Investigating the Neuroprotective Effects of Curcumin in Scopolamine-induced Animal Model of Dementia: A Synergistic Approach to Mitigate Cognitive Decline

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ABSTRACT

The primary objective of this study was to investigate the neuroprotective effects of curcumin in animal models of scopolamine-induced dementia. Given that cognitive decline in dementia is often linked to oxidative stress, the study aimed to explore whether curcumin, a natural polyphenol known for its antioxidant and anti-inflammatory properties, could mitigate memory impairment and improve cognitive function in these models. To induce dementia, scopolamine was administered to rats, leading to memory impairment. The cognitive abilities of the animals were evaluated using behavioral tests such as the Morris water maze and the novel object recognition test. In addition to behavioral assessments, biochemical markers related to oxidative stress and cholinergic dysfunction were measured to assess the potential mechanisms through which curcumin might exert its effects. Curcumin was then administered to the scopolamine-treated rats to evaluate its impact on memory function and oxidative stress Rats treated with scopolamine exhibited significant memory impairment, as shown by poor performance in the Morris water maze and novel object recognition test. However, following curcumin treatment, a marked improvement in cognitive abilities was observed, indicating a positive effect on memory. Biochemical analyses revealed that curcumin treatment significantly reduced oxidative stress markers and improved cholinergic function in the treated animals. The findings from this study suggest that curcumin effectively improves cognitive function and reduces oxidative stress in scopolamine-induced dementia models. These results highlight the potential of curcumin as a neuroprotective agent and propose it as a promising candidate for preventing or treating cognitive decline associated with dementia. Further research is warranted to explore its clinical applications and establish its therapeutic efficacy.

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INTRODUCTION

Millions of people worldwide live with dementia, a complex neurodegenerative disease characterized by cognitive decline and imposing a heavy burden on public health systems. 60-80% of patients suffering from dementia are diagnosed with Alzheimer's disease (AD) making it most common type of dementia disorders [1-3]. Despite progress in understanding its pathogenesis, new neuroprotective drugs still need to be investigated due to ineffective/failure of treatment in some cases [4]. Curcumin has attracted attention for its therapeutic benefits in neurodegenerative diseases due to its anti-amyloidogenic, anti-inflammatory and antioxidant properties [5]. Curcumin shows promise as a modifier of cognitive decline through multiple mechanisms.

Animal models are important for studying dementia and potential treatments. Scopolamine is an anticholinergic drug widely used to induce cognitive impairment in animal models to mimic the symptoms of dementia. This model is particularly useful for evaluating neuroprotective drugs because scopolamine blocks the transmission of acetylcholine, causing memory impairments like those seen in Alzheimer's and related disorders [6-8]. Models induced by scopolamine combined with therapeutic agents such as curcumin [9] provide an opportunity to study the effects of the memory impairment over the course of time and to understand neurobiological processes. These cognitive deficits are thought to be treated by different approaches, like reducing oxidative stress and inhibiting neuroinflammation. Prognosis of Alzheimer's and other related disorders could have an important involvement of these factors.

Plasticity and neurogenesis are both important for the regulation of intelligence. Studies have shown that curcumin can scavenge free radicals and regulate signalling pathways such as NF-αβ and MAPK, which can prevent oxidative damage and inflammation in neurodegenerative diseases [10,11]. Medical Ability. Mechanism of action of curcumin and possible cellular/molecular involvement in the focus of current research on cognitive disorders [12]. This study aims to investigate the neuroprotective effects of curcumin in an animal model of scopolamine-induced dementia, focusing on its ability to modify cognitive decline caused by synergism. By exploring these effects, this study may provide new insights into the development of a combination therapy that simultaneously targets multiple pathological pathways for dementia.

MATERIALS AND METHODS

Animals

The experimental design strictly followed the guidelines of the Institutional Bioethics Committee (IBC). Locally bred male Albino Wistar rats weighing 180–200 g from HEJ Institute of Chemistry, Karachi were individually housed under a 12-h light-dark cycle and maintained at room temperature of 22 ± 2 °C. They had free access. Tap water and standard rat diet were administered for 7 days before the start of the experiment to allow them to acclimate to their environment. Before starting this study, the rats were familiar with various techniques to reduce environmental stress [13]. All reasonable precautions were taken to minimize pain or discomfort. All experimental procedures were approved and complied with the Guides for the Care and Use of Animal Vaccines (Publication No. 85-23, revised 1985) of the National Institutes of Health and the IBC.

Drugs and Doses

Scopolamine was purchased from Sigma, dissolved in physiological saline and injected intraperitoneally at 0.5 mg/kg body weight [14]. Curcumin was purchased from the local market and administered orally the dose of 200mg/kg [15]. Respective control animals were injected with saline/ administered with water in volumes of 1.0 ml/kg body weight.

Experimental Protocol

24 rats were treated with (ii) saline-curcumin, (iii) scopolamine-water and (iv) scopolamine-curcumin. Each group was containing 6 rats each. Baseline activity in the Morris water maze test and novel object recognition were assessed before the start of the experiment (day 0). Rats were re-treated with scopolamine and curcumin for three weeks. Tasks in the Novel Object Recognition Test and Morris Water Maze Test were assessed weekly. Following three weeks of treatment regime, brain and plasma samples were collected from the rats after decapitation. Samples were collected and stored at –70°C until analyses.

Behavioural Assessment

Morris Water Maze (MWM) Test

The Morris Water Maze Test procedure was based on previously established procedures [16,17]. The Morris water maze (MWM) test is a behavioral test used to measure spatial learning and memory in rats. It consists of a large pool filled with opaque water and a small hidden platform submerged in a fixed area below the surface. Rats were placed in a swimming pool and had to swim to find the platform using pictures provided in the chamber. During training, rats learned the location of the platform and the time required to reach the platform during testing was monitored from 1 to 6 hours after drug administration (short-term and long-term memory).

Novel object recognition test

The Novel Object Recognition (NOR) test is a behavioral test used to measure memory in rats. In this experiment, rats are first introduced to two identical objects in a familiarization phase. After a short delay, one of the objects is replaced with a novel object and the rats are reintroduced to the scene. Memory is measured by the time the rats spend exploring the novel objects compared to the familiar objects. A preference for the novel items suggests that the rats are remembering the familiar items and reflects poor memory. The NOR test is widely used in the study of memory, learning, and the effects of neurodegenerative diseases or treatments [18,19].

Oxidative parameters

Determination of Superoxide Dismutase (SOD) Activity

Add 50 µL of serum to a well containing 20 µL of EDTA (0.1 mM), 100 µL of NBT reagent (24 µM), and 100 µL of sodium carbonate (50 mM). Place the 96-well microplate in the absorbance reader and shake the mixture for 15 s. 40 µL of hydroxylamine hydrochloride (1 mM) was added to start the reaction and the change in absorbance was recorded at 560 nm at time zero and after 5 min, the samples stored at 25 °C were compared with the plasma-free reagent blank [20].

Determination of Catalase (CAT) Activity

0.4 mL of H_2O_2 solution (0.2 M) and 1 mL of sodium phosphate buffer (0.01 M, pH 7.4) were added to a test tube. Quickly add 100 µL of blood and mix by gentle swirling. Bake the tube at 37°C for 1.5 min. To stop the reaction, the mixture was immediately transferred to 2 mL of dichromate/acetic acid (5%). Then, the tube was placed in boiling water (100°C) for 15 min and cooled in ice water at 4°C. A 250 µL sample was collected from the mixed results and transferred to a 96-well microplate, and the absorbance of the supernatant was measured at 570 nm using an absorbance reader [20].

Determination of Glutathione Peroxidase (GSH-Px) Activity

Glycopeptide (2 mM), 30 µL of plasma, 10 µL of sodium azide (10 mM), and 10 µL of hydrogen peroxide solution (1 mM), all together in a 2 mL microcentrifuge tube. The mixture was incubated at 37°C for 15 min. Stop the reaction by adding 50 µL of 5% TCA and mixing vigorously. After centrifugation at 8,325 rpm for 5 min at 4 °C, 25 µL of the supernatant was transferred to a 96-well microplate. Add 50 µL of sodium phosphate buffer (0.1 M, pH 7.4) and 175 µL of DTNB (1 mM). The mixture was shaken for 10 s with absorbance reading recorded at 420 nm. Control samples were run simultaneously and the reaction was stopped immediately at time zero. GSH-Px activity is expressed as micromoles of GSH converted to GSSG per minute per milliliter of rat plasma [20].

Statistical analysis

The results are represented as the means ± SD. Statistical analysis was performed by two-way or three-way analysis of variance (ANOVA) using SPSS software ver25, where applicable. Post hoc individual comparisons between each group were made using the Tukey's test; p values < 0.05 were considered significant.

RESULTS

Figure 1 shows effects of curcumin in scopolamine treated rats, on Morris water maze test. Figure 1a shows effects of curcumin in scopolamine treated rats on time taken to reach platform in the training session. Figure 1b shows effects of curcumin in scopolamine treated rats on short term memory (time taken to reach platform). Figure 1c shows effects of curcumin in scopolamine treated rats on long term memory (time taken to reach platform). Data were analyzed by two-way ANOVA (df= 1,20). Results are as under:

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	Training session		Short term memory		Long term memory	
	F	p value	F	p value	F	p value
Day 1						
Curcumin	1.25	0.58	14.25	0.001	13.52	0.001
Scopolamine	0.78	0.41	20.19	0.001	25.36	0.001
Curcumin* scopolamine	0.54	0.15	0.38	0.59	28.41	0.001
Day 7						
Curcumin	14.23	0.001	23.14	0.001	24.12	0.001
Scopolamine	29.46	0.001	36.25	0.001	36.25	0.001
Curcumin* scopolamine	34.41	0.001	34.46	0.001	28.41	0.001
Day 14						
Curcumin	25.36	0.001	38.15	0.001	29.52	0.001
Scopolamine	16.32	0.001	46.15	0.001	26.41	0.001
Curcumin* scopolamine	35.21	0.001	54.25	0.001	30.13	0.001
Day 21						
Curcumin	20.32	0.001	52.12	0.001	54.32	0.001
Scopolamine	21.36	0.001	54.25	0.001	32.02	0.001
Curcumin* scopolamine	41.73	0.001	41.66	0.001	35.25	0.001

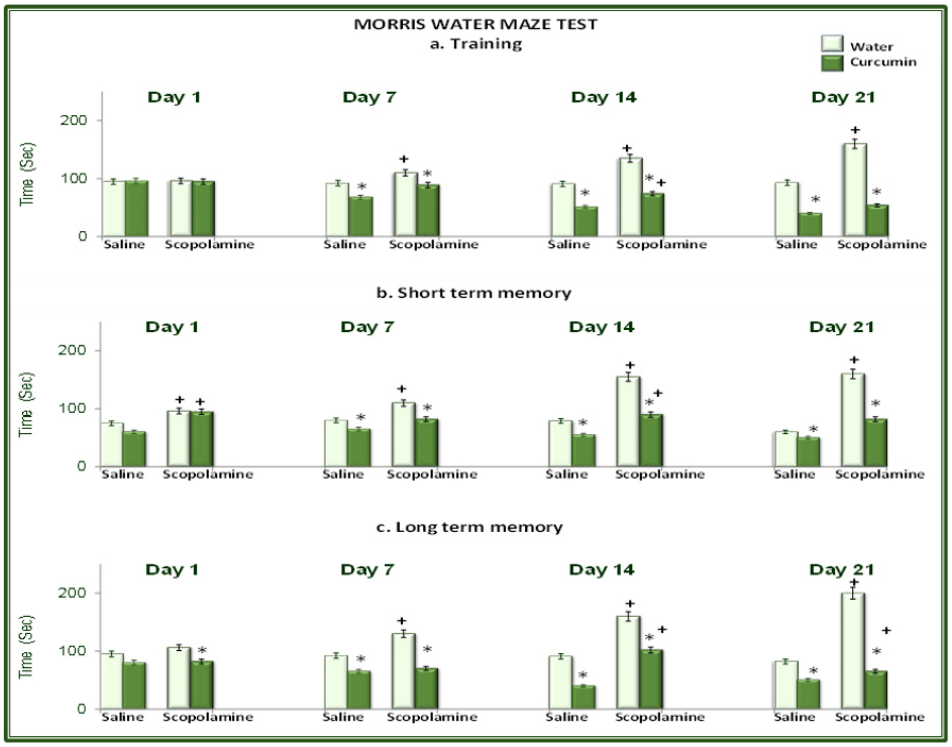

Figure 1. Effects of curcumin in scopolamine treated rats, on Morris water maze test (time taken to reach platform on day 1, 7, 14 and 21). Values are represented as means±SD (n=6). Significant differences by Tukey's test: *p<0.01 as compared to respective water treated rats; +p<0.01as compared to respective saline injected rats following two-way ANOVA.

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Figure 2 shows effects of curcumin in scopolamine treated rats, on novel object recognition test. Figure 2a shows effects of curcumin in scopolamine treated rats on exploration time as monitored on day 1. Figure 2b shows effects of curcumin in scopolamine treated rats on exploration time as monitored on day 7. Figure 2c shows effects of curcumin in scopolamine treated rats on exploration time as monitored on day 14. Figure 2d shows effects of curcumin in scopolamine treated rats on exploration time as monitored on day 21. Data were analyzed by three-way ANOVA (df= 1,40; p= 0.001). Results are summarized as under:

	Day 1	Day 7	Day 14	Day 21
Objects	F= 56.14	F= 28.25	F= 38.12	F= 64.14
Curcumin	F= 41.32	F= 52.36	F= 48.84	F= 38.02
Scopolamine	F= 24.56	F= 32.15	F= 38.45	F= 41.56
Objects* Scopolamine	F= 23.85	F= 25.32	F= 31.48	F= 41.64
Scopolamine* Curcumin	F= 31.45	F= 41.25	F= 31.21	F= 57.41
Objects* Scopolamine* Curcumin	F= 51.36	F= 38.12	F= 29.56	F= 48.65

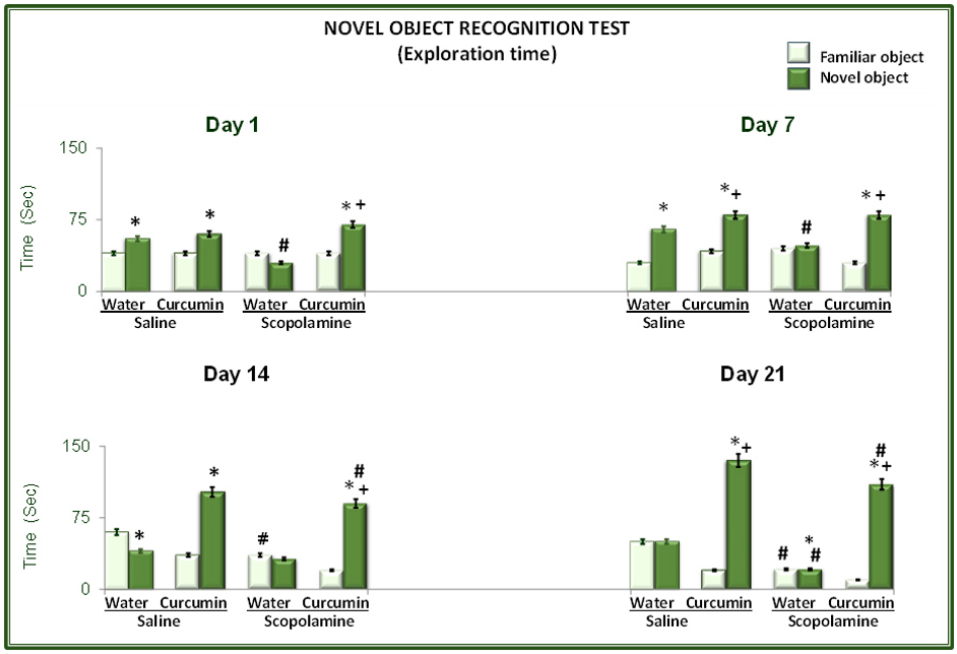

Figure 2. Effects of curcumin in scopolamine treated rats, on Novel object recognition test (object exploration monitored on day 1, 7, 14 and 21). Values are represented as means±SD (n=6). Significant differences by Tukey's test: *p<0.01 as compared to respective familiar object; +p<0.01as compared to respective water treated rats; #p<0.01as compared to respective saline injected rats following three-way ANOVA.

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Figure 3 shows the effects of curcumin in scopolamine treated rats, on antioxidant assays. Figure 3a shows effects of curcumin in scopolamine treated rats on superoxide dismutase activity. Figure 3b shows effects of curcumin in scopolamine treated rats on catalase activity. Figure 3c shows effects of curcumin in scopolamine treated rats on glutathione peroxidase activity. Data were analyzed by two-way ANOVA (df= 1,20; p= 0.001). Results are summarized as:

	Superoxide dismutase	Catalase	Glutathione peroxidase
Brain			
Curcumin	F= 25.47	F= 35.15	F= 25.63
Scopolamine	F= 15.63	F= 28.95	F= 38.46
Curcumin* Scopolamine	F= 22.58	F= 32.97	F= 29.52
Plasma			
Curcumin	F= 23.51	F= 29.85	F= 17.68
Scopolamine	F= 28.45	F= 36.25	F= 28.15
Curcumin* Scopolamine	F= 28.14	F= 32.59	F= 20.74

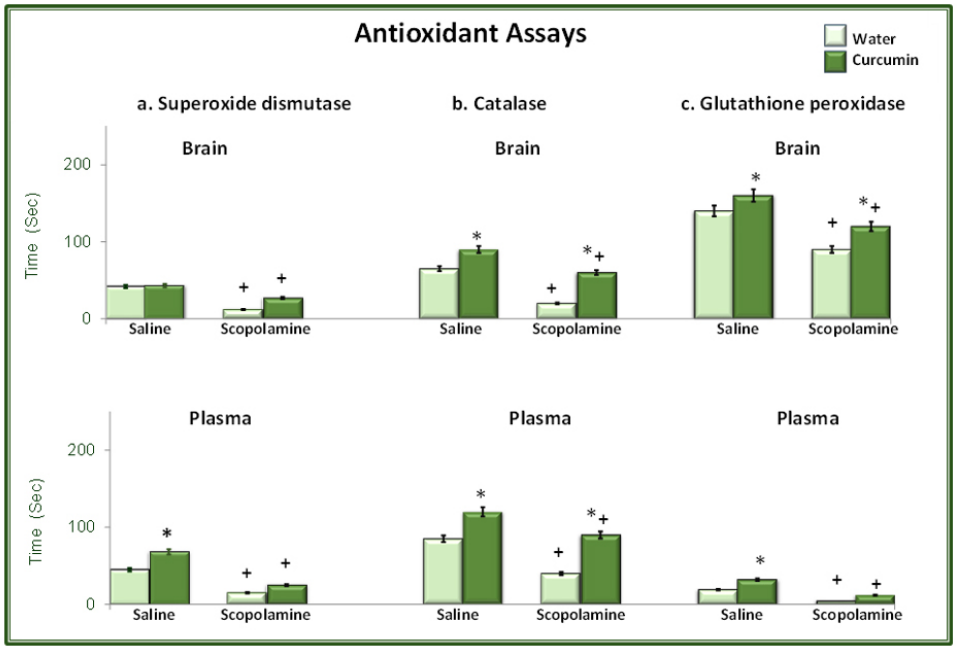

Figure 3. Effects of curcumin in scopolamine treated rats, on antioxidant assays. Values are represented as means±SD (n=6). Significant differences by Tukey's test: *p<0.01 as compared to respective water treated rats; +p<0.01as compared to respective saline injected rats following two-way ANOVA.

DISCUSSION

The neuroprotective properties of curcumin are of particular relevance to the issue of dementia, and especially to Alzheimer's, because of the strong association that exists between disease progression and oxidative stress, neuroinflammation, as well as cholinergic dysfunction. Animals that require cognitive attention but have some drug levels are provided with scopolamine anticholinergic drugs [21]. The scopolamine-induced model of dementia is good and fast in the screening of any putative drug targeting for treatment of dementia, especially multi-target drugs like curcumin [22]. Turmeric, used as a spice, is the source for curcumin has been shown to protect the brain from damage through its antioxidant and anti-inflammatory properties [23]. There had been numerous strategies to alter this aspect though because of low oral bioavailability which prevents achieving the necessary concentration in the target organ, the brain, the promising outcomes in reversal of the degenerative

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changes especially of cognition or even better prevention of onset of those have not been realized.

Results from the Morris water maze (MWM) test showed memory deficits in scopolamine treated rats (Figure 1) which are suggested to be the indicative of impaired cholinergic function [24] that is crucial for normal memory processing. On the contrary, curcumin treatment has been found to alleviate these memory impairments as monitored in Morris water maze. Rats co-treated with curcumin, exhibited decreased time taken to reach the platform when monitored 1hr (short term memory) or 6hr (long term memory) post drug administrations. Curcumin prevented the progressive decline in memory, as induced by scopolamine. The results indicate that curcumin can reverse scopolamine-induced spatial memory dysfunction, perhaps through a mechanism related to its neuroprotective effects such as reducing oxidative stress in the brain.

In the present study, scopolamine decreased novel object recognition in the novel object recognition test, including a substantial impairment in novel object discrimination reflecting deficits in recognition memory. However, administration of curcumin significantly improved this recognition memory. Curcumin-treated animals spent significantly more time exploring new objects compared to scopolamine-treated animals. Therefore, we suggest that curcumin could preserve recognition memory despite scopolamine-induced deficits. The reason for these improvements in cognitive behaviour could be curcumin's modulation of the neurotransmitter system, neuroinflammation and to protect against oxidative damage. It has also been reported that curcumin could reduce memory impairment and other brain complications after ischemia as well [25].

In addition to memory enhancing effects, curcumin's neuroprotective benefits are also closely related to its ability to increase the brain's antioxidant defence. A key factor contributing to neurodegeneration in dementia is oxidative stress. This leads to nerve damage and cognitive decline [26]. Many types of antioxidant enzymes including superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx), play important roles in neutralizing reactive oxygen species (ROS) and maintains redox balance in the brain. These antioxidants in rats treated with scopolamine were significantly decreased in the present study (Figure 3) which could result in increased oxidative stress. These enzymes act synergistically to reduce ROS accumulation, protecting neurons from oxidative damage and promote cognitive flexibility in response to neurological insults. Curcumin's ability to regulate antioxidant system i.e., Keap1-Nrf2 pathway is suggested to be an important mechanism by which it could exert a protective effect on the nervous system and attenuates scopolamine-induced dementia in rat models [27]. Superoxide dismutase (SOD) is one of the main antioxidant enzymes that catalyzes the breakdown of superoxide particles into oxygen and hydrogen peroxide [28,29]. SOD activity was significantly reduced in the scopolamine injected rats, which contributes to the accumulation of harmful free radicals in the brain. Curcumin has been shown to counteract this decrease and restore SOD activity to near-normal levels (Figure 3). This regeneration is important in reducing oxidative damage to nerve cells and reduce the progression of cognitive impairment. Similarly, catalase (CAT), which splits hydrogen peroxide into water and additional oxygen, was also suppressed in scopolamine-treated animals. Clinical and genetic studies indicate a direct correlation between mutations in SOD gene and neurodegenerative diseases, like Amyotrophic Lateral Sclerosis (ALS), Huntington's disease (HD), Parkinson's Disease (PD) and Alzheimer's Disease (AD). Therefore, inhibitors of OS are considered as an optimistic approach to prevent neuronal loss [30]. Increasing oxidative stress as induced by scopolamine administration was significantly attenuated by curcumin administration with increased CAT activity. By further reducing oxidative damage and promotion of nerve survival, curcumin exerts neuroprotective effects and mitigates memory impairment.

Glutathione peroxidase (GPx), another important antioxidant enzyme, plays an important role in the detoxification of hydrogen peroxide and organic hydroperoxides [31,32]. In the scopolamine-induced dementia model, GPX activity is markedly reduced. Leads to increased oxidative stress and nerve fragility. Curcumin's ability to restore GPX activity is an important part of its neuroprotective profile. This is because it helps maintain cellular redox balance and prevents oxidative damage to nerve cells. The combined restoration of SOD, CAT and GPx activities by curcumin highlights its potent antioxidant potential and underlines its important role in the prevention of oxidative stress. It has the potential to be a therapeutic agent to reduce dementia caused by oxidative stress.

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CONCLUSION

In summary, the neuroprotective effects of curcumin in animal models of scopolamine-induced dementia are multifaceted. This includes both behavioral and biochemical mechanisms. Curcumin effectively improves cognitive performance in tasks such as the Morris water maze and a novel object recognition test. At the biochemical level curcumin increases the activity of important antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase. It reduces oxidative stress and protects nerve cells from damage. These findings suggest that curcumin, when used synergistically could improve memory.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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