of serum total cholesterol in mice for dementia research typically involves several steps: Blood samples are collected from mice via by obtaining blood from the tail vein. The collected blood is then separated from other blood components, including healing components and red blood cells, by centrifugation [17].

The liquid component is called serum of blood that remains after clotting and contains various proteins, lipids, and other molecules. The concentration of total cholesterol in the serum is measured using biochemical assays. Various methods are available for measuring cholesterol levels, including enzymatic assays. Enzymatic assays are commonly used due to their specificity and sensitivity. Once the cholesterol levels are measured, the data is analyzed to assess the relationship between serum cholesterol levels and dementia. This may involve statistical analysis to determine correlations or differences between groups of mice with varying cholesterol levels and cognitive function.

Evaluation of the lipid profile

Serum total cholesterol estimation: The cholesterol oxidase peroxidase (CHOD-PAP) methodology 17 would be used to estimate the serum total cholesterol using a commercially available kit (Sigma Aldrich, Mumbai, India). A volume of 1000 µl of cholesterol will be mixed with 20 microliters of serum, 20 microliters of a cholesterol standard arrangement (200 mg/dl), and 20 µl of filtered water, separately. At that point, brood all the tubes at room temperature for 10 min.

Using spectrophotometry, the absorbance of the test and standard samples will be measured at 505 nm in relation to the blank.

Cholesterol esterase facilitates the hydrolysis and esterification of cholesterol into free cholesterol. The liberated cholesterol undergoes oxidation, generating Hydrogen peroxide subsequently reacts with phenol and 4-aminoantipyrine when peroxidase is present, leading to the formation of a red-colored quinone imine pigment complex. The strength of the resulting color correlates directly with the cholesterol concentration in the sample.

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RESULTS

The effect of other drugs on escape latency time (ELT) was assessed on days 1, 7, and 14 (measured in seconds) using the Morris Water Maze (MWM) test in a high-fat diet (HFD)-induced dementia model.

Table 1: Experimental design

Groups	Treatment	No. of animal
Group-I	Naïve group or Control group, normal saline 0.9% NaCl (10 ml/kg, or 1 ml of/100 g body weight p. o.)	06
Group-II	High-fat diet (HFD) control group	06
Group-III	Piracetam (150 mg/kg *p. o.*)+HFD	06
Group-IV	HFD+CRELE 250 mg/kg (p. o)	06
Group-V	HFD+CRELE 500 mg/kg (p. o)	06
Total no. of animals required (no. of groups x no. of the animals in each group)		30

Duration of study: 07 d, CRELE-Citrus reticulate Ethanolic Leaves Extract (Test drug), PCT: Piracetam

Table 2: Table showing the effect of pharmacological interventions of citrus reticulate ethanolic leaves extract

Group	Day 1 Elt (sec)	Day 7 Elt (sec)	Day 14 Elt (sec)
Normal control	107.68±3.6	98.50±9.1	51.2±7.8
HFD control	105.47±1.4	96.16±3.6	88.45±4.6
HFD+Piracetam	97.84±2.6	84.46±5.3	59.59±3.8***
HFD+Crele (LD)	104.16±3.2	91.83±1.4	69.15±1.6*
HFD+Crele (HD)	102.46±5.6	85.25±2.6	63.19±3.2**

"*P<0.05, **P<0.01, ***P<0.001 in comparison to the control group. Data are expressed as mean±SEM, with n = 6 per group.", HFD = High fat diet, C. R. E. L. E.(LD) = Citrus reticulate Ethanolic Leaves Extract a lower dose (250 mg/kg; administered orally)., C. R. E. L. E.(HD) = Citrus reticulate Ethanolic Leaves Extract a higher dose (500 mg/kg; administered orally).

Table 3: The table presents the impacts of Citrus reticulata ethanolic leaf extricate and other drugs on different pharmacological parameters, particularly the cruel time went through within the target quadrant (TSTQ), surveyed utilizing the morris water labyrinth test in an HFD-induced dementia show

Group	Time spent (sec.) in target quadrant
Normal control	53.2±7.6
HFD control	94.45±4.8
HFD+Piracetam	56.59±3.6***
HFD+CRELE (LD)	64.15±1.8*
HFD+CRELE (HD)	63.19±3.6**

"*P<0.05, **P<0.01, ***P<0.001 in comparison to the control group., Data are expressed as Mean±SEM, with n = 6 per group.", HFD = High fat diet, C. R. E. L. E.(LD) = Citrus reticulate Ethanolic Leaves Extract a lower dose (250 mg/kg; administered orally)., C. R. E. L. E.(HD) = Citrus reticulate Ethanolic Leaves Extract a higher dose (500 mg/kg; administered orally).

The above graph illustrates the impact of pharmacological therapy, including Citrus reticulata ethanolic leaf extract and other medications, on the latency of escape time (IELT) measured in seconds on days 1, 7, and 14 using the Morris Water Maze test in an HFD-induced dementia model.

The above graph depicts the effect of Citrus reticulataethanolic leaf extract and other drugs on cruel time went through within the target quadrant (TSTQ) utilizing the Morris Water Labyrinth test in an HFD actuated dementia demonstrate.

Tables showing the Effect of Pharmacological interventions of Citrus reticulate ethanolic leaves extract and the effects of other drugs on the Forced Alternation Task (FAT), Left-Right Discrimination (LRD) latency time (LT), and distance traveled (DT) in mice were assessed using the T-maze in an HFD-induced dementia model.

Table 4: The table presents the effects of pharmacological interventions, including Citrus reticulata ethanolic leaf extract and other drugs, on exchange inactivity time (TLT) in mice, measured in seconds, utilizing the hoisted also labyrinth in an HFD-induced dementia show

Group	Day 1 tlt (sec)	Day 7 tlt (sec)	Day 14 tlt (sec)
Normal control	109.63±3.6	97.51±9.2	53.21±6.6
HFD control	103.56±1.6	99.17±3.6	84.47±4.6
HFD+Piracetam	96.74±2.8	73.34±5.8	58.58±3.8***
HFD+CRELE (LD)	92.63±3.4	88.87±1.8	67.13±1.8*
HFD+CRELE (HD)	95.45±5.4	84.21±2.6	62.17±3.8**

"*P<0.05, **P<0.01, ***P<0.001 in comparison to the control group., Data are expressed as mean±SEM, with n = 6 per group.", HFD = High fat diet, C. R. E. L. E.(LD) = Citrus reticulate Ethanolic Leaves Extract a lower dose (250 mg/kg; administered orally)., C. R. E. L. E.(HD) = Citrus reticulate Ethanolic Leaves Extract a higher dose (500 mg/kg; administered orally).

Table 5: Forced alteration task (FAT)

Group	Day 1 fat (sec)	Day 7 fat (sec)	Day 14 fat (sec)
Normal control	53.66±3.8	36.52±9.4	21.22±6.2
HFD control	74.68±1.8	73.19±3.6	61.47±4.4
HFD+Piracetam	57.80±2.8	37.48±5.2	27.58±3.8***
HFD+CRELE (LD)	55.30±3.6	43.32±1.8	33.17±1.6*
HFD+CRELE (HD)	58.67±5.8	41.22±2.6	27.17±3.4**

"*P<0.05, **P<0.01, ***P<0.001 in comparison to the control group., Data are expressed as mean±SEM, with n = 6 per group.", HFD = High fat diet, C. R. E. L. E.(LD) = Citrus reticulate Ethanolic Leaves Extract a lower dose (250 mg/kg; administered orally)., C. R. E. L. E.(HD) = Citrus reticulate Ethanolic Leaves Extract a higher dose (500 mg/kg; administered orally).

Table 6: Left right discrimination (LRD)

Group	Day 1 lrd (sec)	Day 7 lrd (sec)	Day 14 lrd (sec)
Normal control	18.66±3.8	16.50±9.4	15.21±6.8
HFD control	26.67±1.6	24.15±3.6	23.47±4.2
HFD+Piracetam	16.83±2.6	15.45±5.4	13.58±3.6***
HFD+CRELE (LD)	18.17±3.4	17.84±1.4	16.11±1.0*
HFD+CRELE (HD)	17.45±5.4	16.26±2.6	15.13±3.6**

"*P<0.05, **P<0.01, ***P<0.001 in comparison to the control group. Data are expressed as mean±SEM, with n = 6 per group.", HFD = High fat diet, C. R. E. L. E.(LD) = Citrus reticulate Ethanolic Leaves Extract a lower dose (250 mg/kg; administered orally)., C. R. E. L. E.(HD) = Citrus reticulate Ethanolic Leaves Extract a higher dose (500 mg/kg; administered orally).

Table 7: Latency time (LT)

Group	Day 1 Lt (sec)	Day 7 Lt (sec)	Day 14 Lt (sec)
Normal control	104.66±3.2	94.52±3.2	52.21± 6.6
HFD control	103.67±1.6	98.15±3.5	82.47±4.8
HFD+Piracetam	82.86±2.6	76.47±5.8	58.60±3.6***
HFD+CRELE (LD)	92.17±3.4	84.84±1.4	64.11±1.6*
HFD+CRELE (HD)	92.44±5.4	82.24±2.4	62.18±3.4**

"*P<0.05, **P<0.01, ***P<0.001 in comparison to the control group., Data are expressed as mean±SEM, with n = 6 per group.", HFD = High fat diet, C. R. E. L. E.(LD) = Citrus reticulate Ethanolic Leaves Extract a lower dose (250 mg/kg; administered orally)., C. R. E. L. E.(HD) = Citrus reticulate Ethanolic Leaves Extract a higher dose (500 mg/kg; administered orally).

Table 8: Distance travelled (DT)

Group	Day 1 DT (sec)	Day 7 DT (sec)	Day 14 DT (sec)
Normal control	28.67±3.6	25.52±9.2	21.22±6.2
HFD control	34.56±1.6	32.18±3.5	32.47±4.8
HFD+Piracetam	31.83±2.6	28.47±5.8	27.58±3.6***
HFD+CRELE (LD)	34.15±3.8	32.88±1.4	30.18±1.6*
HFD+CRELE (HD)	32.36±5.4	38.28±2.8	28.20±3.2**

"*P<0.05, **P<0.01, ***P<0.001 in comparison to the control group, Data are expressed as mean±SEM, with n = 6 per group.", HFD = High fat diet, C. R. E. L. E.(LD) = Citrus reticulate Ethanolic Leaves Extract a lower dose (250 mg/kg; administered orally)., C. R. E. L. E.(HD) = Citrus reticulate Ethanolic Leaves Extract a higher dose (500 mg/kg; administered orally).

DISCUSSION

Numerous investigations have discovered natural substances that act as nootropics. Based on their importance in the conventional medical system, extracts and chemicals from medicinal plants have been chosen and extracted. The pharmaceutical industry has so far spent a great deal of revenue trying to find substances that could be able to treat crippling conditions and delay the onset of mental retardation. These include properties such as cholesterol-lowering, pain-relieving, antiseptic, anti-asthmatic, anti-inflammatory, anti-scurvy, cough-suppressing, digestive aid, expectorant, liver-protective, anticancer, antimicrobial, antigenotoxic, antioxidant, cholesterol-regulating, stomachic, and cardiovascular benefits. Although their full potential is still unknown, phytochemicals are being studied because they appear to have various qualities [18]. This study examined the effects of Citrus reticulataethanolic leaf extract on dementia. Two doses, a high dose (500 mg/kg; orally) and a low dose (250 mg/kg; orally), were chosen based on prior research, aiming to induce behavioral changes, particularly in learning and memory. The findings from the Morris Water Maze, Elevated Plus Maze, and T-Maze tests suggest that the high dose (500 mg/kg; orally) of Citrus reticulataethanolic leaf extract produced results comparable to the standard drug piracetam. However, the low dose (250 mg/kg; orally) did not exhibit any significant positive effects. These results indicate that oral administration of the high dose improved learning and memory in mice. Additionally, no notable behavioral changes were observed during exploration in the Passive Avoidance Paradigm. Given the importance of these plants, extensive chemical analyses have been conducted, identifying hesperetin, a flavonoid, as a key compound supporting memory enhancement. This study suggests that hesperetin may contribute to improved learning and memory, as it has demonstrated neuroprotective effects against lipopolysaccharide (LPS)-induced neuroinflammation, oxidative stress, neuronal damage, and memory impairment in both *in vivo* and *in vitro* models.

CONCLUSION

Research findings have shown that abnormal cholesterol levels in animals and humans may lead to cognitive impairment and excessive intake of a cholesterol-rich high-fat diet may cause Aβ accumulation in nerve cells, induce protein misfolding, self-aggregation of cytoskeleton proteins, generate oxidative stress, and impair the cholinergic system by increasing the activity of acetylcholinesterase. This consider pointed to assess the potential of Citrus reticulata in high-fat slim down (HFD)-induced dementia. Markers of oxidative stress and inflammation were quantified to elucidate the mechanism involved in the effects of HFD-induced dementia.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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