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Original Article

Experimental Neurobiology

Curcumin, the Main Part of Turmeric, Prevents Learning and Memory Changes Induced by Sodium Metabisulfite, a Preservative Agent, in Rats

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Sodium metabisulfite is used as a disinfectant, antioxidant, and preservative agent in the food, beverage, and drug industries. Neurons are highly sensitive to sulfite toxicity. Curcumin is the main part of turmeric and has neuroprotective effects on a variety of nervous system damages. The present study aimed to investigate the possible protective role of curcumin in learning and memory after exposure to sulfite in rats. The rats were divided into five groups receiving distilled water (solvent of the sulfite), olive oil (solvent of the curcumin), sodium metabisulfite (25 mg/kg/day), curcumin (100 mg/kg/day), and sulfite + curcumin. All the animals received daily gavages for 8 weeks. At the end of the 8th week, learning and memory were assessed in a partially-baited eight arm radial maze. The animals treated with sulfite showed fewer correct choices and more reference and working memory errors during the learning phase, at the end of the learning phase, and during the retention testing ($p<0.001$). The study results demonstrated that sulfite-exposure was associated with impaired learning and memory in rats. Adding curcumin to the rat nutrition plays a protective role in learning and memory after exposure to sulfite.

Key words: curcumin, sulfite, learning, memory, rats

INTRODUCTION

Sulfiting agents are widely used in the food, beverage, and drug industries. Sodium metabisulfite or sodium pyrosulfite is an inorganic compound of chemical formula $Na_2S_2O_5$ and is used as a disinfectant, antioxidant, and preservative agent.

Sulfiting agents (sulfur dioxide, sodium or potassium sulfite, bisulfate, and metabisulfite) can cause cellular toxicity by reacting with a variety of humoral and cellular components [1-7]. Wide quantities of sulfite are also generated in the body by natural catabolic processing of amino acids and other compounds that contain sulfite [8, 9]. Sulfite oxidase is an enzyme located in the intermembranous space of the mitochondria which oxidizes sulfite to sulfate in a two-electron oxidation step and protects the cells from the toxic effects of sulfite [10, 11]. Sulfite oxidase deficiency is a hereditary disorder and can show the importance

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of this detoxification process. The most striking effects of this disease are neurological abnormalities, such as attenuation of the brain growth and mental retardation [12]. Different tissues exhibit different sulfite oxidase activities. High sulfite oxidase activities can be seen in liver, kidney, and heart tissues, whereas brain, spleen, and testis show very low sulfite oxidase activities [13, 14], suggesting that neurons are highly sensitive to sulfite toxicity. Many investigations have shown that sulfite may cause toxic effects for the nervous system. It has also been reported that the number of hippocampal neurons decreased in rats after exposure to sulfite [15]. Moreover, it was shown that sulfite increased the excitability of the spinal reflexes after sulfite treatment [16, 17]. The toxic effects of sulfite on mesencephalic cell lines have been reported, as well [18].

Curcumin is a yellow spice that has shown beneficial pharmacological effects, including anti-inflammatory, antioxidant, anticancer, antiapoptotic, and anti-infectious effects [19-22]. It has also been shown that curcumin has many neuroprotective effects. A good example is that curcumin showed protective effects on the dorsal root ganglion and sciatic nerve after crush in rats [23]. Yet, another example is that curcumin displayed protective effects in diabetic neuropathy [24]. Also, several studies have demonstrated the protective effects of curcumin on cerebral ischemia in the rats and gerbils [25].

In spite of these reports revealing the possible sulfite toxicity of neurons and neuroprotective action of curcumin, no researches have been conducted on the behavioral test. Thus, the present study was undertaken in order to assess the learning and memory in rats after exposure to sulfite and determine the possible protective role of curcumin. Curcumin was considered to be evaluated in this study because it can be found in turmeric and can be added to the foods easily.

In doing so, we assessed the rats' performance in a partially baited eight arm radial arm maze (RAM) task.

MATERIALS AND METHODS

Animals and treatments

The present study was conducted on 50 adult male Sprague-Dawley rats (250-280 g). The animal experiment was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran (Agreement Licensee No: 90-5954). The study animals were divided into five groups each containing 10 rats. Group 1 received distilled water by gavage. Group 2 received daily gavages of olive oil. Group 3 received daily gavages of curcumin (100 mg/kg/day) solved in olive oil [23]. Group 4 received daily gavages of sulfite in the form of sodium metabisulfite (25 mg/kg/day) solved in distilled water [15]. Group 5 received sodium metabisulfite (25 mg/kg/day) and curcumin by gavages. All the animals received daily gavages for 8 weeks. It should be mentioned that they were housed in plastic cages under standard conditions. The doses of sodium metabisulfite were selected according to the previous studies. Human body is exposed to sulfite through the ingestion of the sulfites that are used as preservatives in foods and beverages. Earlier studies have determined the acceptable daily intake from foods and beverages in a single day or meal (163 mg/day) by World Health Organization (WHO, 1994) [26-28]. The acceptable daily intake of 0-0.7 mg/kg was assigned to sulfur dioxide as well as sulfur dioxide equivalents arising from $Na_2S_2O_5$. It should be noted that the mean per capita of sulfite intake limit from foods and beverages is estimated as 19 mg sulfur dioxide equivalents per day. This level has been reported to be 163 mg in the 99th percentile of the population [26-28]. The dose of curcumin was selected according to our earlier results. Our previous study showed 100 mg/kg/day as the appropriate dose of curcumin with no side effects on the liver, kidney, blood levels of aspartate aminotransferase, alanine aminotransferase, urea nitrogen, and creatinine [22, 29].

Assessment of behavior in the eight arm radial maze

Working memory can be defined as a memory for an object, stimulus, or location that is used within a testing session, but not typically between the sessions. It is differed from reference memory which is a memory that would typically be acquired with repeated training and would persist from days to months. Reference memory is often the memory for the 'rules' of a given task. For example, a bar press gives a food pellet or a water maze contains a hidden platform or entrances into the baited arms of the radial maze. On the other hand, working memory allows the animal to remember which arms it had visited in a session. On the next day, this memory is no longer useful since the entire maze arms are baited again [30-32].

The Radial Arm Maze (RAM) was designed to measure the learning and memory in rats. The original apparatus consists of eight equidistantly spaced arms (42×12×12 cm^3). The arms were designed to radiate from a central octagonal platform like the spokes of a wheel. Behavior experiments were performed by a blinded observer. The animals were assessed for learning and memory in a partially baited RAM. Prior to the training, the animals were kept on a restricted regime; so that their body weight would reach 85% of that prior to the training [30-32].

Adaptation session

The animals were offered two sessions of adaptation on two

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continuous days prior to the beginning of the learning career. During these adaptation sessions, they were allowed to explore the baited arms of the maze for 10 min. After the adaptation sessions, the acquisition session was started.

Acquisition session

During the acquisition session (learning career), the animals were given two acquisition trials per day until they attained the learning criteria. The learning criteria were defined as follows. The trial was continued for 5 min and the training was continued until the rats reached the criteria of 80% correct choice; i.e., at least four correct entries out of five. This session lasted for eight to fifteen days. At the beginning of each trial, the maze was cleaned with ethanol (70%) and thereafter four of the arms (2, 3, 5, and 7) were baited with food reward. The rat was placed on the central platform and was allowed a free action. When a rat ate bait or reached the end of an arm, the arm choice was recorded. Only the first accession to the baited arm was recorded as a correct choice and the maze arms were not rebaited. Entrances into the unbaited arms were recorded as Reference Memory Errors (RME), while reentrances into the baited arms were recorded as Working Memory Errors (WME). Each rat was given two trials daily and the data obtained from the two trials were averaged and entered into the final data analysis. The rats' performance was scored by the percentage of the correct choices, RME, and WME [30-32].

Retention session

Ten days after acquisition, the rats were evaluated for retention of the task. The rats were given two trials and the mean scores of the percentage of the correct choices, WME, and RME was used for analysis [30-32].

Statistical analysis

The data is expressed as mean±SD. Either two-way or one-way analysis of variance (ANOVA) followed by Tukey's post-hoc test was used to compare the means. Besides, $p \leq 0.05$ was considered as statistically significant.

RESULTS

The total time required for acquisition

In comparison to the controls, the performances of sodium metabisulfite-treated rats were impaired in acquisition of the task. Also, it took significantly more number of days for this group to acquire the criterion of 80% correct choices ($p<0.001$) (Fig. 1). Compared to the sodium metabisulfite treated rats, it took significantly fewer days for the rats receiving sodium metabisulfite and curcumin to reach the criterion of 80% correct choice ($p<0.001$) (Fig 1). This suggests that curcumin prevents impairment in acquisition of the criterion of 80% correct choices induced by sodium metabisulfite.

Correct choices during the acquisition

A two-way repeated measures ANOVA was performed with training day (Day) as within-subjects factor and experimental group (Group) as between-subjects factor. A significant difference was found for Day [$p<0.001$), $F(7, 315)=28.36$], Group [$p<0.001$), $F(4, 45)=24.42$], and the Day by Group interaction [$p<0.001$), $F(28, 315)=4.86$]. This suggests that the rats' performance changed during the acquisition and that this change in performance was different among the groups ($p<0.001$) (Fig. 2). The rats in the sulfite-treated group showed less progress in the selection of the correct choices compared to the control animals from the 1st to

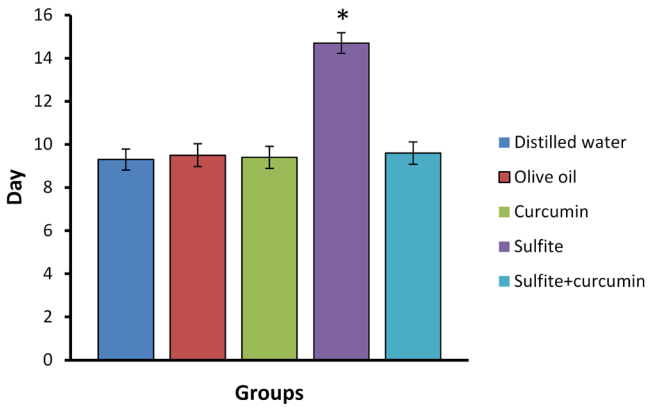

Fig. 1. Mean±SD of the total time required for reaching the average criteria of 80% correct choices. *$p<0.001$, Sulfite-treated *vs.* (sulfite+curcumin) or (control).

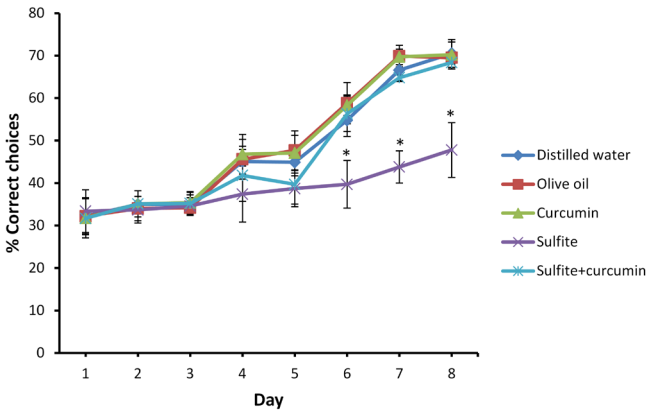

Fig. 2. Mean±SD of the percentage of the correct choices during the acquisition session. *$p<0.001$, Sulfite-treated *vs.* (sulfite+curcumin) or (control).

the 8th day (Fig. 2). The score of the correct choices was increased in the rats of the sulfite+curcumin group in comparison to the sulfite-treated animals (Fig. 2).

Performance on Day 8 was further analyzed within the repeated measures ANOVA framework to assess the group differences in learning. The study results revealed a significant difference among different groups regarding the percentage of the correct choices at this time point [p<0.001), F (4, 45) =72.75], Furthermore, in comparison to the control groups, the sulfite group showed a significant reduction in the percentage of the correct choices (p<0.001). Nevertheless, no significant difference was found between the sulfite+curcumin group in comparison to the control groups (Table 1). This demonstrated that concomitant treatment of curcumin during sulfite consumption prevented the reduction of scores of the correct choices in the acquisition session.

Reference memory errors during the acquisition

A significant effect was observed for [p<0.001), F (7,315) =19.23], Group [p<0.001), F (4, 45) =4.45], and the Day by Group interaction [p<0.001), F (28,315) =4.17]. This suggests that the RME during the acquisition phase changed with the days of training and these changes were different among the study groups (Fig. 3). The rats in the sulfite-treated group showed more reference memory errors compared to the control animals from the 1st to the 8th day (Fig. 3). Fewer errors were observed in evaluation of the reference memory in the rats of sulfite+curcumin group in comparison to the sulfite-treated animals (Fig. 3).

RME on the 8th day of the acquisition session were analyzed to assess the group differences in learning. A significant difference was found among different groups regarding the number of reference memory errors at this time point [p<0.001), F (4, 45) =51.85]. The study results revealed significantly more reference memory errors in the sulfite group on day 8 compared to the control groups (p<0.001). Nonetheless, no significant difference was found between the sulfite+curcumin group and the control groups (Table 1). This demonstrated that concomitant treatment of curcumin during sulfite consumption caused fewer errors during evaluation of the reference memory in the acquisition session.

Working memory errors during the acquisition

A two-way repeated measures ANOVA was performed with the training day (Day) as within-subjects factor and the experimental group (Group) as between-subjects factor. A significant effect was observed for [p<0.001), F (7,315) =18.72], Group [p<0.001), F (4, 45) =33.86], and the Day by Group interaction [p<0.001), F (28,315) =5.71] (Fig. 4). The rats in the sulfite-treated group showed more working memory errors compared to the control animals from the 1st to the 8th day (Fig. 4). Fewer errors were observed in evaluation of the working memory in the rats of sulfite+curcumin group in comparison to the sulfite-treated animals (Fig. 4).

WME on day 8 were analyzed to assess the group differences in learning. A significant difference was found among different groups regarding the number of WME [p<0.001), F (4, 45) =19.81].

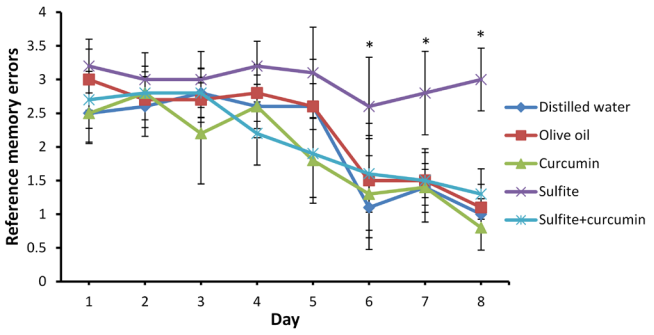

Fig. 3. Mean±SD of the number of reference memory errors during the acquisition session. *p<0.001, Sulfite-treated *vs.* (sulfite+curcumin) or (control).

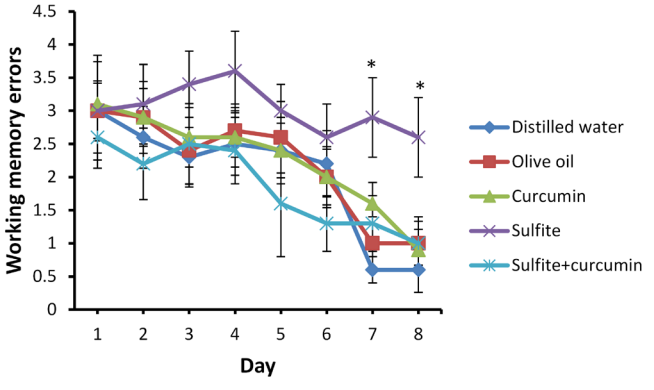

Fig. 4. Mean±SD of the working memory errors during the acquisition session. *p<0.001, Sulfite-treated *vs.* (sulfite+curcumin) or (control).

Table 1. Mean±SD of the percentage of the correct choices and the number of the reference memory errors (RME) and working memory errors (WME) on 8th day of the acquisition session in the rats receiving distilled water, olive oil, curcumin, and sodium metabisulfite with or without curcumin treatment

Groups	Correct choices	RME	WME
Distilled water	70.5±3.2	1.0±0.4	0.6±0.7
Olive oil	69.0±1.5	1.1±0.7	1.0±0.8
Curcumin	70.2±3.0	0.8±0.6	0.9±0.7
Sulfite	47.8±6.4*	3.0±0.9*	2.6±1.5*
Sulfite+curcumin	68.4±1.5	1.3±0.6	1.0±0.6

*p< 0.001, Sulfite vs. all other groups.

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Moreover, the sulfite group showed significantly more WME on the 8th day in comparison to the other groups ($p<0.001$). No significant difference was found between the sulfite+curcumin group and the control groups (Table 1). This demonstrated that concomitant treatment of curcumin during sulfite consumption caused fewer errors during evaluation of the working memory in the acquisition session.

Correct choices during the retention

A one-way ANOVA was used to analyze the percentage of the correct choices during the retention session. A significant difference was found among the study groups regarding the percentage of correct choices [$p<0.001$), $F (4, 45) =37.80$] (Fig. 5). Furthermore, the sulfite group revealed a significant reduction in the percentage of the correct choices compared to the control groups ($p<0.001$). Nevertheless, no significant difference was found between the sulfite+curcumin group and the control groups (Fig. 5). This demonstrated that concomitant treatment of curcumin during sulfite consumption prevented the reduction of scores of the correct choices in the retention session.

Reference memory errors and working memory errors during the retention

A significant difference was observed among the groups regarding the number of reference memory errors [$p<0.001$), $F (4, 45) =38.00$] and the number of working memory errors [$p<0.001$), $F (4,45) =44.85$]. Besides, in comparison to the other groups, the sulfite group showed more RME and WME during the retention testing ($p<0.001$) (Fig. 6, 7). No significant difference was found between the sulfite+curcumin group and the control groups. This demonstrated that concomitant treatment of curcumin during sulfite consumption caused fewer errors during evaluation of the reference and working memories in the retention session (Fig. 6, 7).

DISCUSSION

The first stage of the present study showed the effects of sodium metabisulfite as a preservative on the learning and memory in the rats subjected to an eight-armed radial maze task. In the current study, sodium metabisulfite was found to impair the learning of the task in the eight-armed radial maze. In radial arm maze, sulfite exposure was associated with a decline in the correct choices as well as a significant increase in the reference and working memory errors. These results suggest that sodium metabisulfite causes learning and memory changes in rats. These changes may be due to the impaired cognitive function resulting from sulfite toxicity in the brain. This finding agrees with the previous studies reporting the toxic effects of ingested sulfite on the nervous system. For instance, sulfite oxidase-

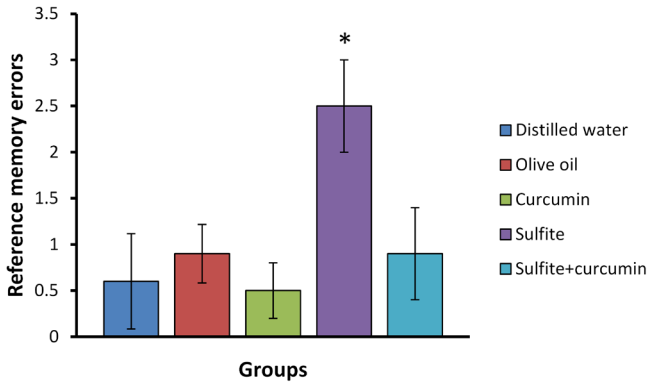

Fig. 6. Comparison of the mean±SD of the reference memory errors during the retention session. *p<0.001, Sulfite-treated *vs.* (sulfite+curcumin) or (control).

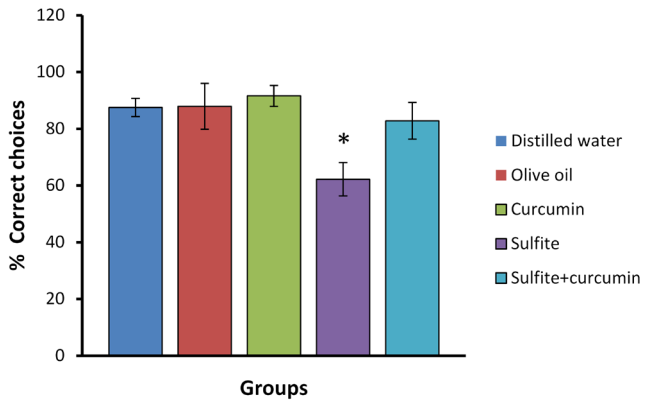

Fig. 5. Comparison of the mean±SD of the percentage of the correct choices during the retention session. *p<0.001, Sulfite-treated *vs.* (sulfite+curcumin) or (control).

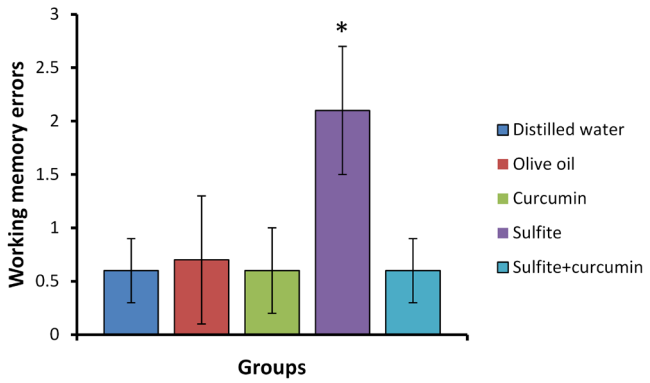

Fig. 7. Comparison of the mean ± SD of the working memory errors during the retention session. *p<0.001, Sulfite-treated *vs.* (sulfite+curcumin) or (control).

deficient rats treated with sulfite showed an impairment of active avoidance learning [16]. Moreover, treating the rats with sulfite was found to cause cell death in the rats' neuronal cell line [18]. A stereological study has recently shown that sodium metabisulfite at the same dose as the present study (25 mg/kg) decreased the total number of the pyramidal neurons in three subdivisions of the rat hippocampus [15]. Although there are many reports of the toxic effects of sulfite on the nervous system, the mechanism of these effects on the brain cells remains poorly understood. A proposed mechanism that can describe the toxicity of sulfite is that oxidative stress causes mitochondrial damage. It has been shown that sulfite causes impairment in mitochondrial membrane integrity and also decreases the ATP production [33]. Cysteine-S-sulfate is a metabolite of sulfite which is structurally similar to excitotoxic amino acids, such as glutamate, and may also play an important role in sulfite toxicity. Indeed, a high affinity uptake system in the brain has been shown for excitotoxic amino acids, such as glutamate and aspartate, but not for cysteine-S-sulfate [41]. Another possible mechanism is that sulfur and oxygen-centered free radicals may be responsible for the observed detrimental effects of sulfite [3, 34-36]. Sulfite also causes toxic effects on many cellular components, such as DNA [37]. Sodium metabisulfite also has effects on the motor function. Our unpublished data showed that the performance of the rats in the rotarod evaluation was disturbed after exposure to sulfite.

Another finding of this study indicated that curcumin prevented sulfite-induced learning and memory changes in rats. This is the first study demonstrating that curcumin has a protective role in learning and memory in the rats subjected to an eight-armed radial maze task after exposure to sodium metabisulfite. This finding is in line with the previous studies reporting the neuroprotective effects of curcumin. In one of the earlier studies, beta-amyloid infusion induced spatial memory deficits in the Morris water maze and post-synaptic density protein-95 losses were prevented by curcumin and curcumin reduced beta-amyloid deposition [38]. Yet, another study showed that curcumin prevented lead-induced memory deficit in rats [39]. Curcumin can attenuate the cognitive impairment in diabetic rats [40]. Thus, curcumin may prevent the oxidative stress in hippocampal neurons and, consequently, may improve the synaptic plasticity [22, 40]. It is suggested that curcumin can act as a neuroprotectant against the neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases [20]. In addition, it has been reported that curcumin has anti apoptotic effects on the neurons [42]. Also, several studies have demonstrated that curcumin has anti-inflammatory and antioxidants properties due to its ability to modulate the regulation of the inflammatory cytokines, such as interlukin-6, tumor necrosis factors-α, and cyclooxygenase-2 [19, 22]. Our previous studies demonstrated that curcumine with the same dose as the present study could protect the neurons from damage [22, 23].

The protective effects of curcumin against sulfite in the present study can be explained by its anti-inflammatory, antioxidant, and anti-apoptotic effects reported in the previous studies.

The study results demonstrated that sulfite-exposure was associated with impaired learning and memory in rats. It was also revealed that curcumin played a protective role in learning and memory in the rats after exposure to sulfite.

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