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ZATARIA MULTIFLORA BOISS IMPROVES LEARNING AND MEMORY IMPAIRMENT INDUCED BY *TOXOPLASMA GONDII* INFECTION

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Abstract

Recent epidemiological and experimental studies also showed that latent toxoplasmosis can lead to a number of neurological and behavioral disorders such as learning and memory impairments. Recent studies showed that the essential oil and methanolic extract of the *Zataria multiflora* revealed a significant anticholinesterase activity on in vitro ().Here, we evaluated the effect of *Z. multiflora* essential oil to ameliorate learning and memory impairments induced by *T. gondii* infection in BALB/c mice. The animal model of *Toxoplasma* infection was established by the intraperitoneal inoculation of 20-25 tissue cysts from Tehran strain of *T. gondii.* Morris water maze (MWM) task was used to assay spatial learning and short term spatial memory in all groups. The findings revealed that in this study demonstrated that *latent toxoplasmosis* impaired spatial leaning and short term spatial memory of the infected BALB/c mice, while ZME, due having AChE inhibitor activity, improved impairments induced by *Toxoplasma* infection. The obtained findings demonstrated ZME as an AChE inhibitor to improves learning and memory disorders in mice with latent toxoplasmosis probably via restoring ACh levels in brain. However, additional studies are needed to clarify these mechanisms and also other possible ones.

Keywords: *Zataria multiflora*" learning″ Memory" *Toxoplasma gondii.*

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1. Introduction

Toxoplasmosis caused by protozoan parasite *Toxoplasma gondii* which affects a broad range of animals as well as humans. According to the previous reports, nearly one-third of the human world's population is infected with toxoplasmosis (Hill, D, & Dubey, (2002). Human infection to toxoplasmosis can be occurred by way of eating of tissue cysts in undercooked meat, consumption of water and food contaminated with the oocysts exerted in the feces of cats and transmission from mother to child during pregnancy (Dubey, 2004). In general, human toxoplasmosis is without any specific symptom and signs. However, in immunocompromised persons the disease may cause severe complications such as encephalitis, chorioretinitis, and systemic involvements (Tavakoli et al, 2017; Rostami et al, 2014). After infection with toxoplasmosis, bradyzoites from the tissue cysts or sporozoites liberated from oocysts convert to the tachyzoites forms that are the quickly multiplying in cells and result in tissue demolition and dispersal the infection. Tachyzoites finally develop to tissue cysts in the different organs chiefly in muscles and central nervous system (CNS).

2. Problem Statement

Nowadays it has been proven that tissue cysts are able to influence several biological activities of cells for example synthesis of some neurotransmitters, synapse contrauction, and signaling (Prandovszky, 2011; Gatkowska, 2013). Recent epidemiological and experimental studies also showed that latent toxoplasmosis can lead to a number of neurological and behavioral disorders such as learning and memory impairments (Celik, 2010; Alipour, 2011).

3. Research Questions

Acetylcholine (ACh) represents a key function in the regulation of cognitive and behavioral activities (Blockland, 1996). Recent investigations exhibited that toxoplasmosis enhances the activity of acetylcholinesterase (AChE) as a membrane-bound enzyme which hydrolyses ACh (Tonin et al, 2013; 2014). Herbal medicines are usually well-known as prosperous source for prevention and treatment of numerous diseases such as behavioral and neurological disorders in the various countries around the world (16). *Zataria multiflora* Boiss. from the Laminaceae family usually grows in Iran, Afghanistan and Pakistan (Hosseinzadeh, Ramezani, & Salmani, 2000). Modern pharmacological study demonstrated that *Z. multiflora* have some medicinal uses for example antimicrobial, anti-oxidant, antinociceptive, and anti-inflammatory effects (Sajed, 2013). Moreover, recent studies showed that the essential oil and methanolic extract of the *Z. multiflora* revealed a significant anticholinesterase activity on in vitro (Sharififar, 2012). Reviews have reported that major components of the *Z. multiflora* essential oil (ZME) are monoterpenoid derivates including carvacrol, thymol and eugenol (Sajed, 2013); on the other hand, some studies demonstrated that several factors for instance geographical resource of plant and collection time may be touching on the chemical composition and functional activity of essential oils (SaediDezaki, 2016; Yesil Celiktas, 2007).

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4. Purpose of the Study

Here, we evaluated the effect of *Z. multiflora* essential oil to ameliorate learning and memory impairments induced by *T. gondii* infection in BALB/c mice.

5. Research Methods

5.1. Animals

Thirty two male BALB/c mice (6–8 weeks old) weighing from 20 to 25 g were purchased from the Pasteur Institute of Iran (Karaj, Iran). Mice were kept in a colony room of Kerman Neurosciences Research Center with a 12:12 h light/dark cycle at 21 ± 2°C and were handled in line with the standard protocols for the employ of laboratory animals. Animals were randomly divided to four experimental groups (eight mice per each group) following: (i) mice infected by *T. gondii*; (ii) non-infected mice as control group; (iii) infected mice treated with ZME at the dose of 0.1 ml/kg; (iv) infected mice treated with ZME at the dose of 0.1 ml/kg. The protocol was approved by the Committee on the Ethics of Animal Experiments of the Kerman University of Medical Science (No.93/20) and Kerman Neurosciences Research Center, Kerman, Iran.

5.2. Parasite

Here to induce the latent *T. gondii* infection, the Tehran strain of *T. gondii* was compassionately prepared by Prof. Hossein Keshavarz at Tehran University of Medical Sciences (Teharan, Iran). Tissue cysts of *T. gondii* to infect animals were isolated from the brain tissue of infected mice and the number of cysts was counted under a microscopy with a 10× objective.

5.3. Establishment of T. gondii infection

The mice model of latent toxoplasmosis was established based on the method explained by Saraei et al (Saraei, 2014). In brief, 0.5 ml of the brain suspension of infected mice containing the 20-25 tissue cysts was intraperitoneally administrated tested mice.

5.4. MAT test

To confirm the establishment of chronic toxoplasmosis, 60 days post-infection, all the inoculated mice were examined for anti-*T. gondii* IgG antibody via the modified agglutination test (MAT) using a commercial kit (Toxoscreen DA, Biom´erieux, Lyon, France) in agreement with the manufacturer's instructions, and starting at a 1/20 dilution. Sera showing an agglutination titer of 1/20 or higher were considered positive and were end-titrated using 2-fold dilutions.

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5.5. Treatment with ZME

ZME at the dose of 0.1 and 0.2 ml/kg was orally administrated once a day for two weeks starting from post-infection day 90.

5.6. Morris water maze (MWM) test

The MWM task was used to assay spatial learning and memory (Aghaei, (2014). The MWM consisted of a black circular swimming pool which was painted with nontoxic materials black circular pool, 160 cm diameter, 80 cm height-filled with water maintained at room temperature to a depth of 40 cm. The pool was geographically divided into four quadrants of equal size and starting points were designated at each quadrant as N, S, E, and W. A square platform (10 cm diameter) was hidden just below (1.5 cm) the surface of the water in the center of the northeast quadrant. The experiments were carried out in a dimly light room with various and fixed extra maze geometric images (e.g., circles, squares or triangles) attached at different points on the walls around the maze. Performances were recorded by a smart video tracing system (Noldus Ethovision® system, version 5, USA) and animals could be traced on the screen of a computer.

5.6.1. Spatial learning

In the spatial acquisition phase, the mice were allowed to find a submerged hidden platform during a 60-second-interval in four training trials (inter-trial interval = 60 s) repeated in three blocks (inter-block interval = 30 min). After finding the platform, the animals were allowed to rest on the platform for 20–30 s. The mice were dried with a towel and returned to their cages. After 20 to 30 s of rest, they were once again put in the chamber for the next trial. When mice did not find the platform within 60 s, the experimenter would put it on the platform. On each trial, mice were randomly released into the water from one of the four quadrants of the maze with their faces toward the wall of the quadrant where they were released. Each mouse had 4 different releasing points. Parameters such as latency and the traveled distance to find the platform were recorded in each trial.

5.6.2. Short term spatial memory

Two hours after the acquisition phase, a probe test was performed to evaluate spatial memory retention. For the probe test, the platform was removed and each mouse was allowed to swim for 60 s. The time and distance spent in the target quadrant (quadrant 4) were analyzed as a measure of spatial memory retention.

5.6.3. Latency to visible platform and swimming speed

Following the probe trial, mice had to complete a visible platform test to determine any possibility of *Toxoplasma* infection and $A\beta_{1-42}$model interference with sensory and motor coordination or

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motivation. In this test, the ability of animals to escape to a visible platform was evaluated (the platform was raised 2 cm above the water level and was visible with aluminum foil).

5.7. Statistical analysis

Obtained results are expressed as the mean ± SEM. Data analysis was carried out by using SPSS statistical package version 17.0 (SPSS Inc., Chicago, IL, USA). One-way ANOVA with Tukey's post-hoc test was used to assess differences between experimental groups (20). In addition, $P<0.05$ was considered statistically significant.

6. Findings

6.1. Latency to visible platform and swimming speed

Table 1 demonstrated that mice in all tested groups had similar escape latency and swimming speed in the MWM test, which demonstrated no considerable differences between the groups in visual and motor functions.

Table 01. Comparisons of swimming speed and latency to escape onto the visible platform in Morris water maze among groups using one way analysis of variance (ANOVA) (the differences were not significant). Data are means ± S.E.M

Group	Swimming speed (cm/s)	Escape latency (s)
Control	20.4 ± 3.6	18.8 ± 2.4
Toxoplasma	19.4 ± 1.8	20.1 ± 3.6
ZME (0.1 ml/kg)	21.6 ± 2.7	19.2 ± 2.1
ZME (0.2 ml/kg)	23.3 ± 3.1	21.8 ± 3.21

6.2. Spatial learning

The obtained results showed that the distance traveled to reach the platform was considerably increased in mice with toxoplasmosis ($P < 0.05$) in comparison with the control group, demonstrating a weaken learning in infected mice. After treatment of infected mice with ZME in doses of 0.1 and 0.2 ml/kg, the distance travelled to reach the platform was decreased compared to the control group (Figure 01A). Figure 01B showed, the escape latency of infected mice significantly ($P < 0.01$) enlarged compared to mice in the control group; however after treatment infected mice with ZME in doses of 0.1 and 0.2 ml/kg the escape latency significantly reduced ($P < 0.05$) in comparison to the untreated-infected mice. The statistical analysis also showed that there was no considerable difference in the swimming speed of mice in the the all tested groups (Figure 01C).

6.3. Short term spatial memory

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In term of spatial memory, the statistical analysis demonstrated that in the infected mice with *T. gondii* significantly ($P < 0.001$) spent less distance and time in the target quadrant in comparison with uninfected mice (control groups) (Figures 02A, B), which demonstrated short term memory impairment in them. While the treatment of infected mice with the ZME in doses of 0.1 and 0.2 ml/kg neutralized the effect of toxoplasmosis, since the infected mice treated with the ZME spent more distance and time in the target quadrant in compassion with untreated mice ($P < 0.01$). Based on statistical analysis, *T. gondii* infected mice treated with ZME in doses of 0.1 and 0.2 ml/kg the crossing number was significantly ($P < 0.001$) increased in comparison to non treated infected mice (Figure 02C).

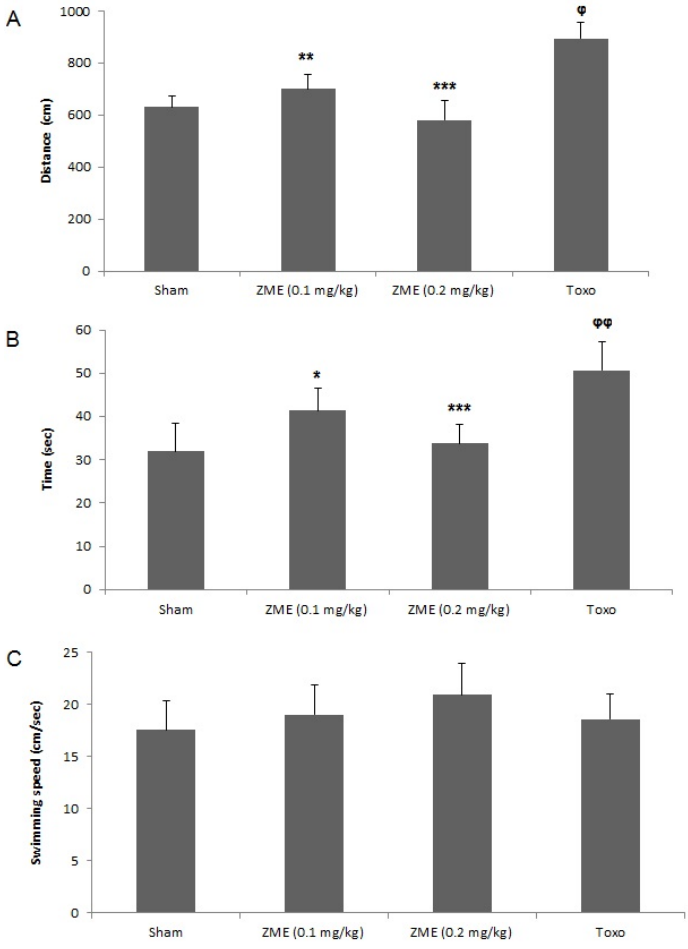

Figure 01. Impaired learning observed in the *Toxoplasma* group compared to the control groups in Morris water maze task. Increased distance (A) and time spent (B) to reach the hidden platform were observed in the *Toxoplasma* group in compared with control group; while they were significantly decreased in mice treated by ZME. There was no significant alteration in swimming speed of mice in all groups (C). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.01$ indicating the significant differences with the *Toxoplasma* group. φ $p<0.05$ compared with the control group.

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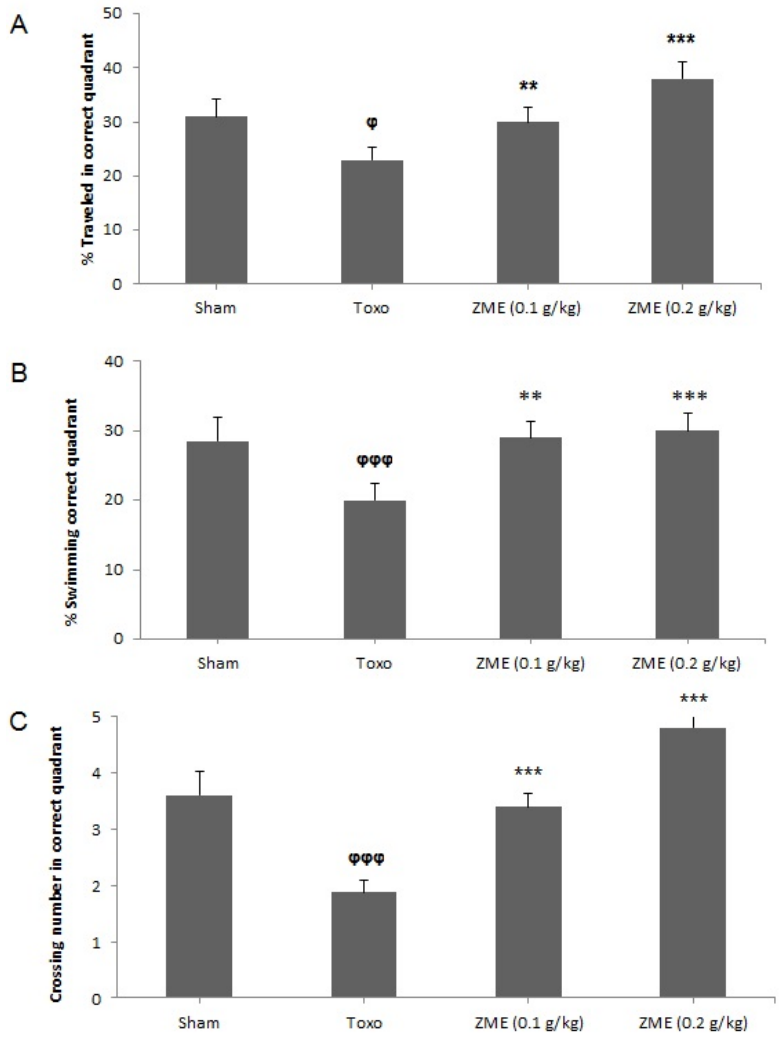

Figure 02. The effects of *Toxoplasma gondii* infection and ZME on spatial short term memory. The distance (A) and time (B) in the target quadrant decreased significantly in the *Toxoplasma* group compared to the control group. The number of crossing from the platform region was also significantly decreased in the *Toxoplasma* group compared to the control group. The distance, time, and the number of crossing were significantly increased in infected mice treated by ZME* $P < 0.05$, ** $P < 0.01$, *** $P < 0.01$ indicating the significant differences with the *Toxoplasma* group. φ $p<0.05$ compared with the control group.

7. Conclusion

The previous studies demonstrated that *T. gondii* as a neurotropic protozoan parasite can affect the behavior of their host such as human (Fekadu, Shibre, & Cleare, 2010). Reviews also showed the association between chronic toxoplasmosis and risk of a number of neurological disorders including schizophrenia, personality disorders, obsessive compulsive disorder, and Parkinson's disease (Celik, 2010; Alipour, 2011; Mahmoudvand, 2015; 2016). The present investigation was aimed to evaluate the effect of *Z. multiflora* essential oil to ameliorate learning and memory impairments induced by *T. gondii*

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infection in BALB/c mice. The obtained findings revealed that mice with latent toxoplasmosis had notable impairments in the spatial learning and short time memory in MWM test in comparison to the healthy mice (control group). Previously Zhou et al (2011) showed that by Prugniaud strain of *T. gondii* which caused chronic toxoplasmosis could damage to the learning and memory function in Kunming mice. Daniels et al (2015) also have indicated that latent toxoplasmosis in rats can cause several neurocognitive impairments such as memory impairment (Daniels, Sestito, & Rouse, 2015). On the contrary, in a study it has been shown that in chronic toxoplasmosis can recover learning and memory impairments in mice with Alzheimer's disease (Jung, 2012). However, these variations regarding the impacts of chronic toxoplasmosis on behavioral functions might be associated to a number of criteria such as type of rodent, infection route, strain of *T. gondii*, and etc (Haroon, 2012; Worth, 2013).

Recently, Tonin et al (2014) have reported that latent toxoplasmosis has ability to influence cholinesterase activity and improve the AChE levels in brain of infected mice (Tonin et al, 2013; Tonin et al 2014). Since last years, reviews have reported that ACh play a chief function in the regulation of learning and memory functions (Blockland, 1996). Nowadays, the successful approaches to treat neurocognitive disorders considered to improve the ACh activity via enhancement of level of Ach level using production promoters and also inhibitors of its metabolizing enzyme. Between the diverse methods studied, the blockage of AChE is the main useful one (Giacobini, 1996; Easton et al., 2013). In the recent years, AChE inhibitors extensively applied to get better the cognitive disorders including learning and memory ones by increase acetylcholine levels at synapses (Giacobini, 1996; Easton, 2013). Recently, Sharififar et al (2012) have reported that the essential oil and methanolic extract of the *Z. multiflora* showed a considerable anticholinesterase effect that was comparable to eserine (Sharififar, 2012). Here, we found that a protecting function for ZME as an AChE inhibitor on learning and memory changes caused by latent toxoplasmosis. Several studies on chemical composition of ZME exhibited that the major components of essential oil are thymol and carvacrol, and p-cymene (Sajed, 2013). Jukic et al (2007) have demonstrated the potent AChE inhibitory effect of Tymole and carvacrol (Jukic et al, 2007). On the other hand, Azizi et al (2012) have demonstrated cognitive-enhancing activity of thymol and carvacrol in two rat models of dementia; so that they improved spatial learning and memory impairment in tested mice (Azizi et al., 2012). Therefore, it can be suggested that these compounds are probably responsible for AChE inhibitory activity of ZME and consequently its cognitive-enhancing activity on improvement of spatial learning and memory disorders. The obtained findings demonstrated ZME as an AChE inhibitor to improve learning and memory disorders in mice with latent toxoplasmosis probably via restoring ACh levels in brain. However, additional studies are needed to clarify these mechanisms and also other possible ones.

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