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Effects of *Ziziphus jujuba* fruits extract on Memory Impairment Induced by Hypothyroidism During Breastfeeding and Adolescence in the Rats

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Abstract

Objective: The effects of *Ziziphus jujuba* (ZJ) fruits extract on hypothyroidism-related learning and memory loss in rats were studied during breastfeeding and adolescence. **Methods**: Twenty-four pregnant rats were kept in separate cages. After delivery, the mothers and their offspring were randomly divided into five groups including (1) control, (2) propylthiouracil (PTU), (3) PTU-ZJ100mg, (4)PTU-ZJ150mg and, (5) PTU-ZJ200mg (PTU plus ZJ extract 100, 150 and 200 mg/kg respectively). All dams except the control group received 0.005% PTU in their drinking water during lactation. After the lactation period, pups continued to receive the same experimental treatment for the first 60 days of their life. Then, 10 male offspring of each group were randomly selected and assessed for the learning and memory abilities in the Morris water maze (MWM) and passive avoidance (PA) test and biochemical assessments. **Results**: ZJ strengthened BDNF and avoided oxidative disruption to the brain tissue and deterioration of learning and memory in hypothyroid rats induced-PTU. ZJ also decreased hippocampal AChE activity relative to the PTU community in both hippocampal and cortical tissues. **Conclusion**: The provided evidence in the present study indicates that enhancing amyloid-beta, BDNF, and protective influences against oxidative damage to brain tissue can be related to the useful impacts of ZJ on hypothyroid rats' cognitive function. ZJ also attenuates the activity of AChE in hypothyroid rat brain tissue. Also, ZJ administration increased the amount of serum T4.

Keywords: *Ziziphus jujuba*; Hypothyroidism; Memory; Oxidative Stress; BDNF; Amyloid-beta.

1. Introduction

Hypothyroidism, especially during developmental time, can lead to irreversible disruption to the central nervous system (CNS) (Timiras and Nzekwe, 1989). There are also numerous studies showing that hypothyroidism can cause memory loss during puberty in humans and animals (Hosseini *et al.,* 2020). Evidence indicates that a mother's hypothyroidism during childbirth often impairs the development of the brain and may lead to multiple brain disorders, including memory loss; furthermore, hypothyroidism may cause a decrease in neuronal brain synapses (Morreale de Escobar *et al.,* 2004). Hypothyroidism during childhood can trigger cognitive impairment as well as structural changes in the hippocampus, according to other proof (Zoeller and Rovet, 2004).

Hypothyroidism has been linked to brain oxidative stress (Tenorio-Velazquez *et al.,* 2005). The CNS tissue has a lipid structure, making it susceptible to oxidative harm (Halliwell, 1992; Piotrowski *et al.,* 1996; Floyd, 1999). The role of oxidative stress and free radicals in memory is crucial (Kontush, 2001). Also, it was shown that hypothyroidism increased amyloid-beta level in the brain that induced oxidative stress and cognitive dysfunction (Chaalal *et al.,* 2019).

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family, is an important protein in neuronal production, development, and survival (Mattson *et al.,* 2004). A number of previous reports have documented that, in response to hypothyroidism in developing and adult rats, a decreased level of BDNF occurs in the cerebellum, cortex, and hippocampus (Cortés *et al.,* 2012).

To reduce hypothyroidism's effects on the brain, we sought to find a herbal treatment with low side effects. Herbal remedies have been shown to have antioxidant effects, and their benefits on memory have been demonstrated in studying animals (Zhu *et al.,* 2004). The fruit of ZJ for more than 3,000 years, plant, jujube was usually utilized both as food and as herbal medicine in China (Chen *et al.,* 2017). ZJ is known for its high antioxidant concentrations like polyphenols, tannins, and flavonoids (Al-Reza *et al.,* 2009). Jujube seeds are rich in mucilage, malic acid, citric acid, and vitamin C (Zhao *et al.,* 2006). The ZJ fruit has also demonstrated inhibitory activity against acetylcholinesterase (AChE) (Zare-Zardini *et al.,* 2013). However, its effects on spatial memory weaknesses encouraged by hypothyroidism have not been scientifically documented so far. The study aims to clarify the impacts of ZJ fruits hydroalcoholic extract on hypothyroidism-related learning and memory impairment in rats through breastfeeding and adolescence. Oxidative

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stress indicators, BDNF, amyloid-beta concentration, and AChE activity were also reformed as a probable mechanism.

2. Materials and Method

2.1. Plant collection and extract preparation "

The fruits of *Zizyphus jujuba* were collected from Mabian district, Hajjah, Yemen during September and October 2019, and were identified and authenticated by Dr. Hassan H, Sugail, Assistant professor of Plant Taxonomy, Department of Microbiology, Faculty of Applied Science, Hajjah University, Yemen. The fruits were dried at room temperature in the shade before being finely powdered with an electric mill. The powdered sample (500g) was extracted four times with hydroalcoholic and then shaken at 35°C. The mixture was purified after two days of continuous shaking. In the desiccator, the filtrate was fully dried under a vacuum.

2.2. Treatments of rats

Pregnant Wistar rats were twenty-four (12 weeks of age and 220-250 g in weight), and they were bought from the Zoo, Sana'a, Yemen and put in separate metal cages in a room with 12 hours of darkness and light (from 7 a.m. onwards) at a temperature of 22±2 ^{o}C. The treatment by animals was the Experimental Animals Care and Use Guide. Following delivery, the animals and their infants divided randomly assigned into five experimental groups:

Group I: control rats delivered daily drinking water.

Group II: Propylthiouracil (PTU) rats received drinking water plus 0.005 percent PTU to induce hypothyroidism (Farrokhiet al., 2014).

Group III: received 0.005 percent PTU plus 100 mg/kg ZJ fruits hydroalcoholic extract.

Group IV: received 0.005 percent PTU plus 150 mg/kg ZJ fruits hydroalcoholic extract.

Group V: received 0.005 percent PTU plus 200 mg/kg ZJ fruits hydroalcoholic extract (Taati *et al.*, 2011; Mashhadi *et al.*, 2019).

Rat-dam provided the experimental therapies through the lactation phase, from the first day after delivery. The pups' therapies were extended for the first 60 days after the lactation period. Then, 10 male offspring of each group were randomly selected and assessed for the learning and memory abilities in the Morris water maze (MWM) and passive avoidance (PA) test and biochemical assessments. Procedures authorized by the Animal Experiments Local Ethics Committee at the Zoo, Sana'a, Yemen, "have been extended to animal handling and all related procedures."

2.3. Behavioral test

2.3.1. MWM

A black circular tank (60 cm high, 136 cm long, and 30 cm deep) filled with water (25 1 ° C) was used to assess spatial working memory in this study. Inside the tank, a circular platform was mounted 2 cm below the water's surface in the center of the southwest quarter. The platform was made of clear fiberglass. Based on the explanation given by Beheshti et al. (2017), the rodents wished to explore an invisible platform. Each experimental animal went through four trials daily, five days in a row. Also, the rodents were put in different release positions in each trial. A testing trial was conducted on the sixth day, by eliminating the platform. Each rodent was given 60 seconds to move through the maze during these procedures, and the entire time spent in the target area was recorded.

2.3.2. PA

In this analysis, the PA experiment was designed to estimate the aversive memory of the rats. The experiment was carried out using a two-chambered system consisting of different light compartments and dark ones. For separate chambers, a guillotining door was introduced. To habituate the rodent models at the start of the experiment, each rat was put 5 min/day (two days in a row) in the apparatus. The rats conducted an acquisition trial on day three; each rat was put in a well-illuminated chamber facing the adjacent room. The rat got into the dark space with the door removed, and the door instantly closed. An electric foot-shock (50 Hz and 1.5 mA for 2 s) has been triggered, the last step of which is 1-3sec. The rodents were then moved to the cages and took place in the bright chamber in 1, 24, and 48 hours at the post-training level to check for PA retention (Beheshti *et al.*, 2017).

2.4. Biochemical assessments

After the behavioral trials were completed, the rats were euthanized with urethane. The brains were extracted and the samples of the hippocampus and cortex on an ice-cold surface were precisely excised and isolated. The homogenization of the hippocampal and cortical tissues was performed employing a solution of phosphate buffer (pH=7.4) for 10 min at 1500 rpm.

2.4.1. Measurement of amyloid-beta and BDNF

To establish amyloid-beta and BDNF (MyBioSource Co, San Diego, CA, USA) concentrations in the hippocampal tissues, identical ELISA kits (Ebioscience Co, San Diego, CA, USA) and the manufacturer's instructions were used. In a microplate reader (Biotek, USA), the measured absorbance of the samples was compared with the defined standard curve in the same measurement and the concentrations were measured at 570 nm.

2.4.2. Malondialdehyde (MDA) test

In the cortical tissues and hippocampal, as a lipid peroxidation index, the concentration of MDA was calculated based on a previous procedure. Briefly, to create a red complex, MDA interacts with thiobarbituric acid (TBA). The absorbent was read in 535 nm (Farrokhi *et al.*, 2014).

2.4.3. Total Thiol Concentration Determination

The total thiol levels of tissue homogenates were achieved using the method described by Habeeb (1972). This process involves derivatization with 1-benzyl-2-chloropyridinium bromide and ultraviolet detection of S-pyridinium derivatives at 316 nm.

2.4.4. SOD Determination

Measurement of SOD level was analyzed according to the Madesh and Balasubramanian (1997) methods. The SOD Concentration behavior was read at 570 nm based on a colorimetric technique. The value of enzyme needed to prevent the rate of reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) by 50 percent was equivalent to one unit of SOD.

2.4.5. Determination of Catalase

Catalase measurement was done using by Aebi method (Aebi, 1984). I took 50 mM phosphate buffer, pH (7.0) (2.4 mL), and added 0.5 ml H2O2 - in one spectrophotometer cuvette; to a second cuvette, I added phosphate buffer without the addition of H2O2 (control). I measure at 240 nm, then I added 100 µl of the extract in the first and second cuvette and also all measured at 240 nm.

2.4.6. AChE activity determination

Measures of AChE occurrence in the tissue using the Elman (1961) approach as previously mentioned Hosseini et al. (2015). The absorbance changes were calculated for 5 min at 412 nm.

2.5. Statistical analysis

The mean ± SEM of all data was expressed. To analyze data, SPSS software (11.5) was used. The data were analyzed using the ANOVA method and Tukey's post hoc comparisons. The important level was considered to be less than 0.05, 0.01, and 0.001 of the P-value.

3. Results

3.1. Behavioral tests

3.1.1. MWM results

The results showed that it took less time for the animals dealt with both higher doses of ZJ (150 and 200 mg/kg) to enter the platform within 2-5 days of the training period (Fig. 1A). In the PTU-ZJ150 and 200mg groups, animals also displayed a decrease in the distance traveled relative to rats in the PTU group (Fig. 1B). Also, after admonishing 150 and 200 mg/kg of ZJ relative to the PTU community, expenditure time in the targeted quadrant was significant; Fig. 1C).

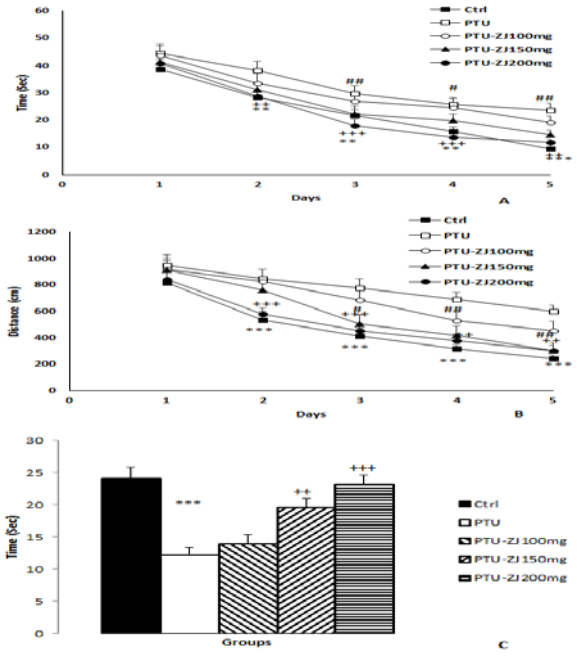

Figure 1. Latency (A) relation, distance traveled between groups (B), and spending time in the target quadrant (C).
"The sample is mirrored as mean± SEM, n= 10. **P<0.01 and ***P<0.001 vs. community of controls. #P<0.05 and ##P<0.01 150mg PTU-ZJ vs. community PTU. ++P<0.01 and +++P<0.001 PTU-ZJ 200mg vs. community of PTUs

3.1.2. PA test results

The findings showed that the delay in coming into the dim space for animals assigned to the PTU category decreased significantly after electrical shock transmission at 1, 24, and 48 h (Fig. 2A). The management of 150 and 200 mg/kg ZJ raised the time to reach the dim chamber at 1, 24, and 48 h after electrical shock induction relative to the PTU group (P < 0.05-P < 0.01, Fig. 2A). The findings also displayed that the PTU group took more time in the darkroom compared to the rats in the dominated group at 1, 24, and 48 h after electrical shock (P < 0.001; Fig. In comparison to the PTU community, administration of total doses of ZJ leads to an increase in spending time in the dim room at 1, 24, and 48 h after electrical shock delivery (Fig. 2B).

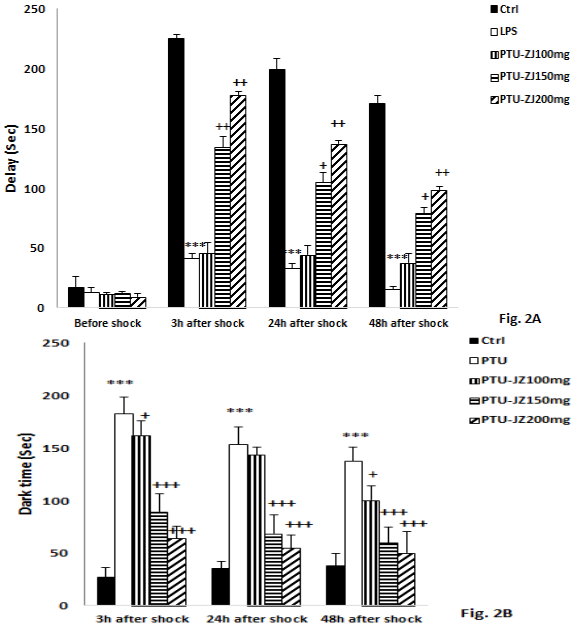

Figure 2. Comparison of latency (A) and post-shock spending time in the dark compartment (B).

"The data is reflected as mean±SEM, n= 10. ***P<0.001 vs. control group, +P<0.05, ++P<0.01, +++P<0.001 vs. PTU group, +P<0.05, ++P<0.01, +++P<0.001 vs".

3.2. Biochemical measurements

3.2.1. concentrations of MDA and thiol content

The biochemical analysis unveils that, the samples of the PTU group manifested higher levels of hippocampal MDA compared to the controls (P < 0.05; Fig. 3A) and also decreased levels of thiol concentration (P < 0.001; Fig. 3B). Administration of 200 mg/kg ZJ declined hippocampal MDA compared to the PTU group (P < 0.05; Fig. 3A). Furthermore, there exist a significant difference between PTU group and the group with the highest dosage of ZJ (200mg/kg) as it was followed by a rise in the hippocampal total thiol concentration (P < 0.001; Fig. 3B). In comparison to the control group, the animals of PTU group had higher cortical MDA concentrations (P < 0.001; Fig. 3C) and lower thiol contents (P < 0.001; Fig. 3D). Administration of all doses of ZJ declined cortical MDA compared to the PTU group (0.001<P < 0.05; Fig. 3C). Furthermore, the highest doses of ZJ (150 and 200mg/kg) vs. the PTU group, elevated the cortical total thiol concentration(P<0.01;Fig. 3D).

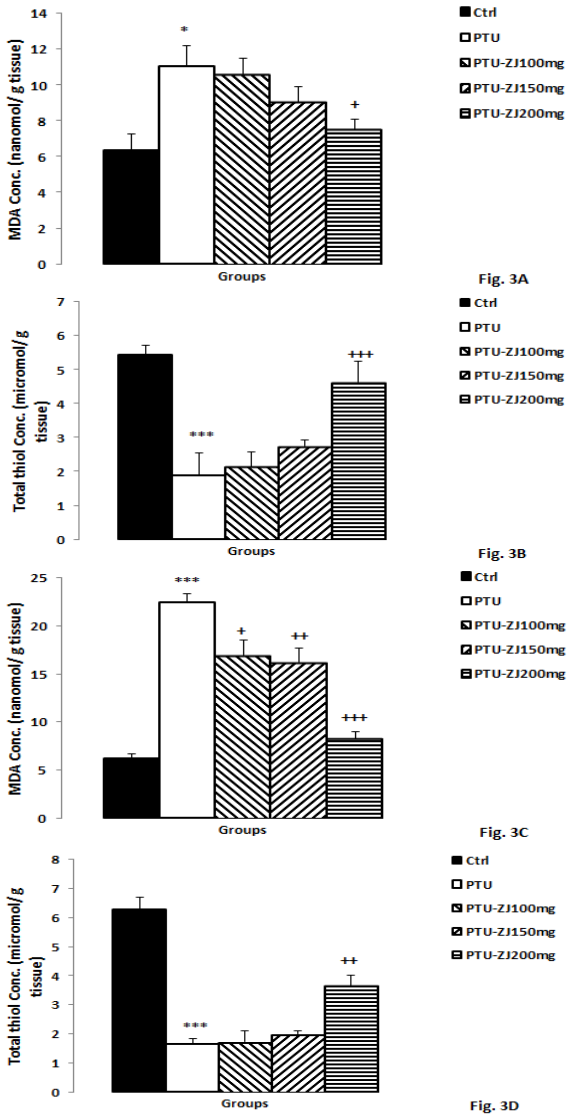

Figure 3. Hippocampal MDA (A) thiol group (B) cortical MDA (C) thiol group concentrations (D).

"The data is shown as mean±SEM, n= 10. *P<0.05 and ***P<0.001 vs. control group, +P<0.05, ++P<0.01 and +++P<0.001 vs. control group, +P<0.05, ++P<0.01 vs. group PTU".

3.2.2. SOD and catalase activities

Hippocampal SOD and catalase amount were decreased by PTU administration (P < 0.001; Fig. 4A & 4B). The two more potent doses of ZJ (P<0.01-P < 0.001; Fig. 4A) weakened this influence of PTU on SOD. Furthermore, hippocampal catalase was higher in the rats dealt with 200 mg/kg ZJ rather than in the PTU community (P < 0.01; Fig. 4B).

The findings also state that cortical SOD and catalase behaviors were decreased by the PTU intervention (P < 0.001; Fig. 4C & 4D). The two more potent doses of ZJ (P<0.01-P < 0.001; Fig. 4C) weakened this influence of PTU on SOD. There was also a substantial difference between the PTU group and those treated with all doses of ZJ, as the latent group had higher cortical catalase levels (P < 0.001; Fig. 4D).

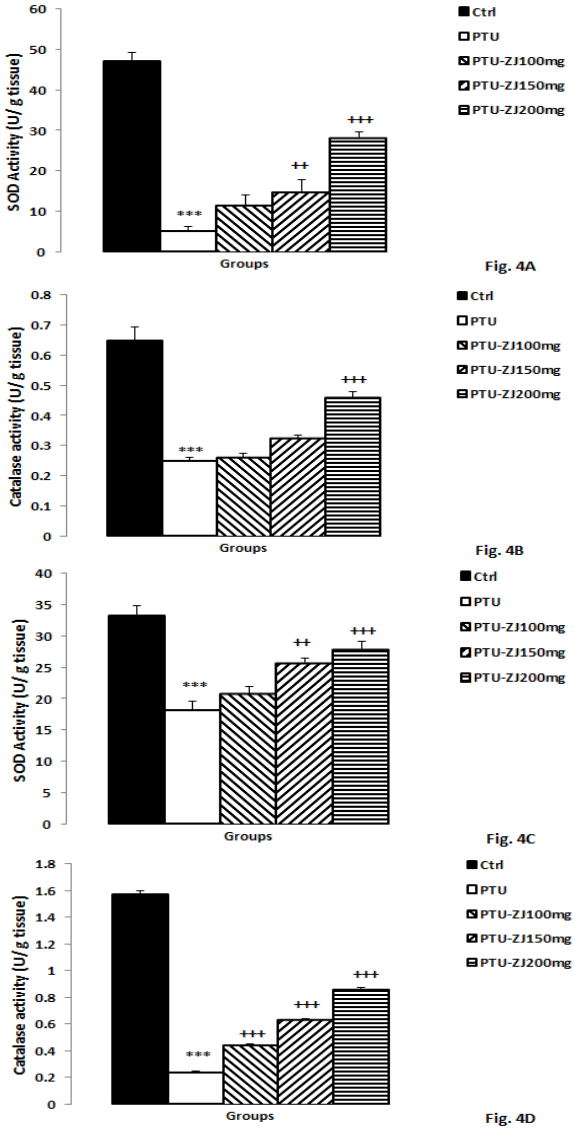

Figure 4. Hippocampal activities of SOD (A), catalase (B), SOD activities (C) and catalase (D), hippocampal (E), and cortical (F) activity of AChE.

"The data is shown as mean±SEM, n= 10. ***P<0.001 vs. control group, ++P<0.01 and +++P<0.001 vs. PTU group, respectively".

3.2.3. AChE activity

AChE activity was mainly higher in both the hippocampus and cortex of the PTU group than in the control group (P < 0.001; Fig. 5A&5B). In the administration of both hippocampal and cortical tissues, all doses of ZJ declined hippocampal AChE activity relative to the PTU community (P<0.01-P < 0.001; Fig. 5A & 5B).

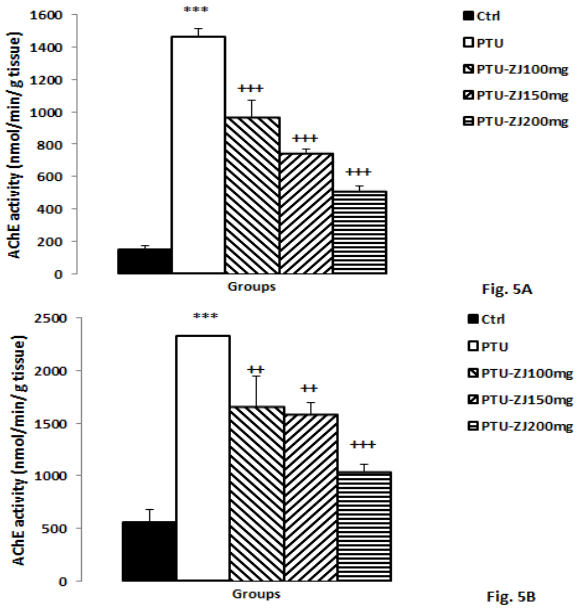

Figure 5. AChE's hippocampal (A) cortical (B) instead of operation.

"The data is shown as mean±SEM, n= 10. ***P<0.001 vs. control group, ++P<0.01 and +++P<0.001 vs. PTU group, respectively".

3.2.4. BDNF level

In the hippocampus of the PTU group than in the control group (P < 0.001; Fig. 6), so the BDNF level was significantly greater. In comparison to the PTU community, administration of all doses of ZJ reduced hippocampal BDNF levels in hippocampal tissues (P<0.01-P < 0.001; Fig. 6).

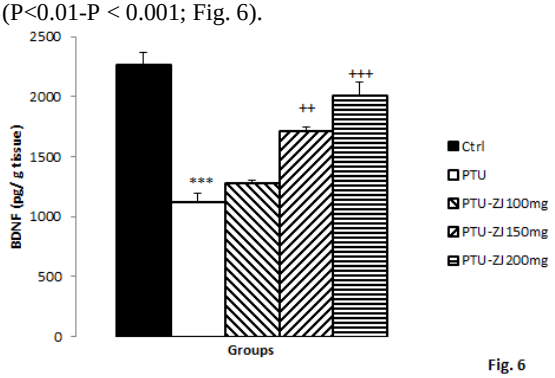

Figure 6. Hippocampal BDNF level.

The data is shown as mean±SEM, n= 10. ***P<0.001 vs. control group, ++P<0.01 and +++P<0.001 vs. PTU group, respectively".

3.2.5. Amyloid-beta concentration

Compared to the PTU community in hippocampal tissues, administration of all doses of ZJ reduced hippocampal amyloid-beta concentrations (P<0.01-P < 0.001; Fig. 7).

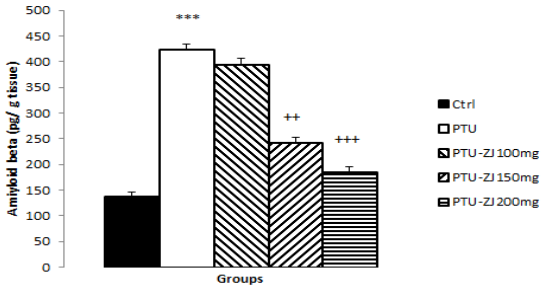

Figure 7. Hippocampal amyloid-beta level.

"The data is shown as mean±SEM, n= 10. ***P<0.001 vs. control group, ++P<0.01 and +++P<0.001 vs. PTU group, respectively".

3.2.6. T4 concentration

The PTU-induced reduction in serum T4 was significantly attenuated by treatment with all three doses of ZJ (P<0.001; Fig. 8).

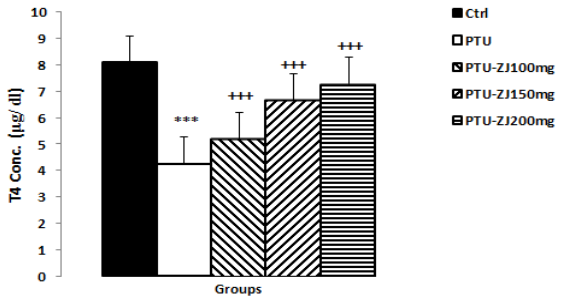

Figure 8. Serum T4 concentrations.

The data is presented as mean±SEM, with n=10 participants. $^{+++}$P0.01 vs. a group of sensors, ***P0.001 vs. group of PTUs.

4. Discussion

The current study shows that exposure of PTU to young discussion groups from breastfeeding results in hypothyroidism and adversely affects memory and learning abilities in rats. These results back up evidence from previous field studies that PTU-induced hypothyroidism may affect learning and memory in neonatal and adolescents (Farrokhi *et al.*, 2014).

Thyroid hormones regulate the expression of genes involved in antioxidant defense, growth, and division. (Santos *et al.*, 2006), and MDA was shown to be a predictor of oxidative damage in patients with hypothyroid (Torun *et al.*, 2009). According to our findings, to determine oxidative stress, we are studying the sum of MDA, whole thiol groups, activities of catalase, and SOD in the hippocampus and cortex. These results of this research were consistent with the previous studies' findings that indicated a link between hypothyroidism and hippocampus oxidative stress (Beheshti *et al.*, 2017). This study's findings indicate that brain oxidative damage due to PTU-mediated hypothyroidism is one of the potential mechanisms included in memory and learning loss during growth and infancy.

The findings of earlier work have also indicated the useful impact of ZJ on learning and memory (Rabiei *et al.*, 2014). In this study, treatment with ZJ extract reduced spending time and traveled distance in the MWM test and raised time spent on the probe day in the target quadrans; it was shown that the effects of PTU on the output of rats

relative to the PTU community in the MWM test could be attenuated by ZJ extract. The PA findings also showed that in comparison to the PTU samples, ZJ increased the time spent in the dark chamber and decreased the time spent in the dark chamber. These results indicate that ZJ extract treatment improves the memory deficits induced by PTU during the learning process as well as the regeneration process of spatial memory and non-spatial performance. Also, it has been asserted that ZJ extract can prevent ethanol-induced memory impairment (Taati *et al.*, 2016). Therefore, the improvement of behavioral performance found in the hypothyroid rats in this research could be attributed to ZJ's capacity to attenuate the brain tissue oxidative stress level. In the present analysis, the levels of MDA were lower. At the same time, the overall abundance of thiol groups and the activities of SOD and catalase were higher in both cortical and hippocampal tissues in the groups treated with the ZJ extract compared to PTU. Such findings support the positive memory effects of ZJ extract. They are compatible with previous research findings showing that ZJ extract enhances memory loss caused by oxidative damage induced by ethanol in rats(Taati *et al.*, 2016).

The current study showed that the amyloid-beta focus in the hippocampal tissues of PTU rats was greater than that of the controlled group. Another study was showed that hypothyroidism increases the amyloid-beta level (Chaalal *et al.*, 2019). Also, it was reported that thyroid hormones. Results of this study were showed that ZJ extract decreased the amyloid-beta level in the treated rat. One explanation for the beneficial effects of the extract on learning and memory may be this process.

Results of this study were demonstrated that in the PTU group, the BDNF level was lower than that in the control group. Baghcheghi et al. (2018) found that hypothyroidism reduced the amount of BDNF in hippocampal tissues. Based on these results, it can be proposed that a potential explanation for the useful impacts of ZJ on memory and learning in this research is the return of BDNF to normal levels; however, further studies are required in the future. Although the mechanism of JZ's interaction with BDNF is still uncertain; it can be suggested that the relationship between BDNF and ZJ can influence the metabolism of free radicals, such as an increase in neuronal SOD activity to decrease the free radical collection, thus protecting the neurons from an assault of the free radical, oxidative stress has been offered to contribute to decreases in BDNF and the resulting deterioration in learning and memory (Xiao *et al.*, 2010).

PTU-induced hypothyroidism has been documented to increase AChE activity (Salvati *et al.*, 1994). Growing AChE mechanism has been linked to learning and memory deficiencies in many studies (Schmatz *et al.*, 2009). Our study findings also indicate that PTU induction of hypothyroidism increases the AChE function. In confirming our results, another study showed that hypothyroidism maximized AChE activity in CNS (Baldissarelli *et al.*, 2017). In the current study, ZJ reduced the activity of AChE, thus leading to an enhancement in the learning and memory capability of the hypothyroid rats. Another experiment revealed that ZJ extract enhanced learning and memory decline by increasing acetylcholine levels by inhibiting AChE activity (Li *et al.*, 2013).

5. Conclusion

In conclusion, the evidence presented in this research indicates that enhancing amyloid-beta, BDNF, and protective influences on oxidative damage to brain tissue can be related to the useful impacts of ZJ on hypothyroid rats' cognitive function. ZJ also attenuates the activity of AChE in hypothyroid rat brain tissue. Also, ZJ administration increased the amount of serum T4. In future research, the mechanism(s) in charge of enhancing the impacts of ZJ on T4 roles should be explored.

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