Potential Neuroprotective Effect of Nanomicelle Curcumin on Learning and Memory Functions Following Subacute Exposure to Bisphenol a in Adult Male Rats

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Abstract

Objective

Bisphenol A (BPA) is an endocrine-disrupting chemical that widely used in plastics production. It can influence on the brain tissue. Curcumin has a strong protective activity against brain disorders. The purpose of this study was to evaluate the protective effect of nanomicelle curcumin (NmCur) on BPA-induced learning and memory disorders in rats.

Material and methods

In this study, after determining the dose of BPA, rats were randomly divided into 8 groups (8 rats in each group); sesame oil, dextrose 5%, sesame oil + dextrose 5%, NmCur (50 mg/kg), BPA (50 mg/kg), and 50 mg/kg BPA plus 10, 25, or 50 mg/kg NmCur, respectively. All materials administered via gavage. Behavioral tests were estimated by shuttle-box, open-field, and Morris water maze devices. Then, stress oxidative, pro-inflammatory cytokines, oxidative stress-scavenging enzymes levels, as well as expression of MAPK proteins, glutamate receptors, and memory-related proteins were determined in the hippocampus and cortex tissues.

Results

BPA significantly increased expression of ROS, MDA, TNF-α, IL-6, IL-1β, SOD, GST, p-P38, and p-JNK; however, considerably decreased GSH, GPx, GR, CAT, p-AKT, p-ERK1/2 levels. In addition, it down regulated expression of p-NR1, p-NR2A, p-NR2B, p-GluA1, BDNF, and p-CREB in rat cortex and hippocampus tissues. BPA significantly also changed behavioral activity. Conversely, BPA (50 mg/kg) plus NmCur (25 and 50 mg/kg) significantly reversed all BPA-induced adverse effects.

Conclusion

The results of this study support that nanomicelle curcumin exhibited preventive effects against neurotoxicity and learning and memory impairment induced by subacute exposure to bisphenol A.

1. Introduction

Bisphenol A (4, 4-Isopropylidene-2-diphenol/BPA), is as one of non-steroid endocrine-disrupting chemicals that contains of two hydroxyphenyl groups [1]. Annually, more than 6 billion pounds of BPA produced in the world for construction of polycarbonate plastics and epoxy resins, such as food containers, water pipes, baby feeding, beverage bottles, dental sealants, eyeglass lenses, dyes, and paper products [2,3]. The ester bonds between BPA molecules in high-temperature and acidic or basic conditions undergo hydrolysis and monomers migrate into food (the main source of exposure), water, atmosphere, and environment. For instance, the rate of separation of BPA monomers from plastic containers into water was observed between 0.2 and 0.8 ng/h that if the water temperature rises, the separation speed of BPA monomers from containers will increase dramatically 55 times [4]. It has been stated that the BPA intake

through food products and packaging is between 0.48 and 4.8 μg/kg/day [5]. The daily oral exposure to BPA that is expressed in the form of the no-observed-adverse-effect level (NOAEL) and reference safe daily limit is 50 mg/kg and 50 μg/kg, respectively [6,7].

BPA considered as an industrial chemical material, which structurally is similar to 17-β-estradiol (E2). So, it can be considered as a synthetic xenoestrogen and weakly effect on classical nuclear estrogen receptor α (ERα and ERβ) [5, 8]. In addition, due to its lipophilic property, it can be absorbed following ingestion and has moderate bioaccumulation ability in almost every tissue with the highest concentration of fatty acids, especially adipose, liver, and brain tissues [5, 8–13]. BPA metabolized through hydroxylation, glucuronidation, and sulfuration reactions in the liver, testes, and brain tissues, which quickly converts to highly water soluble metabolites and excretes in the kidney, urine, intestine, and feces [14, 15]. In outside the liver, oxidation of BPA via a microsomal cytochrome P450 enzyme complex system leads to production of a highly reactive intermediate, BA34Q [16]. Therefore, BPA exposure can lead to numerous adverse effects, including cardiotoxicity [14], hepatotoxicity, immune-toxicity, genotoxicity, mutagenicity, carcinogenicity, and neurotoxicity [17–20].

Neuron cells in the adult brain do not have the power of reproduce except in two specific zones, including the subventricular zone (SVZ) of the lateral ventricle (LV) and in the subgranular zone (SGZ) of the dentate gyrus (DG), which are particularly vulnerable to different types of injuries and diseases [21, 22]. On the other words, there are progenitor cells, which constantly are dividing, in the SGZ of the DG region that could be generated new interneurons and granule cells [23, 24]. The neuronal networks, synaptic plasticity, and newly generated neurons in hippocampal CA1 pyramidal neurons, containing ERβ, have major role in function of learning and memory and novelty detection, so that, any damage in these networks can affect the cognitive performance [25, 26]. BPA can easily pass across the blood brain barrier (BBB), inhibits the proliferation and differentiation of neural and oligodendrocyte progenitor cells, and disrupts the DG formation and the myelination process in the rat hippocampal and prefrontal region [27–29], leading to neurotoxicity [30] in different life stages and species [31].

In fact, it is noteworthy that the most important factor of induction of toxicity associated with BPA attributed to production of reactive oxygen species (ROS) and oxidative stress [32] in the differential tissues, such as heart [14], liver, epididymal sperm [33, 14], and especially brain [34]. Because in the brain, the neural cells have low oxygen storage and high capacity for ROS production and lipid peroxidation, which could affect on neurogenesis activity and dendritic structures in the hippocampal formation, leading to alteration function of learning and memory [35]. In addition to ROS, inflammation as an important factor in many diseases accelerated cognitive deficit. Two important structures for memory, attention, emotion, and perception functions are the hippocampus and basal ganglia, which include many enzymes involved in inflammatory processes [36]. Pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, provoke the production of free radicals [37, 38], causes neuro-inflammation, and impairs learning and memory performance [39]. Nevertheless, the different types of natural ROS-scavenging enzymes are superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). In addition, GSH (reduced form) is a biologically important intracellular thiol and free radical scavenger activity,

which can be reproduced from the oxidized form, glutathione disulfide (GSSG), through glutathione reductase (GR) [40, 41].

So far, many studies have been done in this regard. For example, it has already been demonstrated that BPA exposure reduces the activity of detoxifying enzymes (like SOD, GPx, and CAT) that lead to an increase production of oxidative stress, ROS, and MDA, as an important indicator of lipid peroxidation, levels [42] and a decrease GSH content [43, 44]. These changes in the brain result in necrosis, apoptosis, and cancer [45], especially in cerebellum [9], hypothalamus [10], cortex, and hippocampus tissues [11–13], hampering the proliferation of neural progenitor cells and obliging neural cell death [46]. In addition, other similar studies have shown that BPA exposure (40 μg/kg/day) for 8 weeks also impaired the spatial learning and memory in the male mice [47] by altering the processes of neural plasticity and following inhibits the formation of new memories in the brain of male adult mice [6]. Moreover, the administration of BPA at perinatal period can lead to spatial learning and memory acquisition deterioration [48, 49]. Another study displayed that acute administration of BPA at a dose of 0.04 mg/kg for 2 h impaired memory of visual and spatial information and decreased the density of dendritic spine in pyramidal cells of the hippocampus CA1 region in the adult brain [6].

Apoptosis is programmed cell death that if left unchecked, they can lead to many disorders in different body's cells and tissues [50]. The increasing evidence indicates that various mechanisms, such as Ca2+-induced ROS generation, MAPK activation (such as p-JNK and p-P38), and NF-κB translocation led to neuronal damage induced by BPA in hippocampal neuronal cells [51–53]. The ROS and oxidative stress could also motivate both astrocytes and microglial cells, as well as NF-*κ*B that stimulate the secretion of pro-inflammatory cytokines (including IL-1β, IL-6, TNF-α, TGF-β and NO) and provoke the production of free radicals and amyloid-β (Aβ) protein [37, 38]. The Aβ plaques accumulation could also motivate the microglia, astrocyte, and monocyte cells to produce neurotoxic compounds like glutamate [39]. BPA-related oxidative stress decreased expression of glutamate receptors (NMDA and AMPA) and suppressed activation of memory-related proteins (CREB and BDNF) [52, 54–56] in the hippocampus tissue, leading to an impairment of learning and memory in adult male rats [57, 32]. Thus, it impaired the structures and functions of many enzymes and proteins involved in cell signaling, resulting in deterioration of neurogenesis, synaptic plasticity, and learning and memory in male and female animals [58–60].

In support of the view that antioxidants reduce oxidative stress, ROS, and pro-inflammatory cytokines, various studies have been conducted [61–63]. Several antioxidant agents, including N-acetylcysteine [30], vitamin C [44], and melatonin [43] have decreased BPA-induced oxidative stress and cognitive impairments [64]. Thus, the use of antioxidants, which can pass from BBB, can have therapeutic applications against BPA-associated oxidative stress and pro-inflammatory cytokines-induced destructions. Based on this, many researches have been focused in recent decades to discover the new therapeutic agents with better efficacy in order to reduce or limit the neuronal damage caused by the harmful factors and enhance hippocampal neurogenesis and cognitive function [65, 66]. One of these approaches is the use of agent with multi-modal interaction capability, such as anti-oxidant, anti-inflammatory, anti-apoptotic, and neuroprotective properties [67].

From the distant past until now, the use of medicinal plants has various applications by many people in the world. One of the most popular herbal medicines is *Curcuma*, which to date has been identified more than 100 species, including *Curcuma longa* (also called *Curcuma domestica*), *Curcuma aromatica*, and *Curcuma xanthorrhiza* [68, 69]. It is widely cultivated in tropical and sub-tropical regions of the world, especially in Asian countries, such as India, China, Indonesia, Japan, Taiwan, and Thailand [70, 71], that used as drug, spice, and food products. Curcumin (diferuloylmethane), in Farsi called Zardchoobeh [72], is main hydrophobic, polyphenolic, and flavonoidic bioactive component in the form of pure crystals and bright yellow pigment. It extracted from the dried rhizomes of the *Curcuma longa* Linn (turmeric), belonging to the ginger family Zingiberaceae [73, 74]. Based on several clinical trials studies, it was discovered that the recommended, safe, acceptable, and tolerable daily oral intake dose of curcumin with the optimal therapeutic properties is up to 12 g/day [75, 76]. Due to its biological compatibility and without severe side effects on natural cells and tissues, over the past few decades, considerable attention of many researchers have been paid to curcumin and its derivatives. In addition to items listed above, they showed diversity of biological and pharmacological activities viz., the anti-oxidant, anti-inflammatory, anti-apoptosis, etc. activities in both in vitro and in vivo studies [74, 77]. These curcumin effects have been ascribed to the fundamental features in its structure [78]. In the other words, the existence of electron donating polar substituents, such as phenolic and methoxy groups, improved the potency of the synthesized compounds in all their properties [79].

Past studies have shown that The supplementation of curcumin improved memory and learning function in mice and rats [80–82]. Moreover, curcumin administration can be led to lowering inflammatory cytokines, such as TNF-α and IL-1β, IL-6, and IL-8 via inhibition of TLR4, NF-kB, and MAPK signaling pathway [83, 84, 75]. In similar study, curcumin treatment was significantly attenuated TNF-α and apoptosis by suppression of the p38 and JNK MAPK signaling pathway in chronic colitis-affected rats [85], mice liver [86], and different cell lines [87, 88]. Administration of curcumin at a dose of 1 g/d for 8 weeks also improved antioxidant capacity, while decreased lipid peroxidation in 117 adults with metabolic syndrome disorders [89]. Other similar studies have conducted that curcumin administration considerably improved GSH content and antioxidant enzyme activities, including SOD, GPx, and CAT, but it declined MDA concentration in rat's kidney treated with gentamicin, cyclosporine, and methotrexate [90–92].

Despite of all the above-declared benefits, the use of curcumin has limitations owing to its extremely low water solubility, low intestinal and cellular absorption, poor oral bioavailability, rapid metabolism and elimination, rapid degradation in alkaline pH environment, and sensitivity to metal ions, heat and light [14, 93, 77]. Based on these problems, curcumin in most studies may not be able to achieve important results. Accordingly, in recent decades, numerous approaches, e.g. the use of the nanotechnology-based different drug delivery systems and multiple structural modification strategies to overcome these limitations have been done [14, 94]. The use of nanotechnology makes compounds in various shapes and sizes [95]. Diverse types of delivery systems via a variety of natural or synthetic compounds, including phytosomes, liposomes, polymers, lipids, proteins, conjugates, cyclodextrins, micelles, dendrimers, and nanoparticles have been also used [96–98]. For instance, putting curcumin inside of the micelles can augment

bioavailability up to 185 times, without inducing any adverse effects in healthy persons [99]. In addition, the structural modification approaches have been referred to change of the hydrogen donor group, the β-diketone moiety, the phenyl rings, and the alternative groups on them, resulting in production of curcumin derivatives and/or analogues [96–98]. So that, some of them have amended the water solubility, stability, bioavailability, cellular absorption, efficacy, and prolonged circulation and retention time of curcumin [96–98] in both in vitro and in vivo studies. Based on these changes, numerous commercial formulations of curcumin, such as curcumin nanoparticles, curcumin in lecithin phosphatidylcholine carrier, and solid lipid curcumin nanoparticles have made [100].

In this study, a commercial formulation of nanomicelles curcumin (NmCur) was used, which each soft gel capsules contains curcumin, demethoxycurcumin (DMC), and bisdemethoxycurcumin (BDMC). One of the most important points that can be cited is that NmCur has the constant formulation in condition of simulated gastric and intestinal fluid (SGF and SIF) and released after at least 4 h. It was also proved that in stomach, the NmCur is entirely dissolved in acidic stomach environment (pH 1–2) and nanomicelles remained stable up to 6 h, transferred to the intestine (pH 6), and finally absorbed by different mechanisms [101]. In one study observed that NmCur formulation displayed better absorption and stability, excellent permeation and cellular uptake, and better anti-inflammatory activity than free curcumin in both in vivo and in vitro studies [101]. Therefore, it was observed that the commercialized NmCur with name of SinaCurcumin, which prepared by Exir Nano Sina Company (Tehran, Iran), has better oral solubility, bioavailability, and stability as compared to free curcumin and two other commercial products [101].

Based on the above points, the purpose of this evaluation was to estimate the protective effects of nanomicelle curcumin, as a curcumin derivative, on subacute neurotoxicity and learning and memory impairment induced by BPA in the hippocampus and cortex regions in an experimental model.

2. Materials And Methods

2.1 Chemicals

The analytical reagent grade BPA (CAS # 80-05-7) with purity > 90% was obtained from SRL, Mumbai, India. A commercial formulation of nanomicelles curcuminoid (NmCur) was used, which is called SinaCurcumin®, introducing by Exir Nano Sina Company in Tehran, Iran (IRC: 1228225765).. Ketamine and xylazine purchased from Merck (Rotexmeica, Germany). L-Glutathione reduced (GSH) ≥ 98.0% and SOD taken from Sigma-Aldrich (St Louis, Missouri). Other chemicals such as ethanol, methanol, n-butanol, phosphoric acid, potassium chloride, thiobarbituric acid (TBA), phosphate buffered saline (PBS), 5, 50-dithiobis (2-nitrobenzoic acid) (DTNB), trichloroacetic acid (TCA), etc. were purchased in very high purities from Merck (Germany).

2.2 Animals and treatment

The number of 96 adult male Wistar rats with the weight about 220–250 g (two-month-old) were provided by the Animal Center, School of Pharmacy, Mashhad University of Medical Sciences. Animals were preserved in standard conditions with light/dark cycle of 12 hours, at the temperature of 23 ± 1ºC, and free access to water and food throughout all stages of the experiment. All the experimental protocols were accepted by Ethical Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1394.281) and this experiment was conducted at the Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran [14]. In this study, the basis of work was divided into two parts, including the pilot (to determine the dose of BPA) and the main experimental (to determine the protective effect of NmCur on neurotoxicity and learning and memory impairment induced by BPA) studies.

2.2.1 Pilot study

In the pilot study, rats were randomly divided into 4 groups (each group 8 rats): control group received sesame oil (Sea) (vehicle of BPA) and experimental groups received 10, 25, and 50 mg/kg BPA with Sea. BPA and Sea gavaged once a day, 7 days per week for 4 weeks. After 4 weeks, the rats anaesthetized by intraperitoneal (IP) injection with ketamine/xylazine (60 and 6 mg/kg, respectively) and the brain tissues removed and maintained in -80 ºC. Then, biochemical changes, such as ROS, MDA, and GSH, as well as pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) levels were assessed in hippocampus and cortex tissues (Fig. 1).

2.2.2 Experimental study

According to pilot study in this study, it was proven that a dose of 50 mg of BPA has toxic effects, which this dose was used to continue working. In the experimental study, animals were randomly divided into 8 groups (8 rats in each group), including (1) sesame oil (control 1 group, vehicle of BPA) (Sea), (2) dextrose 5% (control 2 group) (Dex), (3) Sea + Dex (control 3 group), (4) NmCur (50 mg/kg), (5) BPA (50 mg/kg), and (6, 7, and 8) 50 mg/kg BPA plus 10, 25, or 50 mg/kg NmCur, respectively. BPA and NmCur were dissolved in Sea and Dex, respectively. The BPA and NmCur administered via gavage once a day, 7 times per week, for 4 weeks. BPA was administrated an hour following NmCur administration. At the end of 4 weeks' treatment, the hippocampus and cortex tissues were removed and used for determination of ROS level, MDA concentration, GSH content, and pro-inflammatory cytokines, as well as expression of phosphorus types of p38, JNK, AKT, ERK1/2, NMDA, AMPA, BDNF, and CREB proteins. Also, biochemical analysis of SOD, CAT, GST, GR, and GPx enzymatic activities were evaluated in these tissues (Fig. 2).

2.3 Biochemical assays

2.3.1 Measurement of ROS concentration in the hippocampus and cortex tissues

The determination of the ROS level was done according to Muhammad *et al.* (2017) [102] method, but with a slight change on the operation. This method of measuring ROS was mainly based on the

generation of 2'7' dichlorofluorescein (DCF) from the oxidation of 2'7'-dichlorodihydrofluorescein diacetate (DCFH-DA). Briefly, each of the homogenized tissues was separately diluted with a ratio of 1:20 in ice-cold Lock's buffer, until the final concentration of each tissue was adjusted to 2.5 mg tissue/500 µl. The reaction mixture contained 1 ml the Lock's buffer mixture with pH 7.4, 0.2 mL homogenates from hippocampal or cortical tissue, and 10 mL DCFH-DA (5 mM). Then, the mixture was covered and incubated for 15 min at room temperature to the formation of form fluorescent DCF from DCFH-DA, which was assessed through a microplate reader at an excitation of 484 nm and an emission of 530 nm. Initially, in the absence of homogenate, a blank parallel was used to calculation of DCF formation, as background fluorescence. Results of ROS levels were expressed as DCF formed (pmol)/min/amount of protein (mg) in each of the homogenized tissues.

2.3.2 Measurement of MDA concentration in the hippocampus and cortex tissues

The Fernandez *et al*. (1997) method was used to measure the MDA concentration [15]. In summary, after 4 weeks, the different regions of the brain mentioned above were separated and cleaned in normal saline solution. The MDA concentration, as lipid peroxidation index and an indicator of oxidative stress, was evaluated. Each of the different sections of brain was separately homogenized (POLYTRON-PT 10–35, Kinematica, Switzerland) for 2 min at 4°C in 1.15% potassium chloride (KCl) for making a 10% homogenate. After that, 500 µL of each sample was added to 3 ml phosphoric acid (1%) and 1 ml TBA (6%) and then heated in a boiling water bath for 45 min. Reaction of MDA with TBA creates a pink color. The pink color complex is measured spectrophotometrically at 532 nm, which showed equivalent to the concentration of MDA in sample.

2.3.3 Measurement of GSH content in the hippocampus and cortex tissues

The GSH content were evaluated by the Moron *et al.* (1979) method [16]. Briefly, after 4 weeks of treatment, different sections of the brain listed above were removed and cleaned in normal saline solution. These sections were homogenized to provide 10% homogenate in ice-cold PBS with pH 7.4. Then, l300 µl homogenated tissue plus 300 µl TCA (10% w/v) were vortexed for 1 min and then centrifuged at 2500 g for 10 min. Supernatant was separated and added 2 ml PBS with pH 8.0 and 500 µl DTNB. The DTNB created a yellow-colored TNB, because of mixing with sulfhydryl group of GSH. After 10 min, mixed compounds were transferred to glass test tube and the absorbance was read at 412 nm by a spectrophotometer (Jenway 6105 UV/VIS, UK).

2.3.4 Measurement of TNF-α, IL-6, and IL-1β concentrations in the hippocampus and cortex tissues

Summary, the hippocampal and cortical tissues were homogenized by ultrasound and then centrifuged at 2000 g at 4°C for 10 min. The TNF-α, IL-6, and Il-1β levels in the supernatants were determined by ELISA kits (R&D Systems, Minneapolis, MN, USA) in accordance with the manufacturer's guidelines [103].

2.3.5 Determination of SOD enzyme activity in the hippocampus and cortex tissues

The SOD activity was assessed via the method of Kakkar *et al*. (1984) [104]. In summary, tissues were homogenized in 20 volumes of ice-cold 10 mM PBS with pH 8.0 and centrifuged at 10.000 g for 10 min at 4ºC. After that, supernatants were separated and added to 0.4 mM Xanthine, 0.24 mM nitroblue tetrazolium, and 0.049 U/mL xanthine oxidase and then incubated for 20 min at 37ºC. The reaction was stopped by adding 69 mM sodium dodecyl sulfate. Absorbance was measured at 560 nm. The SOD enzyme activity is expressed as unit/mg protein, so that one unit of SOD activity is described as the amount of enzyme that led to %50 inhibition of nitro bluetetrazolium (NBT) reduction.

2.3.6 Determination of GST enzyme activity in the hippocampus and cortex tissues

The GST activity was determined through the method of Lowry *et al*. (1951) [105]. In briefly, the reaction mixture was consisting of 2.75 ml PBS (0.1 M, pH 6.5), 0.1 ml GSH (1.0 mM), 0.05 ml CDNB (1.0 mM), and 0.1 ml renal PMS (10% w/v) in a total volume of 3.0 ml. At the end, the absorbance was read at 340 nm and enzyme activity assessed as nmol CDNB conjugate formed/min/mg protein using a molar extinction coefficient of 9.6 $\times 10^3$/Mcm.

2.3.7 Determination of CAT enzyme activity in the hippocampus and cortex tissues

The CAT activity was evaluated by the modified method of Aebi (1984) [106] and Kawamura *et al*. (1994) [107]. In summary, tissues were homogenized with 20 volumes of ice-cold RIPA buffer (0.1 M PBS with pH 7.4 containing of 5 mM EDTA, 0.01% digitonin, and 0.25% sodium cholate) and centrifuged at 10,000 g for 30 min at 4ºC. A phosphate buffer (50 mM with pH 7.0 containing of EDTA (5 mM) and H_2O_2 (10 mM) pre-incubated for 10 min at 37ºC) was added to the supernatant and the decomposition of H_2O_2 directly assayed by measuring the decrease in absorbance at 240 nm for 2 min. The CAT (Wako Chemical Co.) from bovine liver was used as a standard. Change in the absorbance of 0.01 as unit/min was defined as one unit of CAT.

2.3.8 Determination of GPx enzyme activity in the hippocampus and cortex tissues

The GPx activity was estimated according to the technique of Kabuto *et al*. (2003) [108]. In summary, the tissues were first washed with a cold isotonic normal saline solution. The reaction mixture was consisting of 1.44 ml potassium phosphate buffer (0.1 M, pH 7.4), 0.1 ml EDTA (0.5 mM), 0.1 ml sodium azide (NaN_3) (1.0 mM), 0.05 ml GPx (1.0 EU/ml), 0.1 ml GSH (1.0 mM), 0.1 ml NADPH (0.1 mM), 0.1 ml H_2O_2 (0.019 M), and 0.025 ml renal PMS (10% w/v) in a total volume of 2.0 ml. All stages were done at 22–25 ºC. Finally, the absorbance at 340 nm was registered above a period of 5 min. The enzyme activity was

calculated as nmol NADPH oxidized/min/mg protein using a molar extinction coefficient of 6.22 $\times 10^3$/Mcm.

2.3.9 Determination of GR enzyme activity in the hippocampus and cortex tissues

The GR activity was evaluated through the method of Carlberg and Mannervik (1985) [109]. In first, the reaction mixture was consisting of 1.7 ml sodium phosphate buffer (0.1 M, pH 7.6), 0.1 ml EDTA (0.5 mM), 0.05 ml oxidized glutathione (1 mM), 0.1 ml NADPH (0.1 mM), and 0.05 ml renal PMS (10% w/v) in a complete capacity of 2.0 ml. Enzyme activity was determined by measuring the vanishing of NADPH at 340 nm via spectrophotometer (model 4001/4) and assessed as nmol NADPH oxidized/min/mg protein using molar extinction coefficient of 6.22 $\times 10^3$/Mcm.

2.4 Behavioral studies

In this study, the effect of BPA on spatial and fear learning and memory evaluated in Morris water maze (MWM) test and passive avoidance training test (PAT) or shuttle-box test, respectively. In addition, its effect on locomotor activity was assessed in the free exploration open-field test.

2.4.1 Morris water maze (MVM) test

This test is used to examine the spatial learning and memory. The MWM analysis was described and performed according to Vahdati Hassani *et al.* (2020) with a few modifications. This apparatus is contained of a circular pool, made of black metal sheets, at a size of 136 × 60 cm (diameter circle × height), which was divided into four equal quadrants and labeled north (N), south (S), east (E), and west (W). In addition, it was filled with water (22 ± 1°C) to a depth of 25 cm. A black Plexiglas platform with a diameter of 13 cm is installed 2 cm below the water level in the center of one of the quadrants. Some fixed visual cues that can be seen by rat were hung on the walls around the device. The testing room was dimmed and the room temperature was completely controlled and kept at 22 ± 1°C. A computer-connected video camera was installed on top of the device to scout the position and analyze the collected data of each rat [4].

2.4.1.1 Acquisition test

During the training trials period (day 24–28), in the acquisition test protocol, each rat performed four tests per block per day for five consecutive days. Rats were let to swim for 60 sec to discover the hidden escape platform and after finding the platform, rats were stayed on it for 15 sec; if a rat could not detect the platform for 60 sec, it was manually located on the platform for 15 sec. This 15 sec of resting time is to identify the environment. After the end of each test, the rat was dried with towel, returned to its holding cage, and immediately placed back to the colony room. The escape latency (sec) to detect the hidden platform, the escape pathlength or the total swimming distance (cm, distance traveled to the hidden

platform, as the basic motor function), and the swim speed (cm/sec) were automatically recorded by the mounted video camera on top of the device [4].

2.4.1.2 Probe test

On the twenty-ninth day of treatment (the sixth day of the test or 24 h after the last training test), the probe test comprising of four trials per block was done. After removing the hidden platform, the rat performed to only one search trial for 60 sec to assess the spatial memory. The starting position for each rat was such that the rat was accidentally immersed in the water, toward the wall, in the center of one of the non-platform quadrants. The total time spent for detecting the hidden platform, as the escape latency, was recorded that was inversely related to spatial learning and memory ability. The travelled distance during the probe test was also automatically recorded by the video-camera tracking software connected to a computer (Noldus EthoVision XT, Noldus Information Technology, Wageningen, Netherlands) [4]. All experimental tests were carried out in 8:00 and 16:00 to remove confounding due to time-difference effects. The number of rats was 8 for each group.

2.4.2 Passive avoidance training test (PAT)

Two days after the MVM test, the PAT was performed. Generally, the PAT evaluates two (step-down and step-through) avoidance behaviors. The PAT, which performs with the shuttle-box apparatus, is used to measure fear learning and memory in animal models of neurological disturbances to elude from a plaguesome excitation, such as a foot-shock. The PAT protocol used in this study was slightly modified according to Taherian *et al.* (2021) method [110]. In summary, this apparatus forms a box containing two equal separate compartments (a dark and a light chambers) that made of transparent acrylic resin epoxy plexiglass sheet panels in the size of 20 cm × 20 cm × 30 cm (length × width × height). These boxes are connected through a sliding (guillotine) door in the size of 7 cm × 9 cm that can be raised up to 10 cm. A parallel stainless steel grid, at a size of 2.5 mm diameter and 1 cm intervals, connected to a shock simulator, which can produce the electrical signals and transmit to grid, located in the floor of the dark chamber. This test has three steps, including habituation, training (acquisition trial), and retention stages.

2.4.2.1 Habituation phase

In the first step, in the day 31, the rat for habituate with the device was gently placed in the light chamber and following that a 10-second delay, the sliding door was raised. The rat was let to enter the dark chamber and stayed in the experimental rooms for 10 min. After 10 min, the rat was immediately comeback to its home cage. Then, 30 min after the first stage of the habituation, another habituation test was performed according to the first stage and finally the rat was immediately returned to its home cage. Rats that waited for more than 120 s to introduce into the dark box were excluded from this test.

2.4.2.2 Training phase (acquisition trial)

This step was conducted 30 min after from the second habituation trial. The procedure is as follows that rat was slowly placed in the light chamber and the middle guillotine lid was opened. The rat tends to enter

the dark chamber depending on its innate desire. After the rat completely entered the dark chamber (four paws in) (exploration time), the middle guillotine lid was closed. Next, a single electric current (intensity: 1 mA; frequency: 50 Hz; duration: 3 sec) (Borj Sanat Co., Tehran, Iran) was instantly imposed via an electrical generating apparatus to the steel grids of the dark chamber floor to induce shock to the rat's foot. Twenty seconds after foot shock, the rat was removed from the apparatus, placed back to its home cage, and immediately returned to the colony room. The maximum training phase for each rat was three times.

2.4.2.3 Retention (retrieval) test

The last stage or the memory retention phase was done 24 h after training procedure (on the thirty-two day), but the electrical shock was not delivered to the rats' foot. After placing the rat in the light box, the door was opened with a 10-second delay. Then, the interval time between rat movement behavior from light box to the dark box, which known as the step-through latency (STL) or the time latency, was recorded as an inhibitory avoidance memory. The cut-off time of this step for STL measurement for all animals that stayed in the light chamber was 300 sec or this test was ended when the rat entered to the dark box. Each rat separately performed all the behavioral steps in the same sequential order and all steps were manually carried out between 8:00 a.m. to 2:00 p.m. to remove confounding due to the negative impact of time differences. The number of rats in each group was 8. All trials were digitally recorded by a camera, which located directly above the device. The camera was connected to a computer that automatically analyzed all events (Noldus EthoVision XT, Noldus Information Technology, Wageningen, Netherlands). The boxes were cleaned with a moistened sponge with 100% ethanol and then dried with a clean towel to remove odors of the previous rat after behavioral testing each animal.

2.4.3 Open-field test

The open-field test, as a free-exploration apparatus, is performed to evaluate behavioral functions, e.g. locomotor activity, hyperactivity, and stereotypical and exploratory behaviors. In this study, the experiment was carried out to further evaluate the rat’s motor function with or without BPA treatment. The test was performed according to the method of Taherian *et al*. (2021) [110], but with a few changes. Briefly, the open-field device was prepared from white wood at a size of 45 cm × 45 cm × 45 cm (length × width × height). Each rat was located in the center of the cage and for three consecutive days, each rat was let to explore the environment for 10 min for adapting to the environment before the main test day. On the day 35, all rats were only tested once for 5 min in the device. The rat’s locomotor activity was evaluated by evaluating the number of peripheral (those adjacent to the walls), central, and total square crossings via a digital camera for 5 min and next, assessed by EthoVision 8.5. In fact, the three measures were referred to as peripheral (PL), central (CL), and total (TL) locomotor activity, respectively. All behavioral tests were manually tested between 8:00 a.m. to 2:00 p.m. After behavioral trial each animal, the open-field apparatus was cleaned via a moistened sponge with 100% ethanol and then dried with a clean towel to remove odors of the previous rat.

The rats could not see the investigator or experimenter during the all conducted behavioral tests and all data analysis were also performed using a trained observer, which blind to experimental groups.

2.5 Western blot analysis in the hippocampus and cortex tissues

Western blot assays of phosphorylation types of protein Kinase B (AKT), extracellular signal-regulated protein kinases 1 and 2 (ERK), p38-mitogen-activated protein kinase (P38), c-jun NH2 terminal kinases (JNK), N-Methyl-D-aspartic acid or N-Methyl-D-aspartate (NMDA; subunits of NR1, NR2A, and NR2B), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA; subunit of GluA1), and cAMP-response element binding protein (CREB), and non-phosphorylation type of brain-derived neurotrophic factor (BDNF) were carried out on protein extracts from hippocampus and cortex tissues. About 200 mg of tissue samples were homogenized in homogenization buffer containing of 50 mM Tris-HCL (pH 7.4), 2 mM EDTA, 2 mM EGTA, 10 mM NaF, 1 mM sodium orthovanadate (Na3VO4), 10 mM β-glycerol-phosphate, 0.2% W/V sodium deoxycholate, 1 mM phenylmethylsulfonyl fluoride (PMSF), and protease inhibitor cocktail (1% protease and phosphatase inhibitor cocktail) (Sigma, P8340) in ice and then centrifuged at 10,000 g for 10 min at 4ºC [27, 14]. The total protein content was measured from supernatant using the Bradford protein assay kit (Bio-Rad). Briefly, same amounts of proteins in supernatants (50 µg) were separated by 12% SDS-polyacrylamide gel (SDS-PAGE gel), transferred to polyvinylidene difluoride (PVDF) membranes (Millipore), and blocked with 5% skim milk or %1 BSA in Tris-buffered saline Tween 20 (TBS-Tween 20 or TBST) for 2 h at 37ºC (room temperature) to inhibit binding of non-specific proteins. Then, the PVDF membranes were incubated at 37ºC for 120 min with primary rabbit monoclonal antibodies from Cell Signaling Technology (Beverly, MA, USA) including anti-p-P38 MAPK (#4061), anti-p-JNK (#9255), anti-p-ERK1/2 (#9106), anti-p-AKT (#9271), anti-p-NMDA NR1 (#3381), anti-p-NMDA NR2A (#4206), anti-p-NMDA NR2B (#4208), anti-p-AMPA (#8084), anti-p-CREB (#9196), and anti-BDNF (#47808) at a concentration of 1:1000 in TBST. The PVDF membranes were washed (3 × 5 min in TBST) and incubated with the secondary antibodies (anti-rabbit IgG) conjugated with horseradish peroxidase enzyme (HRP) (#7074) at a concentration of 1:3000 in TBST at 37ºC for 90 min with mild vibration. Next, the PVDF membranes were washed (3 × 5 min in TBST). Finally, the enhanced chemiluminescence (ECL) reagent (Pierce ECL Western Blotting Substrate) and Alliance 4.7 Gel Doc (UK) were used to visualize the protein bands. The intensity of bands was analyzed using UVtec software (UK). The levels of all proteins were normalized against beta-actin (#4967) protein levels [14].

2.6 Statistical analysis

All data were expressed as the mean ± standard deviation (SD). The statistical analysis was done by One-way and two-way Analysis of Variance (ANOVA) followed by Tukey-Kramer test or post hoc test using SPSS version 16.0 software and/or GraphPad Prism version 6.00 for Windows, GraphPad Software, La Jolla California USA. $P < 0.05$ was statistically regarded significant.

3. Results

3.1 Effect of BPA on ROS content in different sections of rat brain tissue

Our results showed that treatment with BPA at a dose of 50 mg/kg meaningfully increased ROS generation in the hippocampus and cortex tissues in comparison to control group ($P < 0.001$) (Fig. 3).

3.2 Effect of BPA on MDA and GSH levels in different sections of rat brain tissue

Figure 4 showed that, there is an important enlargement in level of MDA at a dose of 50 mg/kg BPA group ($P < 0.001$) in the hippocampus tissue and a significantly increase in MDA level at doses of 25 ($P < 0.05$) and 50 ($P < 0.001$) mg/kg BPA group in the cortex tissue compared to the control group. Moreover, in the hippocampus and cortex tissues, an important decrease observed in level of GSH in high dose of BPA (50 mg/kg) group in comparison to the control group ($P < 0.001$).

3.3 Effect of BPA on pro-inflammatory cytokines in different sections of rat brain tissue

In the pilot test, it has found that BPA significantly elevated pro-inflammatory cytokines expression, including TNF-α (25 and 50 mg/kg) ($P < 0.05$ and $P < 0.001$), IL-6 (50 mg/kg) ($P < 0.001$), and IL-1β (25 and 50 mg/kg) ($P < 0.01$ and $P < 0.001$) levels in the hippocampus tissue in comparison to control group. In addition, TNF-α (50 mg/kg) ($P < 0.001$), IL-6 (25 and 50 mg/kg) ($P < 0.01$ and $P < 0.001$), and IL-1β (50 mg/kg) ($P < 0.001$) levels increased in the cortex tissue vs control group (Fig. 5).

3.4 Effect of BPA and NmCur on ROS content in different sections of rat brain tissue

The in vivo results confirmed that administration of BPA (50 mg/kg) important enlarged generation of ROS in the hippocampus and cortex tissues than control groups ($P < 0.001$). While NmCur considerably ameliorated ROS generation in both the hippocampus (25 and 50 mg/kg) ($P < 0.05$ and $P < 0.001$) and cortex (50 mg/kg) ($P < 0.001$) tissues, when used with BPA at a dose of 50 mg/kg for 4 weeks compared to BPA (50 mg/kg) group (Fig. 6).

3.5 Effect of BPA and NmCur on MDA and GSH parameters in different sections of rat brain tissue

As shown on Fig. 7, there is a significant increase in MDA concentration ($P < 0.001$) and an important decrease in GSH content ($P < 0.001$) in the BPA (50 mg/kg) group in different part of rat brain (hippocampus and cortex tissues) in comparison to control groups. In addition, a significant decrease in MDA concentration and an important increase in GSH content were observed at groups that received 25 and 50 mg/kg NmCur plus BPA (50 mg/kg) ($P < 0.05$, $P < 0.01$, and $P < 0.001$) in comparison with BPA (50 mg/kg) group in both tissues.

3.6 Effect of BPA and NmCur on pro-inflammatory cytokines in different sections of rat brain tissue

Our other results presented that, in the hippocampus and cortex tissues, BPA significantly increased expression of pro-inflammatory cytokines, such as TNF-α, IL-6, and IL-1β levels than control groups ($P < 0.001$). Conversely, treatment with BPA (50 mg/kg) plus NmCur (25 and 50 mg/kg), especially at a dose of 50 mg/kg NmCur, significantly reversed the levels of these cytokines when compared with the BPA group ($P < 0.05$, $P < 0.01$, and $P < 0.001$) (Fig. 8).

3.7 Effect of BPA and NmCur on enzyme activities in different sections of rat brain tissue

Another result of this study displayed that BPA at a dose of 50 mg/kg was significantly increased the mean of SOD ($P < 0.01$ and $P < 0.001$) and GST ($P < 0.001$) enzyme activities. While considerably diminished the mean of GPx ($P < 0.001$), GR ($P < 0.001$ and $P < 0.01$), and CAT ($P < 0.001$) enzyme activities compared to control groups in hippocampus and cortex tissues. Co-therapy of BPA (50 mg/kg) and NmCur (50 mg/kg) also induced a significant reduce in the mean of SOD ($P < 0.01$) and GST ($P < 0.05$) enzyme activities, whereas an important increase observed in the mean of GPx ($P < 0.001$), GR ($P < 0.05$), and CAT ($P < 0.01$) enzyme activities in the hippocampus tissue. In addition, the activity of enzymes in the tissue of cortex showed that co-administration of BPA (50 mg/kg) and NmCur at doses of 25 and 50 mg/kg led to decreasing the mean of SOD ($P < 0.05$ and $P < 0.001$) and GST ($P < 0.05$ and $P < 0.01$) enzyme activities, while increasing the mean of CAT ($P < 0.05$ and $P < 0.01$) enzyme activity in comparison with BPA group, as well as 50 mg/kg BPA plus 50 mg/kg NmCur enlarged the mean of GPx ($P < 0.01$) and GR ($P < 0.01$) enzyme activities than BPA group (Fig. 9).

3.8 Effect of BPA and NmCur on rat behavioral performance

3.8.1 Effect of BPA and NmCur on passive avoidance learning and memory in rat: Shuttle-box test

Based on data from the shuttle-box test shows that BPA (50 mg/kg) markedly diminished step through latency (STL) than control groups ($P < 0.001$). Nevertheless, combination therapy of BPA (50 mg/kg) and NmCur (25 and 50 mg/kg) significantly increased STL and enlarged fear learning and memory compared to BPA (50 mg/kg) group ($P < 0.05$, $F (7, 56) = 7.802$, and $P < 0.001$) (Fig. 10).

3.8.2 Effect of BPA and NmCur on locomotor activity in rat: Open-field test

As shown in Fig. 11, BPA at a dose of 50 mg/kg significantly displayed a reduction of the peripheral (A) and total (C) locomotor activity, however, an increase of the central (B) locomotor activity than control groups ($P < 0.001$). In addition, the co-therapy of BPA (50 mg/kg) and NmCur (25 and 50 mg/kg)

considerably improved peripheral (A), central (B), and total (C) locomotor activity in comparison to BPA group (50 mg/kg) ($P < 0.05$, $P < 0.01$, $F (7, 56) = 34.17$ (A), 15.11 (B), 8.377 (C), and $P < 0.001$).

3.8.3 Effect of BPA and NmCur on memory dysfunctions in rat: Morris water maze (MVM) test

The supplementary test of MWM was performed to confirm the results of the shuttle box test on BPA-induced learning and memory impairments. Administration of 50 mg/kg BPA noticeably elevated escape latency (the time to find the hidden platform) in training trial (Fig. 12A), while significantly declined the time spent in the target quadrant in probe trial (Fig. 12B). Data analysis demonstrated that BPA treatment (50 mg/kg) × training days significantly also changed the average of escape latency time (sec) than control groups (Fig. 12A) (on day 3, BPA 65.23 ± 5.47 sec, control, 44.67 ± 6.01 sec; on day 4, BPA 57.31 ± 5.47 sec, control, 42.19 ± 7.62 sec; on day 5, BPA 49.07 ± 7.15 sec, control, 36.63 ± 7.48 sec, respectively). In addition, the travelled distance in the target quadrant (cm) was significantly increased interactions of BPA administration × training days compared to control groups on the all days' acquisition trial (Fig. 12C) (on day 1, BPA, 940.14 ± 78.25 cm, control, 512.48 ± 96.48 cm; on day 5, BPA 560.19 ± 46.60 cm, control, 210.36 ± 52.60 cm). Exposure with BPA (50 mg/kg) was also noticeably lessened the time spent in the target quadrant (sec) (Fig. 12B) (BPA, 14.69 ± 4.17 sec, control, 29.61 ± 5.67 sec) and the travelled distance in the target quadrant (cm) (Fig. 12D) (BPA, 224 ± 15.0 cm, control, 460 ± 18.0 cm) when in comparison to control groups. The escape latency time (sec) in co-therapy of BPA (50 mg/kg) and NmCur (25 and 50 mg/kg) × training days during final 3 days of acquisition trial was decreased compared to BPA group (Fig. 12A). Moreover, the travelled distance (cm) in simultaneous treatment of BPA (50 mg/kg) and NmCur at dose of 50 mg/kg and doses of 25 and 50 mg/kg × training days during on 1 day and final 4 days of acquisition trial, respectively was declined when in comparison to BPA group (Fig. 12C). Co-administration of BPA (50 mg/kg) and NmCur at doses of 25 and 50 mg/kg markedly increased the time (sec) spent and the travelled distance (cm) in the target quadrant during the probe trial than BPA group (Fig. 12B and Fig. 12D). In addition, there was no important difference of swimming speed among all groups in the MWM test during all days (5 days) of training and probe trial (Fig. 12E and Fig. 12F).

3.9 Effect of BPA and NmCur on the different types of proteins in rat hippocampus and cortex tissues: Western blot analysis

As shown in Fig. 13, BPA at a dose of 50 mg/kg exhibited lower expression of p-AKT and p-ERK1/2 proteins, however, it displayed higher expression of p-P38 and p-JNK proteins than the control (Dex + Sea) and NmCur (50 mg/kg) groups. Co-administration of BPA and NmCur at a dose of 50 mg/kg significantly enlarged proteins expression of p-AKT and p-ERK1/2, whereas decreased proteins expression of p-P38 and p-JNK in comparison with BPA group in different regions of rat brain tissue (Fig. 13). In addition, administration of NmCur alone (50 mg/kg) and BPA alone (50 mg/kg) than control (Dex + Sea) group increased and reduced, respectively, expression of a variety of glutamate receptors, including NMDA (NR1, NR2A, and NR2B) and AMPA (GluA1) (Fig. 14), and memory-related proteins, such as BDNF and CREB proteins (Fig. 15), in the rat hippocampus and cortex tissues. Moreover, treatment of BPA alone (50

mg/kg) in comparison to NmCur (50 mg/kg) group led to an important reduction in the expression of all the proteins listed above. Nevertheless, administration of BPA (50 mg/kg) and NmCur (50 mg/kg) than BPA (50 mg/kg) group resulted in a significant upregulation in the expression of all the proteins listed above (Figs. 14 and 15).

A summary of the results obtained in this study is shown in Fig. 16.

4. Discussion

Synapses, as major modulatory system, in the hippocampus regulate normal learning and memory processes, especially spatial cognitive functions [111]. In fact, A cognitive process that encodes, reserves, and reminds the received data is memory [112]. Memory as a three-step process, including acquire, integrate, and retrieve information considers, which acts a major task in learning and relationship with the surrounding environment. Memory impairment can be induced by different factors, including stressful conditions [113, 114], some drugs (such as anticonvulsants and sedative agents) [115], improper lifestyle, for instance, high alcohol consumption [116], low physical activity [117], and high fat diet [118], and some environmental toxins, e.g. BPA. BPA accumulates into the mitochondrial membrane and disrupts the cellular respiration cycle that led to an overexpression of ROS and mitochondrial apoptotic signaling pathway [119], especially in the heart, liver, kidney, and brain [52, 46, 120, 14]. In the hippocampus and cortex areas, the BPA-induced ROS motivates MDA production, which effects on the neuronal integrity and function, resulting in inducing learning and memory impairment [121]. It also is noteworthy that chronic systemic inflammation and/or prolonged neuro-inflammatory responses can result in endothelial destruction in BBB area, an increase of penetration of peripheral monocytes into the perivascular spaces [122], a stimulation of microglia cells, an impairment of synaptic and neuronal plasticity, and inducement of neural apoptosis and memory impairments [123, 51]. As previously mentioned, BPA by reducing of ROS-scavenging enzymes and antioxidant levels through disturbance of redox status between quinone and hydroquinone/catechol forms of BPA induced neurotoxicity in the rat striatum and other nervous tissues [104–106].

Accordingly, in this study, the effective toxic dose of BPA pursuant to the pilot study, a dose of 50 mg/kg, was determined. Our experimental data confirmed that oral administration of BPA at a dose of 50 mg/kg for 4 weeks significantly increased ROS and MDA levels, however noticeably moderated GSH content compared to control groups in rat hippocampus and cortex tissues. In line with our work, in another study, Khadrawy *et al*. (2016) was proved that the administration of 10 and 25 mg/kg BPA for 6–10 weeks was important increased MDA concentration and NO level, whereas decreased GSH content in the hippocampus and cortex of adult male albino rats in a dose- and time-dependent manner [107]. In our previous study, similar results were also obtained for heart tissue [14]. Our other results showed that BPA significantly induced levels of SOD, GST, TNF-α, IL-6, and IL-1β, while considerably attenuated levels of GPx, GR, and CAT in rat hippocampus and cortex tissues.

In addition to the stated above, several studies have been cited that NMDA and AMPA receptors are played a role in the formation of excitatory synapses and rapid synaptic transmission between neurons controlling synaptic plasticity and spatial learning and memory formation [124, 125]. Over-stimulating of NMDA receptor can increase calcium influx, which then induces short- or long-term alterations in the hippocampus, e.g. long-term potentiation (LTP) [126]. Moreover, a wide variety of other proteins (BDNF and CREB) [52, 54–56] and signaling pathways (MAPKs and AKT) [127] are also involved in these processes. The BDNF, as a member of the neurotrophins group, prompts the MAPK/ERK signaling pathways, neural survival, growth, and differentiation and improves synaptic plasticity and repair mechanisms [128, 129]. In addition to the BDNF, the CREB, as a translation factor, has a significant effect in neuronal survival [130]. So that these proteins play an important role in regulating learning and memory performance [131–133, 130]. In the other words, the relationship between these two factors can be expressed as follows: the BDNF activates CREB phosphorylation [134], which helps the transcription of BDNF and its receptor, TrKB [135, 136], increases Bcl-2 activity, as an anti-apoptotic protein, which fixes the integrity of the mitochondrial outer membrane, inhibits apoptosis via decreasing levels of BAX and Casp-3, as apoptotic proteins [137], and elevates cellular GSH level [138]. The MAPKs family (ERK-1, ERK-2, JNK, and p38) involved in controlling diverse physiological activities, including stress and inflammation responses and apoptosis. The ERKs is known to regulate transcription factors, such as CREB [139]. In the other words, activated ERKs are translocated into the nucleus and regulated the expression of several genes [140–142], which resulted in the formation and stabilization of long term memory in hippocampus CA1 area [139, 143].

The induction of hippocampal neuronal apoptosis and dysfunction of glutamate receptors and learning and memory-related proteins have been confirmed by BPA [52]. According to present study and in accordance with previous studies, western blot analysis displayed that BPA (50 mg/kg) significantly reduced expression of p-AKT and p-ERK1/2, whereas increased expression of p-P38 and p-JNK proteins in the mentioned different regions of rat brain. Moreover, treatment of BPA (50 mg/kg) led to an important reduction in the expression of p-NR1, p-NR2A, p-NR2B, p-GluA1, p-CREB and BDNF. Several studies have proved that exposure with BPA created apoptosis through increasing the activation of MAPK (ERK/JNK/p38) and AKT signaling pathways in rat sertoli cells [127] and HT-22 cells [52]. The administration of BPA also reduced synaptic plasticity and diminished expression of NR1, NR2A, NR2B, GluR1, and ERβ in male mice and rat hippocampus, leading to impairment of learning and memory [144, 48, 57, 145]. The exposure of pregnant female Sprague Dawley rats to a very low dose of BPA (2.5 μg/kg/day) impacted on ER-α phosphorylation in a sex-dependent manner, especially male fetuses [146], resulting in decreasing the BDNF levels [147]. In addition, other studies have shown that BPA treatment significantly decreased BDNF level [148, 149]. Therefore, it can be stated that inhibition of MAPK/AKT/NMDA/AMPA/CREB/BDNF signaling pathway in the hippocampus lead to the learning and memory impairment [54], which is in accordance with the results of our study.

In fact, it can be claimed that possible mechanisms of BPA-caused learning and memory impairment are related to inhibition of synaptogenesis process, spinal synaptic remodeling, and glutamate receptors expression in the medial prefrontal cortex and hippocampus regions of rodents and primates [150–152].

One way to detect these disorders is by evaluating behavioral studies in animals. So that it has been proven that animals, especially mice and rat, mainly in the first minute of entering to a new environment, naturally reveal the highest desire to explore a novel environment. This behavior has been proven in various behavioral tests. Behavioral tests, including passive avoidance test (PAT) (shuttle-box) and Morris water maze (MWM) test are typically used for evaluation of two (step-down and step-through) avoidance behaviors and spatial learning and memory function, respectively. Open-field test also investigate to evaluation of locomotor activity, exploratory habits, and emotional behaviors [32]. Based on the many studies that have been published in this field [153, 154] [155] and results obtained in our study, it has been proven that BPA treatment (50 mg/kg) markedly attenuated fear learning and memory performances and locomotor activity, which detected through reducing the STL and peripheral and total locomotor activity, respectively. Whereas it enlarged central locomotor activity than control groups. It also noticeably extended the time to finding the hidden platform in training trial, the average of escape latency time (sec), and the travelled distance in the target quadrant (cm) in the all days' acquisition trial, however significantly declined the time spent in the target quadrant (sec) in probe trial when in comparison to control groups. Nevertheless, there was no significant difference in swimming speed among all groups in the MWM test.

Consistent with our results, Jašarević et al. (2013) recently also reported that exposure to BPA (5 and 50 mg/kg/day) in perinatal period severely compromised the spatial navigation and exploratory behaviors in male deer mice offspring [155]. In addition, the exposure to BPA disrupted hippocampus-related learning and memory and synaptic plasticity by the decrease of spine density, synaptic plasticity, and NR2A and GluR1 expression in juvenile Sprague–Dawley rats. These disorders were meaningfully identified by reducing memory retrieval to finding the hidden platform through the MWM test [145]. Other studies have also found that treatment of BPA increased spatial memory impairment and latency time related to hippocampus in the MWM test in 3- and 8-week-old mice [48], 2-weeks-young adult mice [153], 4-week-old rats [156], and adult rats [49]. Administration of BPA for 8 weeks was impaired the passive avoidance memory of the male mice between adolescence and young adulthood [47]. BPA treatment considerably diminished neurogenesis, synaptic plasticity, and dendritic spine density of hippocampal CA1 region neurons in little pups and cultured CA1 neurons, as well as adult male Sprague-Dawley rats and the young adult mice, leading to spatial memory impairment. So that, latency time and distance to finding the hidden platform meaningfully enlarged, however, the time spent in target quadrant and platform crossings important decreased, which identified by the MWM method [153, 154]. In another study, long-term exposure of BPA enhanced time spent in the central area (at doses of 0.4, 4, or 40 mg/kg) and the traveled distance to finding the hidden platform (at dose of 0.4 or 40 mg/kg) for 12 weeks. However, it diminished the step-down latency, synaptic density, and NR1 and GluR1 expression in the male mice hippocampus CA1 region [32]. Furthermore, BPA at a dose of 100 μg/kg for 15 days increased the distance and latency time in discovering the hidden platform, showing reduction of the spatial learning and memory performance, as determined by the MWM test, in adult male Wistar rats [157].

Many natural or synthetic chemical agents that are used to enhance cognitive functions could have more or less side effects or low effectiveness, so the replacement them with other compounds, which

accompanied with fewer side effects and better efficacy may be a desirable choice. Several antioxidants, owing to cross the BBB, are known for their effectiveness against neuronal cell death and memory disorders correlated with oxidative stress. Many of these substances are natural sources of polyphenolic compounds in plants, vegetables, fruits, green tea, olive oil, red wine, etc. [158, 159]. One of the most important herbal compounds is curcumin that considers as an attractive alternative therapy tool for many neurological diseases [160, 161, 3], including learning and memory deficits [162]. Because it can improve the neurogenesis, neuronal differentiation, neuronal plasticity, and learning and memory performance by numerous possible mechanisms, e.g. the diminishment of oxidative stress, the improvement of mitochondrial performance, the amplification of nitric oxide level, and moderation of acetylcholinesterase enzyme activity [163–165]. So that, it can be affected on different type's memory, such as short and long-term memory, working memory, episodic memory, spatial memory, and fear memory [165].

Hereupon, in accordance with previous studies, it was proved that the most characteristic of curcumin's antioxidant effects related to its phenolic structure, which has electron-capturing effects that can destabilize oxidative stress, ROS, and MDA levels, while increase GSH content [90, 79]. In another study also observed that curcumin declined oxidative stress in mouse brain and N27 rat dopaminergic neural cell line (1RB3AN27 cell line) in model of Parkinson's disease [28, 166]. Several other similar studies have conducted that curcumin administration significantly improved GSH content and antioxidant enzyme activities, including SOD, GPx, and CAT, but it declined MDA concentration in rat's kidney treated with gentamicin, cyclosporine, and methotrexate [90–92]. In addition, curcumin administration restored the neurotoxic effect of colistin using increasing the CAT and GSH levels, while decreasing the ROS and MDA concentration in neuroblastoma-2a (N2a) cells [167] and the kidney and brain of adult male albino rats [168]. Moreover, curcumin protects neuronal cell death caused by hemin in the cerebellar granule via the inhibition of ROS production, the improvement of GSH content, and the increase of antioxidant enzymes activity [169, 170]. Based on, the antioxidant effect of curcumin compared to vitamin E is at least 10 times more activity [171]. In addition, it by lowering inflammatory cytokines (such as TNF-α, IL-1β, IL-6, and IL-8, via inhibition of TLR4, NF-kB, and prevention of MAPK (ERK, JNK, and p38) signaling pathway), which are related to several cellular events, including immunity, inflammation, cell survival, and apoptosis, could be led to inhibiting of some diseases, such as Alzheimer's and Parkinson's diseases [83, 84, 75].

As stated in previous studies on the poor performance of free curcumin, based on one of most effective tools to better performance of materials with high adsorption capacities and less conversion to inactive form is using nano-micelles structures [172, 173]. Some other benefits of using micelle-like structures are included cost-effectiveness of these methods, simple transfer of cargo through biological barriers, better solubility in biological body fluids, controlled release of cargo, protection against hydrolysis or degradation and inactivation of cargo [173]. In addition, nanomicelles owing to their small size through endocytosis can easily passed intestinal cells and transferred their cargo [174]. In this study, for the first time, we established that NmCur at doses of 25 and 50 mg/kg has the neuroprotective effect in rats exposed to BPA. So that, a significant decrease in ROS, MDA, TNF-α, IL-6, and IL-1β levels and an important increase in GSH content were observed at groups that received 25 and 50 mg/kg NmCur, especially at a dose of 50 mg/kg NmCur, plus BPA (50 mg/kg) for 4 weeks in the hippocampus and

cortex tissues. Co-therapy of BPA (50 mg/kg) and NmCur (at doses of 25 and 50 mg/kg) also induced a significant reduce in the mean of SOD and GST enzyme activities, whereas an important increase observed in the mean of GPx, GR, and CAT enzyme activities than BPA group in the hippocampus and cortex tissues. In addition to neuroprotective effect of NmCur on rats that observed in this study, in our previous study has found that NmCur at a dose of 50 mg/kg significantly attenuated the cardiotoxic effect of BPA by lowering MDA concentration and increasing GSH content in rat heart tissue [14]. In another study has observed that curcumin improved the BPA-induced disturbance of hypothalamus pituitary gonadal hormone by reduction of intracellular nitric oxide radical and MDA levels; however, enlargement of the SOD and CAT antioxidant enzymes [175], which is in agreement with our finding in this study. In addition to the NmCur form, other forms of curcumin about learning and memory impairment were examined. The solid lipid curcumin particle formulation with commercial name of Longvida® can cross from BBB and causes a concentration of 4 times greater than unformulated curcumin [176]. In a study, one randomized, double-blind, placebo-controlled trial study on 60 healthy adults (approximately 60 to 85 years old) revealed that one hour after single-dose exposure of Longvida® (400 mg) important improved the sustained-attention performance and working memory tasks [177]. In a study has also found that nanoformulation of curcumin (15 and 20 mg/kg/orally) containing bovine serum albumin, as a safe carrier for curcumin, has endothelial transcytosis effects, helps to enter formulation into the cells, decreases passive avoidance memory retrieval deficit induced by pre-test scopolamine (1 mg/kg, i.p.), as the muscarinic receptor antagonist, in male NMRI mice [178].

The evaluation of curcumin's anti-apoptosis action in different studies was observed. For example, curcumin was resulted in the attenuation of apoptosis and inflammatory markers (TNF-α) [85]. curcumin by the suppression of p38 MAPK signaling pathway in rats with chronic colitis [85] and cell lines [87, 88], as well as inhibition of JNK MAPK pathways in the mice liver [86] has also shown the apoptotic effect. In accordance with our previous studies [14], western blot analysis in this study was also proved that co-administration of BPA and NmCur at a dose of 50 mg/kg significantly up-regulated expression of p-AKT and p-ERK1/2, whereas down-regulated expression of p-P38 and p-JNK in different regions of rat brain tissue. In addition, for the first time in this study, it proved that administration of NmCur alone (50 mg/kg) and co-administration of NmCur (50 mg/kg) and BPA (50 mg/kg) increased, while BPA alone (50 mg/kg) reduced expression of p-NR1, p-NR2A, p-NR2B, p-GluA1, p-CREB, and BDNF in the rat hippocampus and cortex tissues.

In several other studies have examined the neuroprotective role of other antioxidants. For instance, lycopene (10 mg/kg) upregulated MAPK/ERK1/2/CREB/BDNF signaling pathway and improved neuronal survival, and synaptic plasticity and GSH content, however, suppressed ROS and MDA concentrations in hippocampal of adult male albino rats. Therefore, all side effects induced by BPA (50 mg/kg) was reduced, so that it reflected on improving the learning and cognition memory by decreasing the escape latency in the daily training trials and increasing the time spent in the target quadrant, which detected by MWM test [179]. Another study on adult male Wistar rats has displayed that BPA administration (100 mg/kg/orally for 4 weeks) prominently attenuated GSH content and GluA 2/3/4 expression, nevertheless, increased ROS and MDA levels in rat hippocampus. It also markedly enlarged the escape latency time to

finding the hidden platform during training trial days, whereas noticeably reduced the spent time in target quadrant in probe trials, resulting memory and learning impairment that evaluated by MWM test. However, crocin, as active ingredient in *Crocus sativus* L. plant, reversed all BPA-treated undesirable effects [4]. The findings of these several studies sufficiently are consistent with the findings of our study. The results of our study on behavioral tests displayed that the combination therapy of BPA (50 mg/kg) and NmCur (25 and 50 mg/kg) considerably increased STL, enlarged fear learning and memory, and improved peripheral and total locomotor activity compared to BPA (50 mg/kg) group. Moreover, in simultaneous treatment of BPA (50 mg/kg) and NmCur (25 and 50 mg/kg) × training days during final 3 days as well as during on 1 day and final 4 days of acquisition trial, respectively were declined the escape latency time (sec) and the travelled distance (cm) when in comparison to BPA group. While markedly increased the time spent (sec) and the travelled distance (cm) in the target quadrant during the probe trial compared to BPA group. In addition, there was no important difference of swimming speed among all groups in the MWM test during all days (5 days) of training and probe trial. In fact, NmCur was inverted all the adverse effects of BPA. These results are similar to other studies. For example, administration of curcumin in adult rat hippocampus and both HT-22 neuronal and BV2 microglial cells markedly down-regulated ROS and MDA productions, p-JNK/p-NF-*κ*B/Akt signaling pathway, and TNF-α and IL-1β expression. Moreover, treatment of curcumin markedly diminished latency time, while enlarged the platform crossings number and the quadrant time spent, which detected using the MVM and Y-maze tasks. It led to the improvement of memory and cognitive impairments correlated with lipopolysaccharide-stimulated microglia cells [180]. The injection of AlCl3 in the hippocampal CA1 region of male Kunming mice stimulated activation of microglia and astrocyte cells, inducing an enlargement of IL-1β, IL-6, and TNF-α that diminished passing times and spatial learning and memory functions, however, increased Aβ production and the escape latency, which measured by the MVM test. Nevertheless, treatment of curcumin on AlCl3-induced Alzheimer's disease (AD) was dramatically reversed the items mentioned above in the hippocampus [181]. Therefore, it can be mentioned that these studies are consistent with our obtained results.

Based on the results of various studies [182–184] and the results of this study in relation to free curcumin and curcumin derivatives, e.g. Longvida® [176, 185, 177] and nanomicelles curcuminoid, it can be suggested that curcumin treatment can decrease learning and memory impairment owing to its antioxidant, anti-inflammatory, and anti-apoptosis properties. So to speak, these effects of curcumin can be related to scavenging free radicals (as an inducer of stress oxidative), pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β), and anti-apoptosis (p-P38 and p-JNK) properties. However, it increases the glutamate receptors (NMDA and AMPA) and learning and memory-related proteins (BDNF and CREB) that can probably protects neural cells, reduces synaptic disturbance, and stimulates hippocampus and cortex neurogenesis [176]. As stated in previous studies, the doses of used curcumin and its derivatives were higher than in our study. So that, our study showed that the nanomicelles form of curcumin is most effective at the highest dose (50 mg/kg), but at the lowest dose (25 mg/kg) also showed the highest efficiency and effectiveness compared to the formulation of commercial and free curcumin. Generally, it can be argued that curcumin could preserve neural cells in the CA1 area in a time- and dose-dependent

manner. So to speak, it can be said that the time-dependent effects of curcumin on memory functions may be exerted via adaptive mechanisms that require time, including neurogenesis, altering synaptic flexibility or gene expression [186]. Nevertheless, the exact mechanism of curcumin effects not yet stated, which needs further studies.

5. Conclusion

In conclusion, in this study for the first time, it is marked that oral administration of nanomicelle curcumin (25 and 50 mg/kg) for 4 weeks significantly down-regulated expression of ROS, MDA, TNF-α, IL-6, IL-1β, SOD, and GST levels, while considerably up-regulated GSH content, GPx, GR, and CAT levels in rat hippocampus and cortex tissues. Western blot analysis also confirmed that nanomicelle curcumin noticeably exhibited higher phosphorylation of AKT and ERK1/2 proteins; however, it displayed lower phosphorylation of P38 and JNK proteins in the mentioned tissues. In addition, nanomicelle curcumin (50 mg/kg) and co-therapy of BPA and nanomicelle curcumin increased the expression of a variety of glutamate receptors, including NMDA (p-NR1, p-NR2A, and p-NR2B) and AMPA (p-GluA1), and the expression of learning and memory-related proteins, such as BDNF and p-CREB, in the mentioned tissues. It markedly extended the step-through latency and fear learning and memory, as well as locomotor activity (peripheral and total events, except central area). In addition, it shortened the time to finding the hidden platform, the average of escape latency time (sec), and the travelled distance in the target quadrant (cm), whereas significantly enlarged the time spent in the target quadrant (sec). However, there was no significant difference of swimming speed among all groups in the MWM test. In fact, our proved for the first time that nanomicelle curcumin has a dose-dependent neuroprotective effect against toxic effects of BPA in rat hippocampus and cortex tissues. Nevertheless, further mechanistic studies are needed in this regard.

Declarations

Author Declarations section

Ethics approval

All the experimental protocols were accepted by Ethical Committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1394.281) and this experiment was conducted at the Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

Consent to participate and or Consent for publication

It is not applicable to this article as this article does not include any studies with human participants done by any of the authors.

Availability of data and materials

All data created and/or analyzed during our study are available from the corresponding author on rational request.

Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest in this study.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation and data collection were performed by Mahmoud Gorji-Valokola. Data analysis and interpretation was done by Somaye

Fallahnezhad, Faezeh Ghorbani-Taherdehi, Azade Nadim, Mehrnaz Kafashzadeh, and Mehrnoosh Kafashzadeh. The first draft of the manuscript was written by Mahmoud Gorji-Valokola and Somaye Fallahnezhad. Its major revision was performed by Mahmoud Gorji-Valokola and Somaye Fallahnezhad. All authors read and approved the final manuscript.

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Compliance with Ethical Standards section

Disclosure of potential conflicts of interest

The authors declare no conflict of interest related to this study.

Research involving Human Participants and/or Animals

All the experimental protocols and procedures in this study were conducted according to the international guidelines for care and use of laboratory animals and approved by the ethical committee of Mashhad University of Medical Sciences (Ethic cod number: IR.MUMS.REC.1394.281). All experiments were performed at the Department of Pharmacodynamics and Toxicology, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

Informed consent

It is not applicable in this study.

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Figures

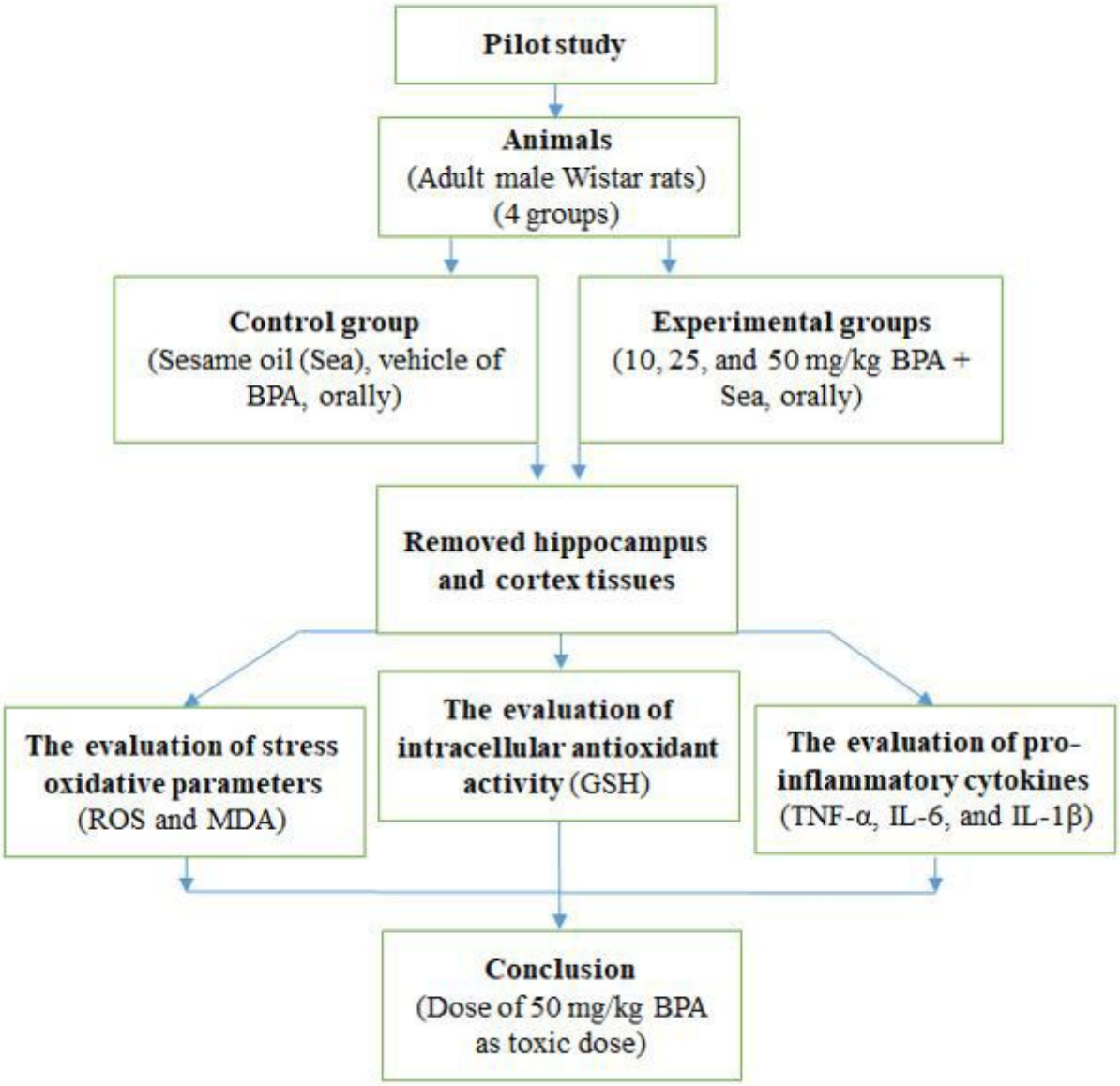

Figure 1

A schematic diagram of the pilot study design

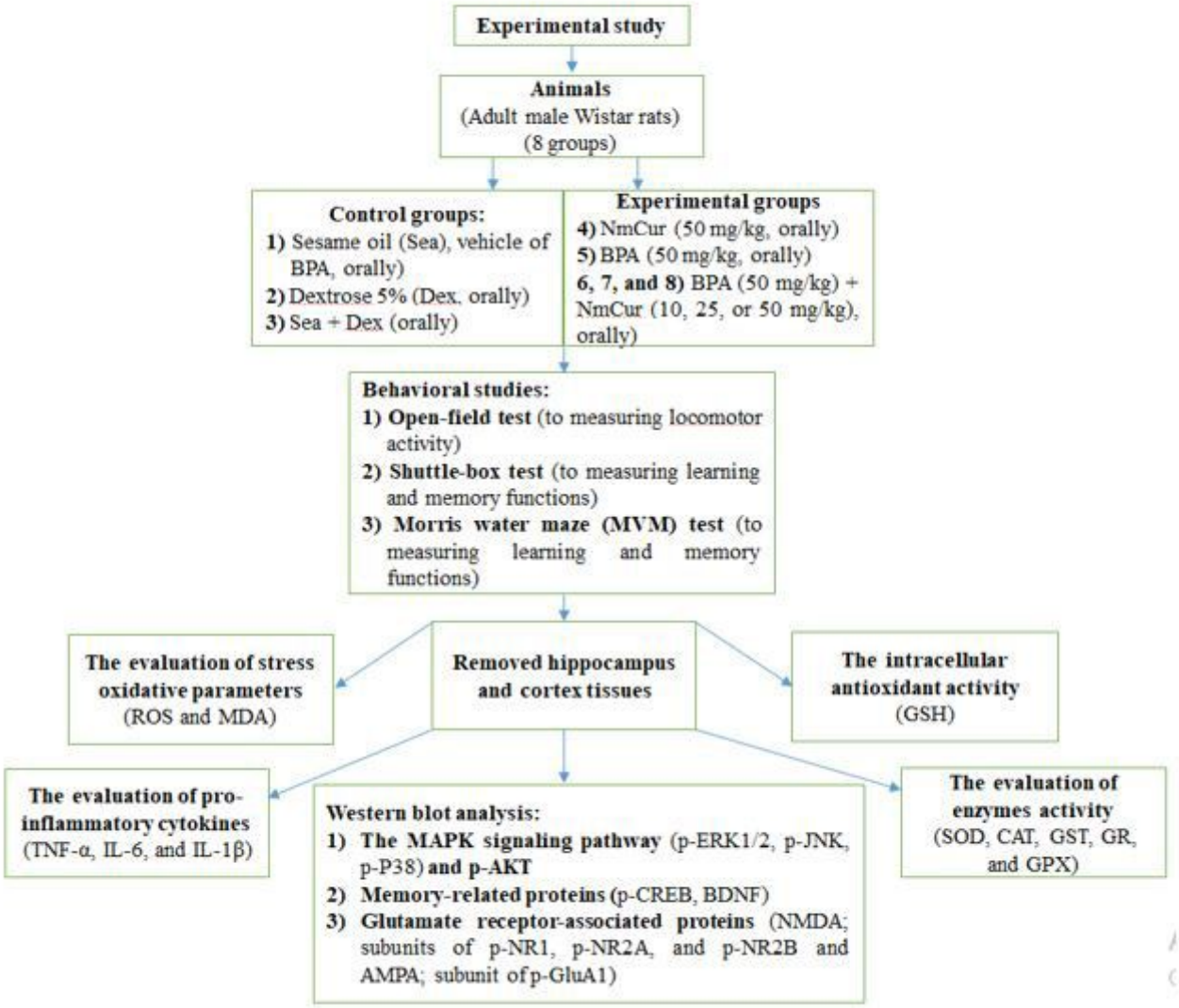

Figure 2

A schematic diagram of the experimental study design

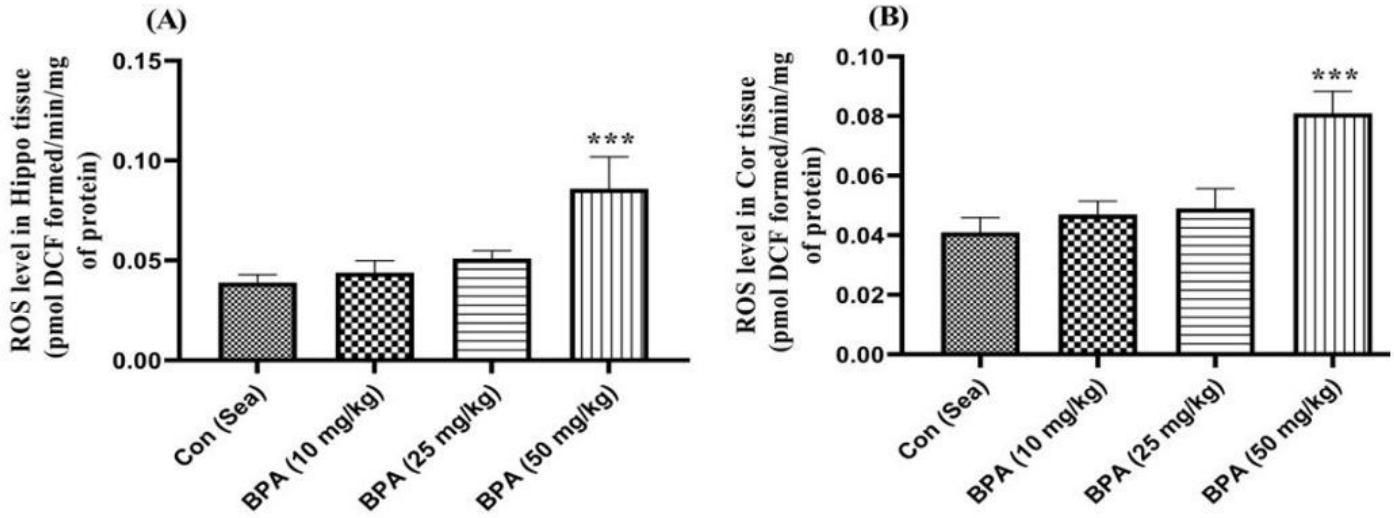

Figure 3

Effects of different doses of BPA exposure (10, 25, and 50 mg/kg) for 4 weeks on the ROS (A and B) level in the rat's hippocampus and cortex tissues, respectively. Data are shown as mean ± SD, One-way ANOVA, and Tukey–Kramer test. BPA was administered via gavage once a day and seven times per week. ***P < 0.001, compared with control group. Abbreviations: Con, control; Sea, sesame oil; BPA, bisphenol A, n = 8.

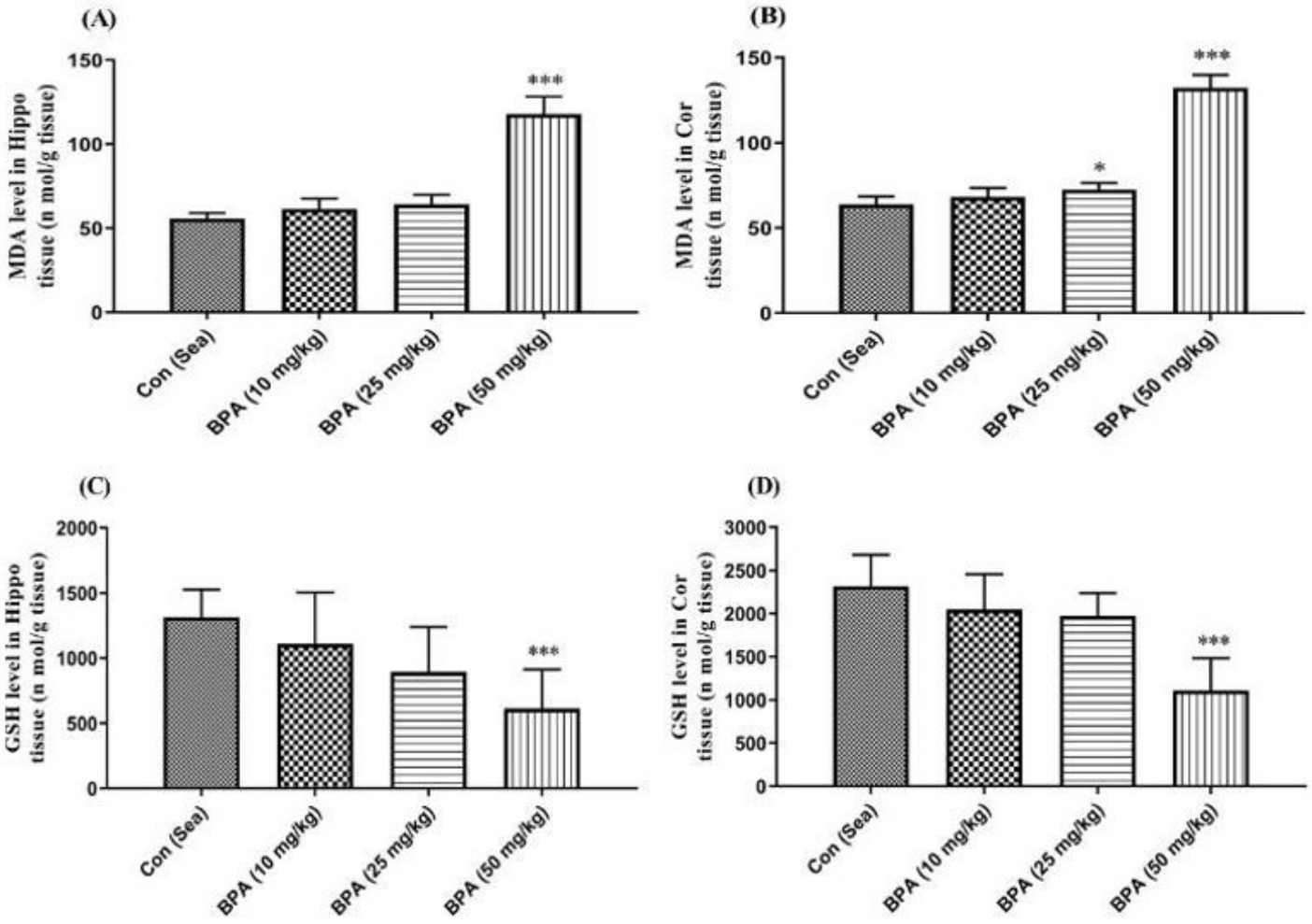

Figure 4

Effects of different doses of BPA exposure (10, 25, and 50 mg/kg) for 4 weeks on the MDA (A and B) and GSH (C and D) levels in the rat's hippocampus and cortex tissues, respectively. Data are shown as mean ± SD, One-way ANOVA, and Tukey–Kramer test. BPA was administered via gavage once a day and seven times per week. *P < 0.05 and ***P < 0.001, compared with control group. Abbreviations: Con, control; Sea, sesame oil; BPA, bisphenol A, n = 8.

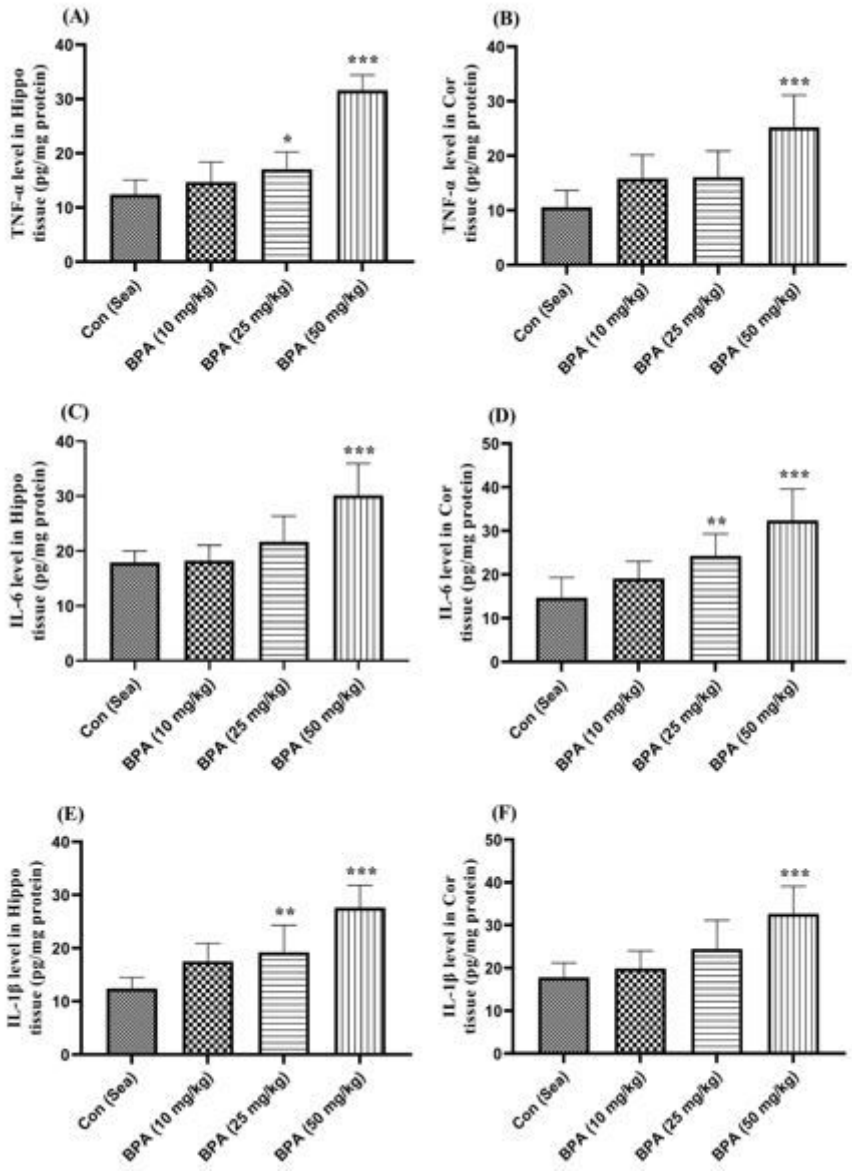

Figure 5

Effects of different doses of BPA exposure (10, 25, and 50 mg/kg) for 4 weeks on the pro-inflammatory cytokines, including TNF-α (A and B), IL-6 (C and D), and IL-1β (E and F) levels in the rat's hippocampus and cortex tissues, respectively. Data are shown as mean ± SD, One-way ANOVA, and Tukey–Kramer test. BPA was administered via gavage once a day and seven times per week. *P < 0.05, **P < 0.01, and ***P < 0.001, compared with control group. Abbreviations: Con, control; Sea, sesame oil; BPA, bisphenol A, n = 8.

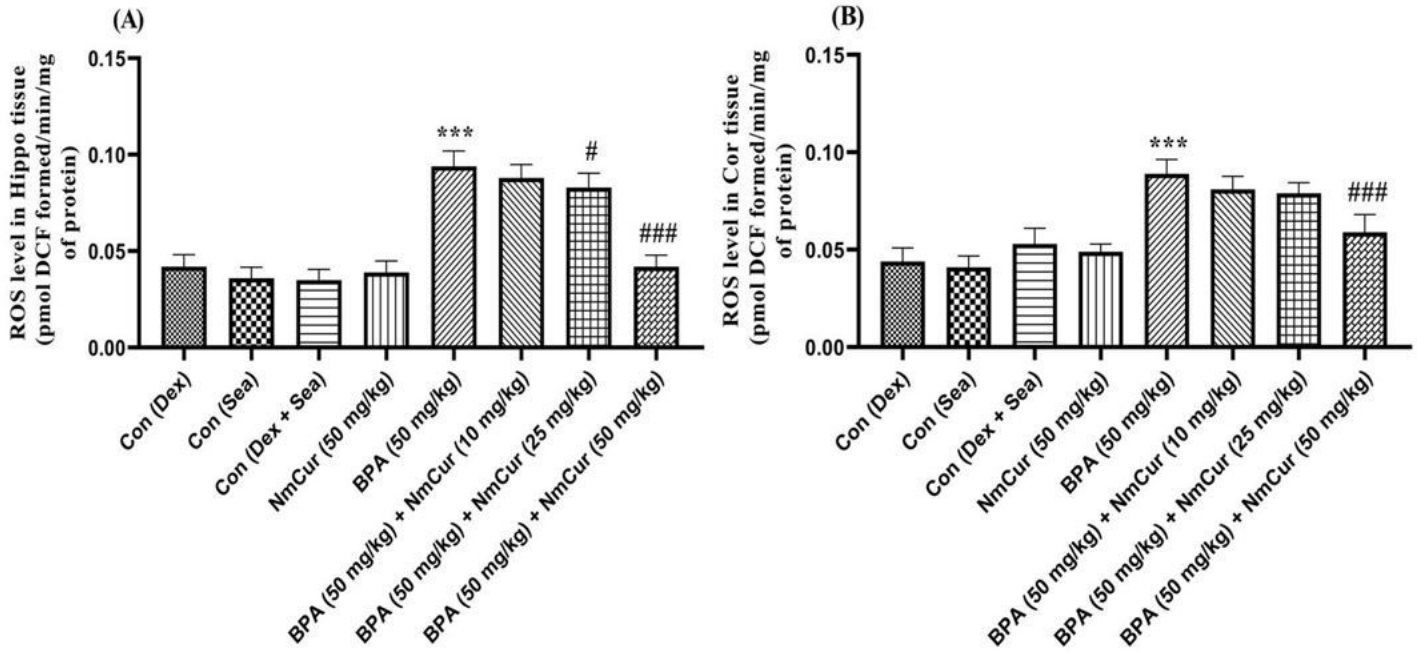

Figure 6

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on the ROS (A and B) level in the rat's hippocampus and cortex tissues, respectively. Data are shown as mean ± SD, One-way ANOVA, and Tukey–Kramer test. BPA and NmCur were administered via gavage once a day and seven times per week. ***P < 0.001, compared with control groups, and #P < 0.05, and ###P < 0.001, compared with the BPA 50 mg/kg group. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin, n = 8.

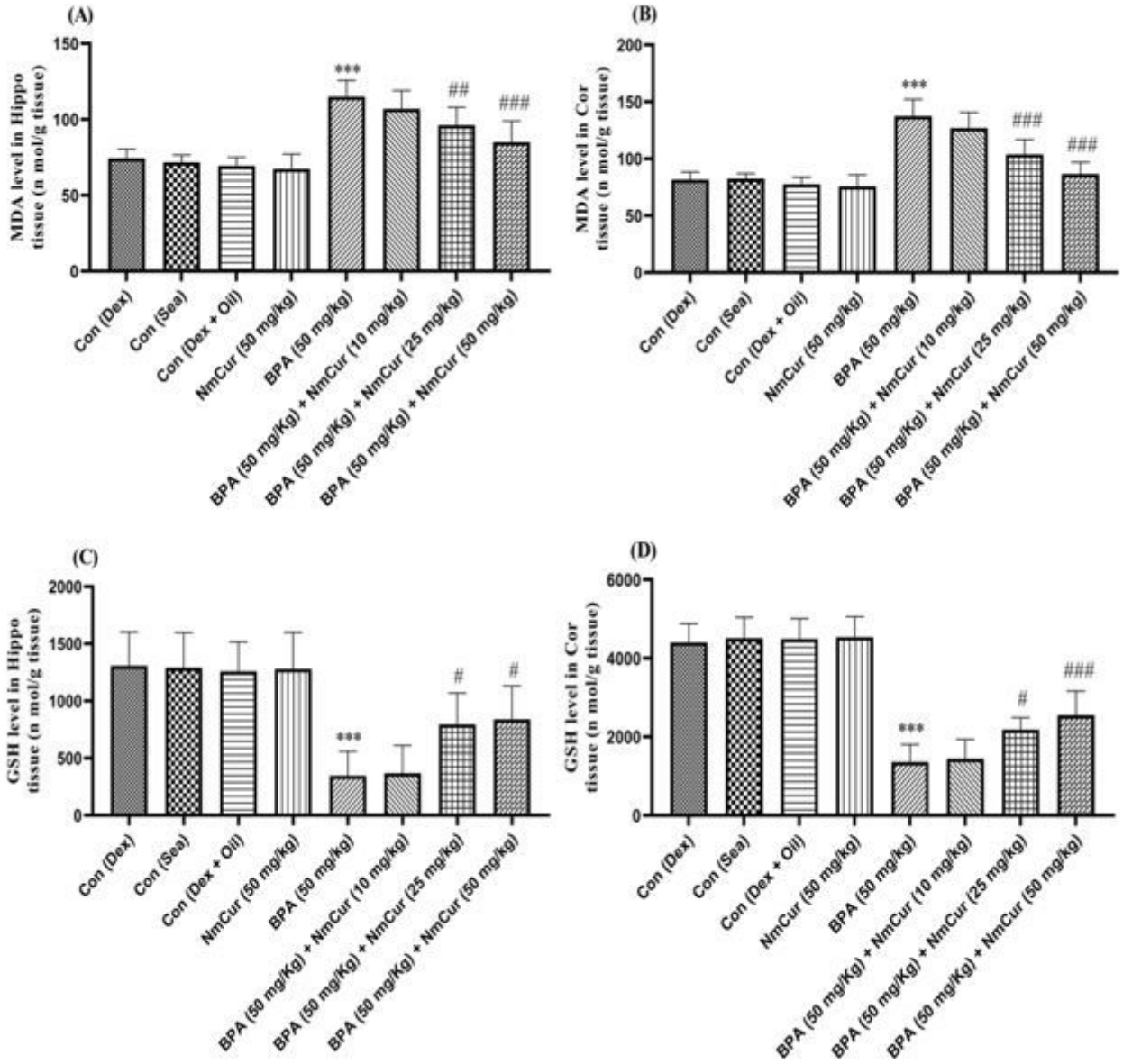

Figure 7

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on the MDA (A and B) and GSH (C and D) levels in the rat's hippocampus and cortex tissues, respectively. Data are shown as mean ± SD, One-way ANOVA, and Tukey–Kramer test. BPA and NmCur were administered via gavage once a day and seven times per week. ***P < 0.001, compared with control groups, and #P < 0.05, ##P < 0.01, and ###P < 0.001, compared with the BPA 50 mg/kg group. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin, n = 8.

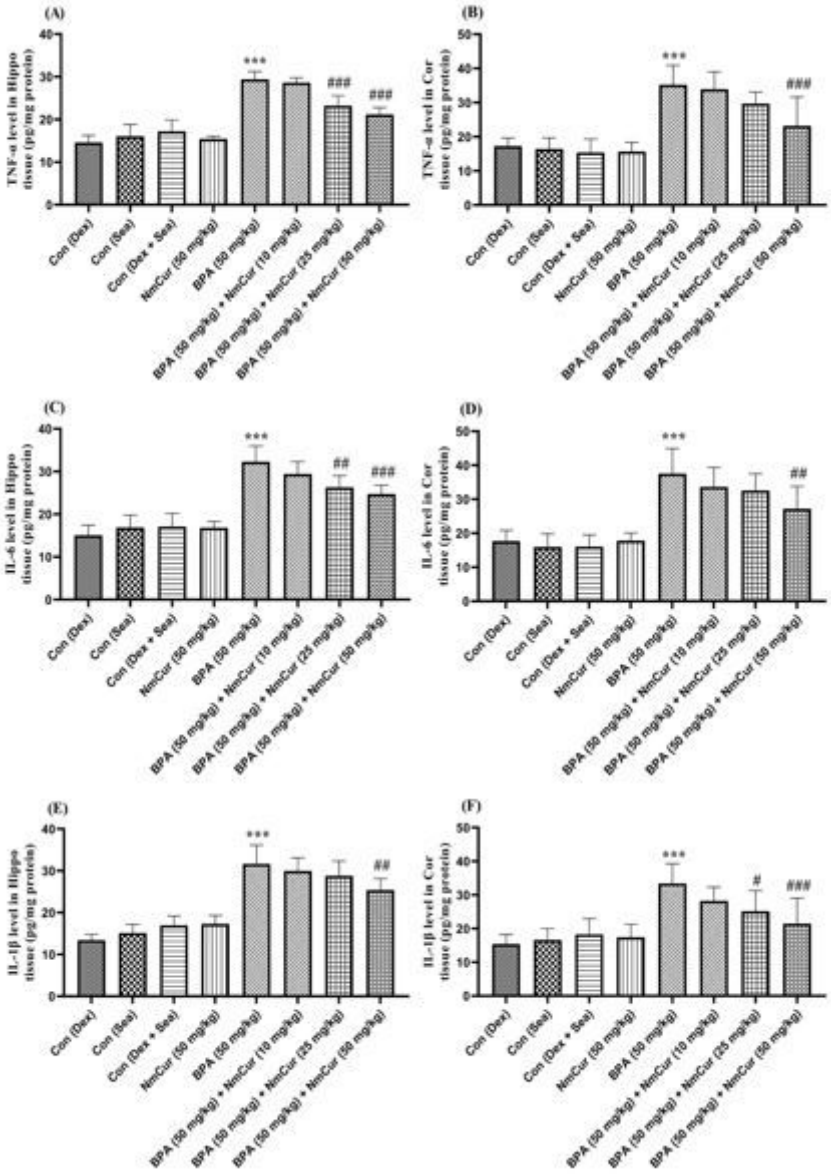

Figure 8

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on the pro-inflammatory cytokines, including TNF-α (A and B), IL-6 (C and D), and IL-1β (E and F) levels in the rat's hippocampus and cortex tissues, respectively. Data are shown as mean ± SD, One-way ANOVA, and Tukey–Kramer test. BPA and NmCur were administered via gavage once a day and seven times per week. ***P < 0.001, compared with control groups, and #P < 0.05, ##P < 0.01, and ###P < 0.001, compared with the BPA 50 mg/kg group. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin, n = 8.

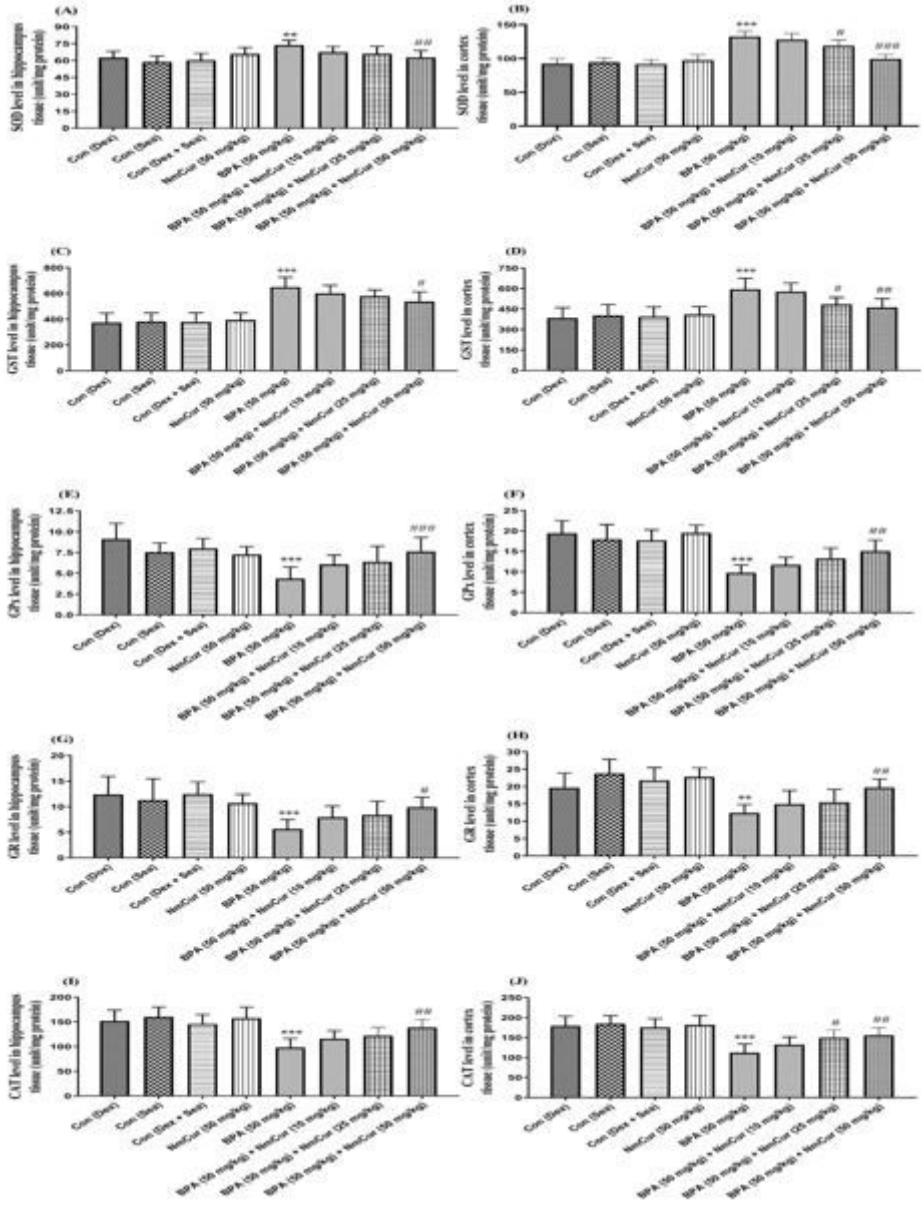

Figure 9

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on levels of the SOD (A and B), GST (C and D), GPx (E and F), GR (G and H) and CAT (I and J) enzymes activity in the rat's hippocampus and cortex tissues, respectively. Data are shown as mean ± SD, One-way ANOVA and Tukey–Kramer test. BPA and NmCur were administered via gavage once a day and seven times per week. **P < 0.01 and ***P < 0.001, compared with control group, and #P < 0.05, ##P < 0.01 and ###P < 0.001, compared with the BPA 50 mg/kg group. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin; SOD, superoxide dismutase; GST, glutathione-S-transferases; GPx, glutathione peroxidase; GR, glutathione reductase; CAT, catalase, n = 8.

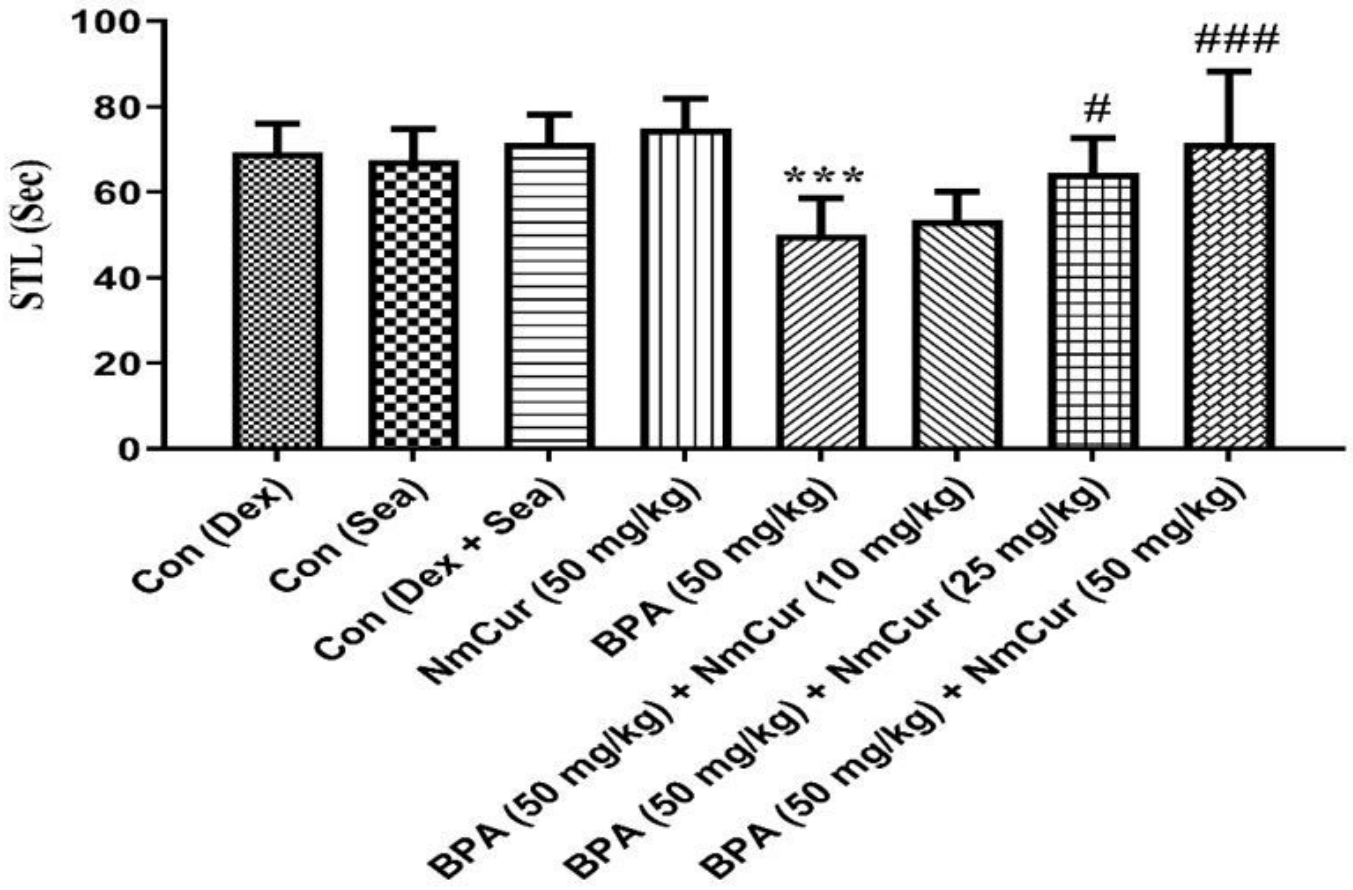

Figure 10

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on passive avoidance test in rat. Data are shown as mean ± SD, One-way ANOVA and Tukey–Kramer test. BPA and NmCur were administered via gavage once a day and seven times per week. ***P < 0.001 compared with the control groups, and #P < 0.05 and ###P < 0.001 compared with the BPA group. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin; STL, step-through latency, n = 8.

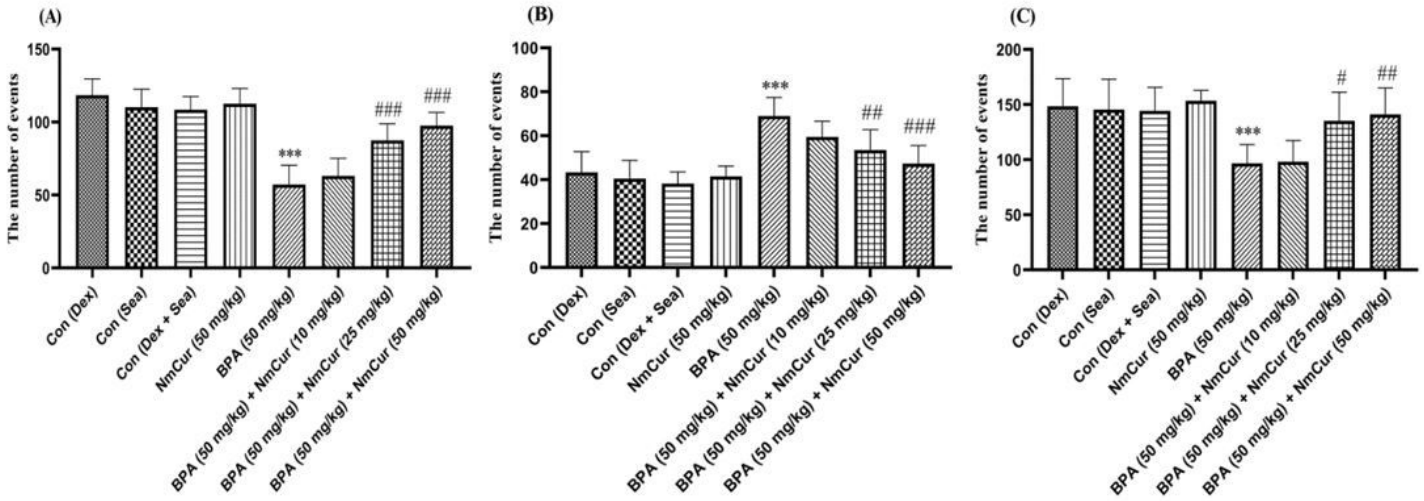

Figure 11

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on peripheral (A), central (B), and total (C) locomotor activity in rat. Data are shown as mean ± SD, One-way ANOVA and Tukey–Kramer test. BPA and NmCur were administered via gavage once a day and seven times per week. ***P<0.001 compared with the control groups, and #P < 0.05, ##P < 0.01, and ###P < 0.001 compared with the BPA group. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin, n = 8.

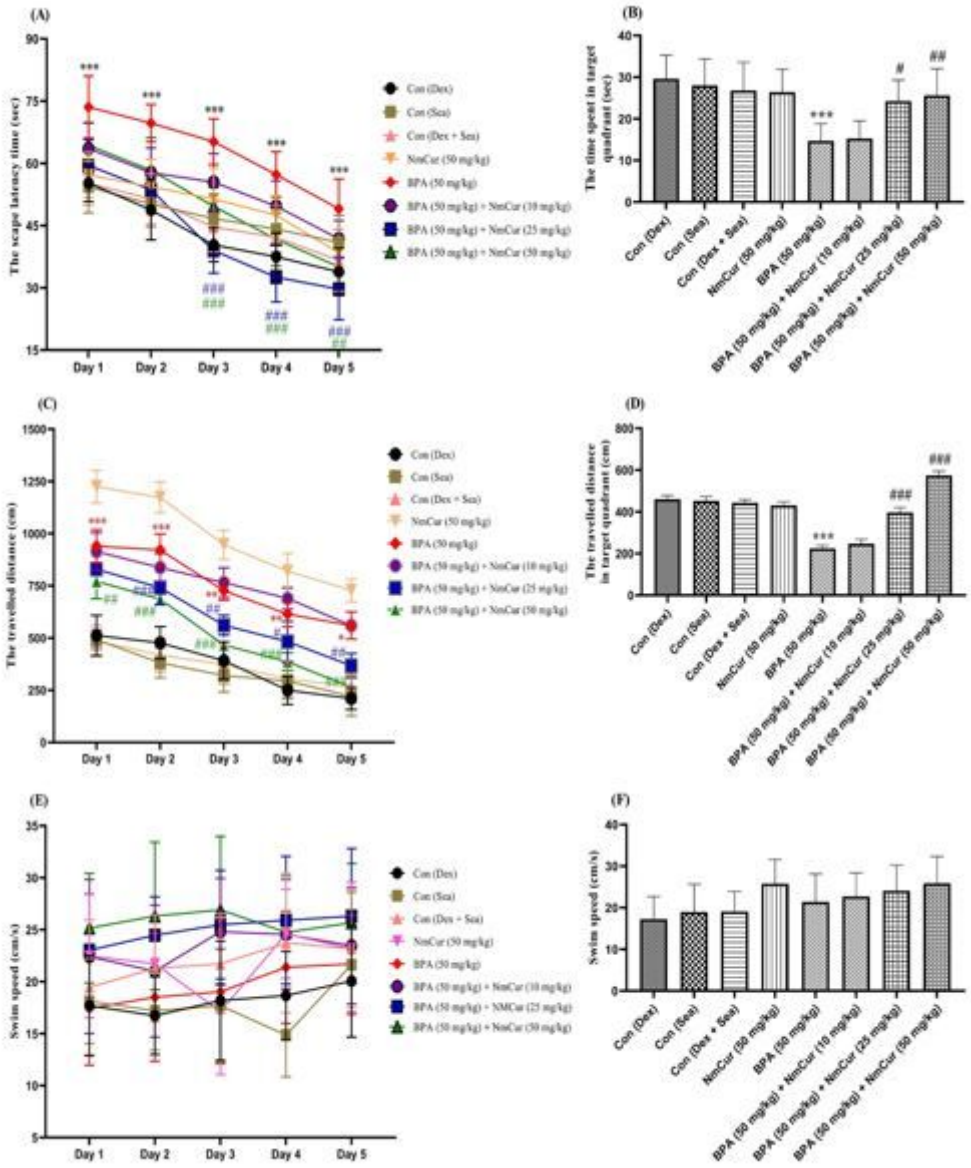

Figure 12

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on the escape latency time (sec) from day 1 to day 5 of training trial (A), the time (sec) spent in the target quadrant (B), traveled distance (cm) from day 1 to day 5 of training trial (C), and traveled distance (cm) in the target quadrant (D) to find the hidden platform in Morris water maze test in rat. In addition, swimming speed (cm/s) from day 1 to day 5 of training trial (E) and probe test (F) after removing the hidden platform in Morris water maze test in rat were evaluated. Data are expressed as the mean ± SD, One-way or Two–way ANOVA coupled with Tukey-Kramer multiple comparisons test. BPA and NmCur were administered via gavage once a day and seven times per week. *P < 0.05, **P < 0.01, and ***P < 0.001 compared with the control groups, and #P < 0.05, ##P < 0.01, and ###P < 0.001 compared with the BPA group. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin, n = 8.

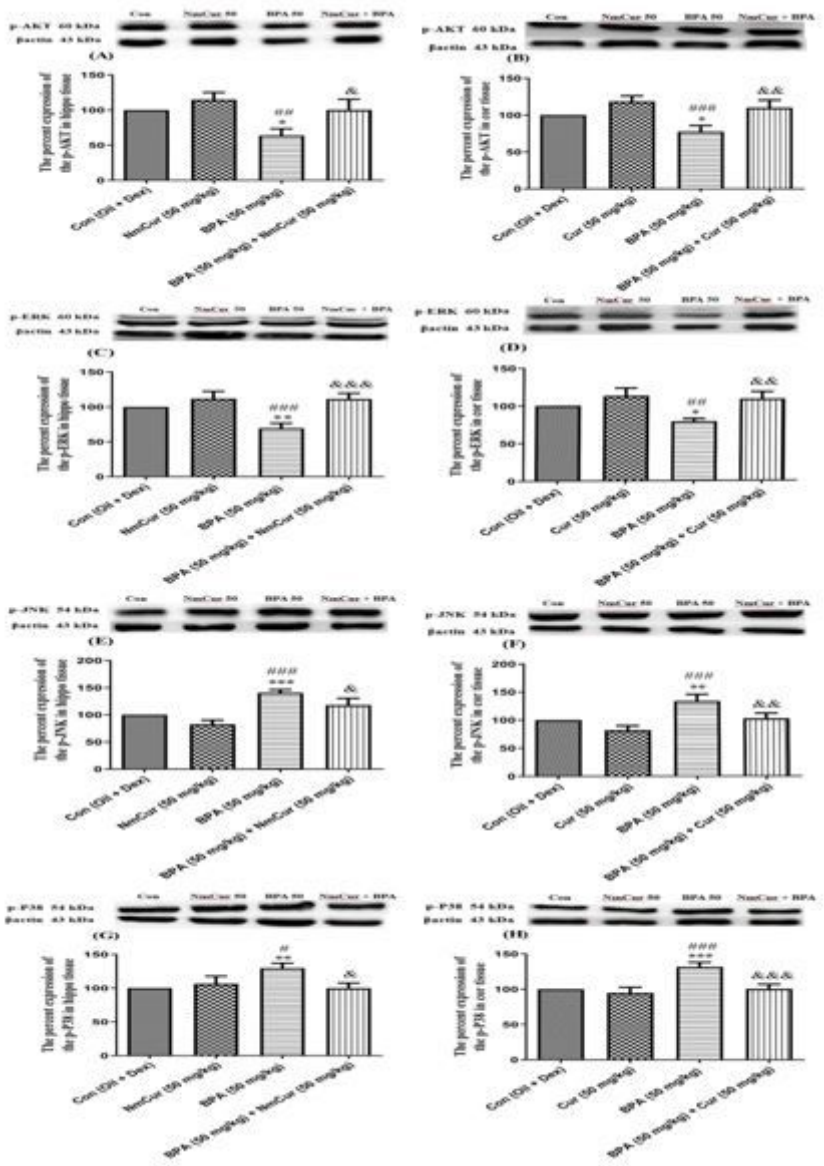

Figure 13

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on the p-AKT (A and B), p-ERK (C and D), p-JNK (E and F), and p-P38 (G and H) protein levels in the rat's hippocampus and cortex tissues, respectively. Data are shown as mean ± SD, One-way ANOVA, and Tukey–Kramer. BPA and NmCur were administered via gavage once a day and seven times per week. *P < 0.05, **P < 0.01, and ***P < 0.001, compared with the control group, #P < 0.05, ##P < 0.01, ###P < 0.001, compared with the NmCur group, and &P < 0.05, &&P < 0.01, &&&P < 0.001, compared with the BPA (50 mg/kg) group. β-actin was used as the internal control. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin, n = 8.

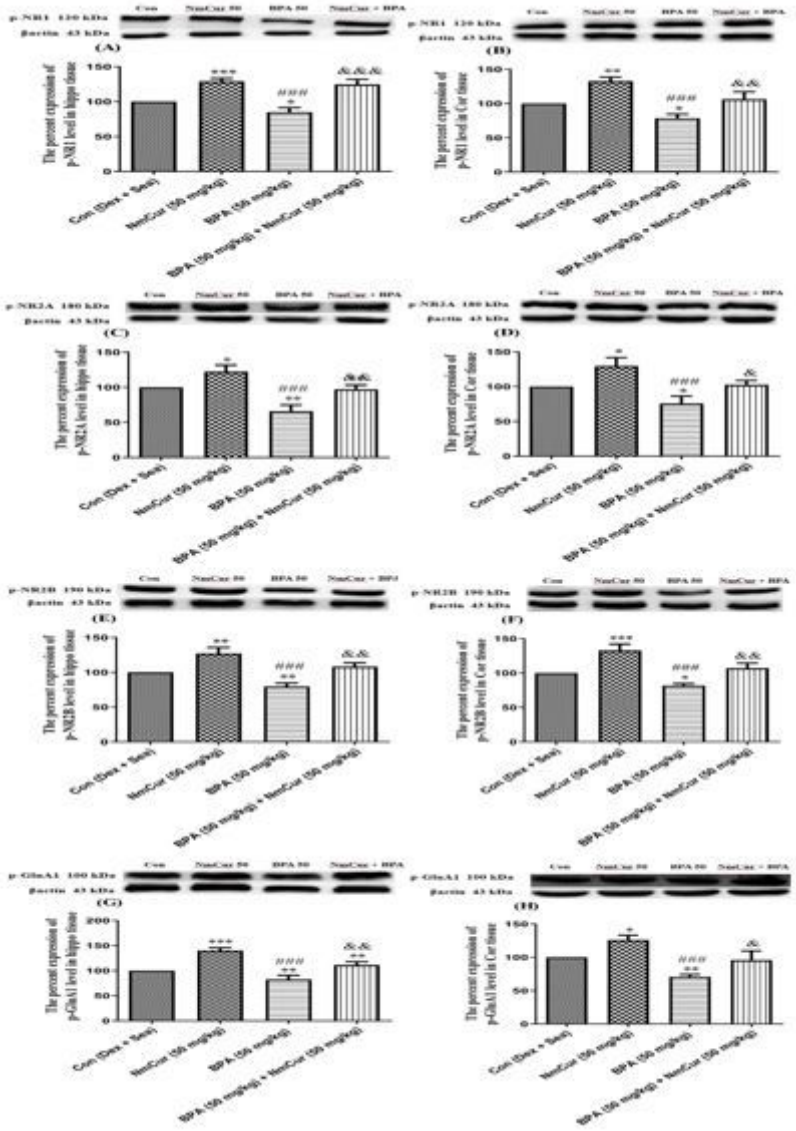

Figure 14

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on the expression of a variety of glutamate receptors, including NMDA (NR1, NR2A, and NR2B) and AMPA (GluA1) in the rat's hippocampus and cortex tissues. Data are shown as mean ± SD, One-way ANOVA, and Tukey–Kramer. BPA and NmCur were administered via gavage once a day and seven times per week. *P < 0.05, **P < 0.01, and ***P < 0.001, compared with the control group, ###P < 0.001, compared with the NmCur group, and &P < 0.05, &&P < 0.01, &&&P < 0.001, compared with the BPA (50 mg/kg) group. β-actin was used as the internal control. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin, n = 8.

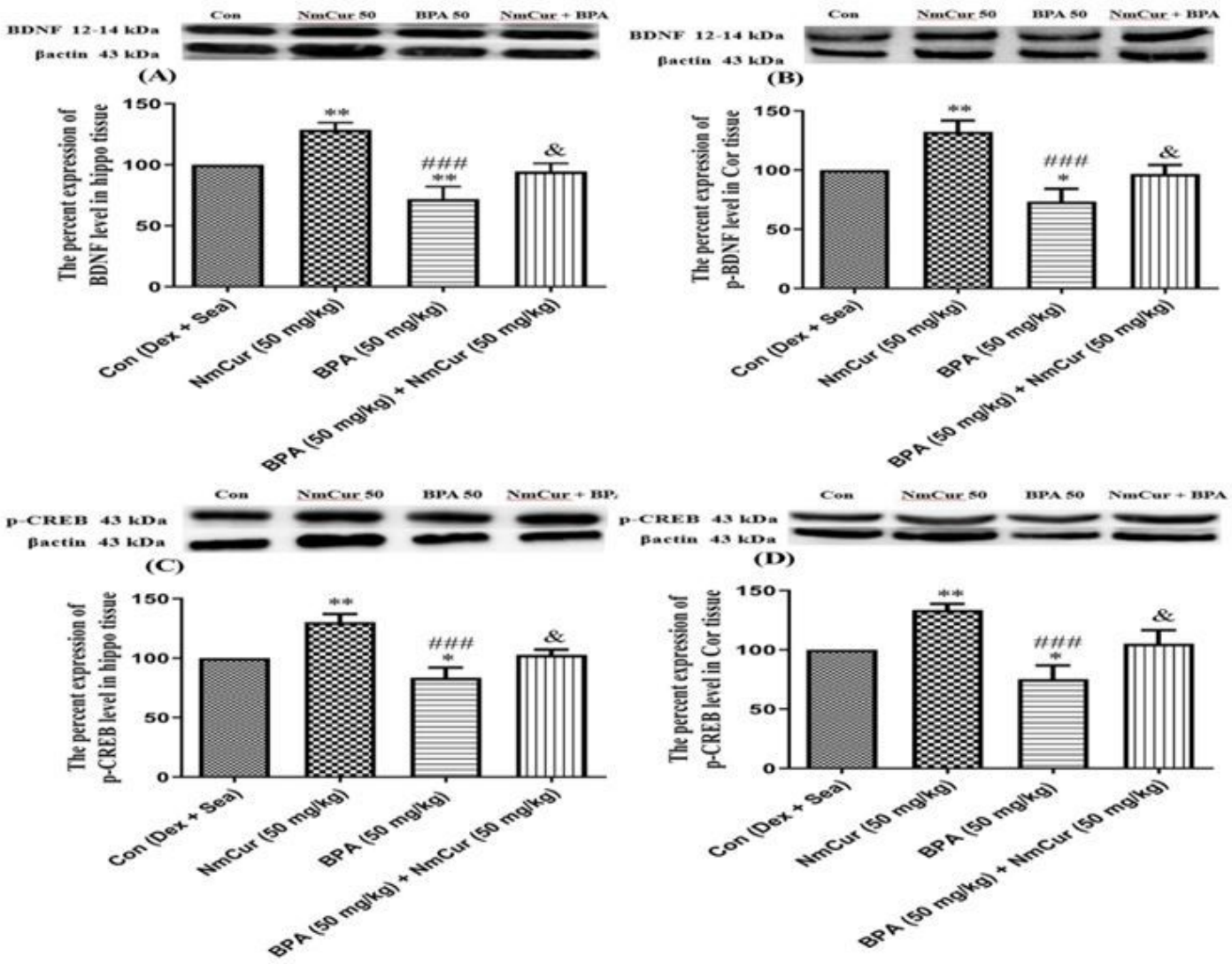

Figure 15

Effects of BPA exposure (50 mg/kg) and different doses of NmCur (10, 25, and 50 mg/kg) plus BPA (50 mg/kg) for 4 weeks on the expression of memory-associated proteins, such as BDNF and CREB, in the rat's hippocampus and cortex tissues. Data are shown as mean ± SD, One-way ANOVA, and Tukey–Kramer. BPA and NmCur were administered via gavage once a day and seven times per week. *P < 0.05 and **P < 0.01, compared with the control group, ###P < 0.001, compared with the NmCur group, and &P < 0.05, compared with the BPA (50 mg/kg) group. β-actin was used as the internal control. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin, n = 8.

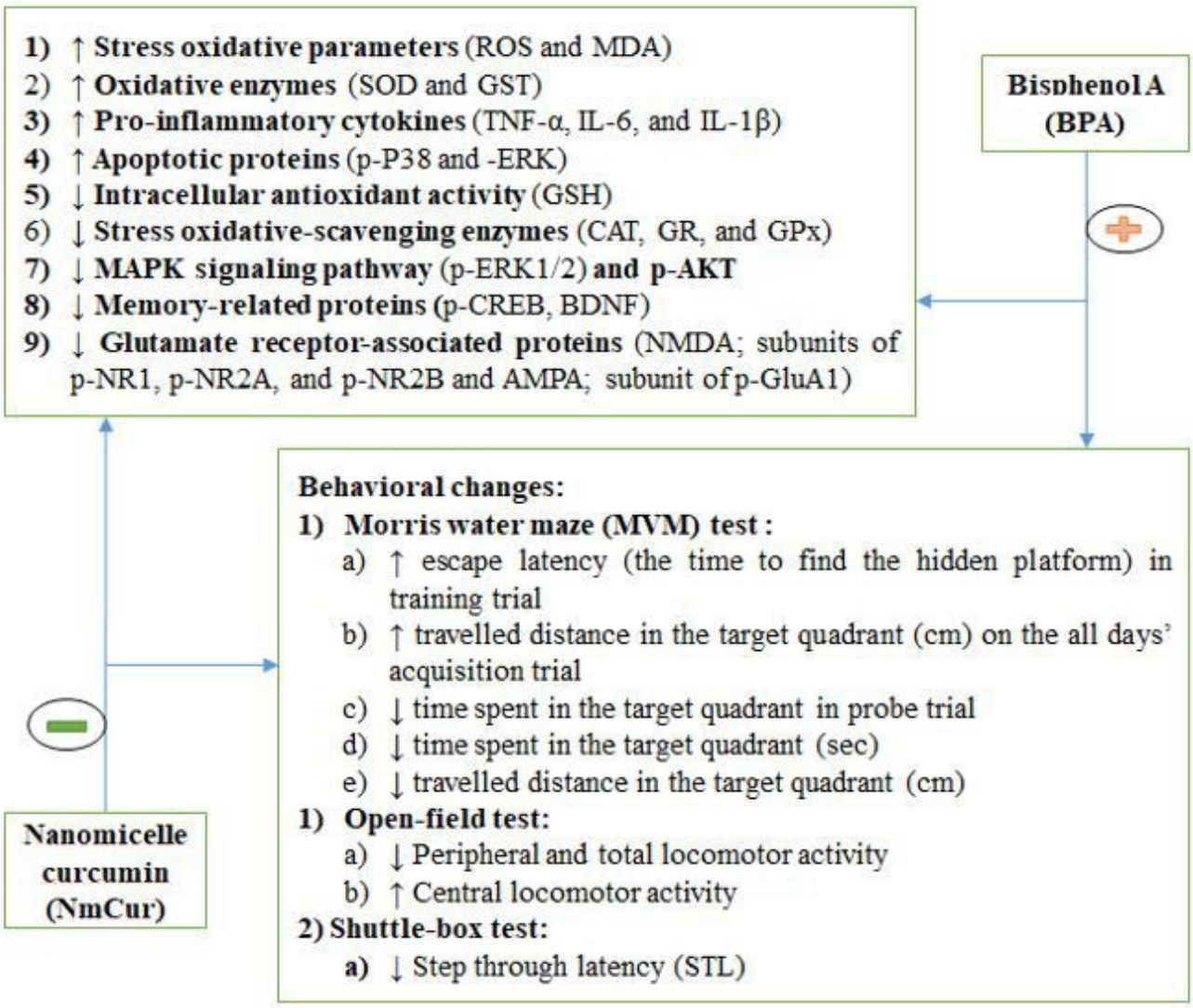

Figure 16

A schematic diagram of the effect of BPA and NmCur on changes of behavioral responses and cortical and hippocampal tissue in rat. Abbreviations: Con, control; Dex, dextrose 5%; Sea, sesame oil; BPA, bisphenol A; NmCur, nanomicelle curcumin, ROS, reactive oxygen species; MDA, Malondialdehyde; GSH, Glutathione; SOD, superoxide dismutase; GPx, glutathione peroxidase; CAT, catalase; GR, glutathione reductase; GST, Glutathione S-transferase; TNF-α,tumor necrosis factor alpha; IL-6, Interleukin 6; IL-1β, Interleukin-1β; AKT, protein Kinase B; ERK, extracellular signal-regulated protein kinases 1 and 2; P38, p38-mitogen-activated protein kinase; JNK, c-jun NH2 terminal kinases; CREB, cAMP-response element binding protein; BDNF, brain-derived neurotrophic factor; NMDA, N-Methyl-D-aspartic acid or N-Methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Positive sign definition, induction by BPA; Negative sign definition, inhibition by NmCur.