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Original Article

Sub-chronic administration of brewed coffee on rat behavior and cognition and oxidative stress Alzheimer's disease model

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SUMMARY

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by intracellular neurofibrillary tangles and neuro-inflammation. Growing experimental evidence indicate diverse biological effects of brewed coffee (BC) including antioxidant, neuroprotective and anti-inflammatory. However, the underlying neuroprotective mechanism of BC is still largely elusive. Keeping this in mind, the present study was aimed to investigate the neuroprotective effects of BC on STZ-induced AD.

We observed that path length and latency time and path length increased in STZ induced AD while BC administration enhanced these indices in the BC-STZ group. After treatment with BC, latency times in groups with memory impairment enhanced in shuttle box and MWM tasks. Biochemical factors including lipid peroxidation marker and tumor necrosis factor-α increased in STZ induced AD and BC treatment ameliorated these. Total anti-oxidant concentration level has reduced in AD rats and otherwise, BC treatment has prevented its reduction.

Our study demonstrated that BC pretreatment significantly improved spatial learning and memory functions, effectively mitigated ICV-STZ mediated neuronal oxidative stress and improved neurobehavioral functions. Moreover, BC attenuated hippocampal

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neuro-inflammatory response in the hippocampus. Thus, our study further provides evidence for the therapeutic supplementation of BC for various neurodegenerative disorders including AD.

1. Introduction

Alzheimer's disease (AD) is a common neurodegenerative disease and one of the reasons for the continued neurological disorders [1]. The AD is characterized by irreversibly progressive impairment of learning, memory and other cognitive deficits leading to death [19]. This neurodegenerative disease has affected millions in recent years and will triple in the next thirty years [26]. Enhanced oxidative stress, weakened antioxidant system, and amplified inflammatory cytokines leading to cholinergic dysfunction are among its pernicious effects [15]. Finally, extracellular deposition of amyloid- β protein causes neuronal death [22]. Cholinergic deficits, memory impairment, oxidative stress, and neuro-inflammation are produced by the ICV injection of sub-diabetogenic dose of streptozotocin (STZ), resulting in the pathological features of AD [31].

The effects of dietary components on the central nervous system have been well studied. Lack of important ingredients in the diet is considered as one of the major causes of neurodegenerative diseases. Recently, studies have shown that the progression of the AD is reduced by foods that have an antioxidant role [38]. For years, data gathered have suggested that some ingredients in the diet play significant roles in regulating immune functions, especially those related to the inflammation.

Coffee is now known as a medicinal plant and is highly popular worldwide because it is a safe and nontoxic beverage that has no side-effects [21]. Heated coffee beans are used for preparing brewed coffee (BC). Therapeutic properties and health benefits of coffee consumption for diabetes and neurodegenerative diseases have been studied broadly, possibly by suppressing inflammatory processes [7]. Several important compounds in the coffee, called caffeine, chlorogenic acid, and javamide-II have been considered as major contributing components related to inflammation [27]. However, its efficacy is often challenged by the requirement of relatively high doses in the experiments. Many studies done to examine the various effects of coffee have used forms of the coffee which are unlikely to be used for the treatment of neurodegenerative diseases. On the other hand, common therapeutic lines of the AD are can neither cure nor prevent it [33]. Since the prevention of disease is often far easier, faster, less expensive, and painful than treating the disease when it occurs, this recognition has led us to choose the prophylaxis strategy. To the best of our knowledge, there is no published scientific report on the effects of BC on cerebral inflammation, passive and spatial learning, and memory deficits induced by STZ in the AD rat model. Therefore, the aim of this study was to investigate the effects of coffee pre-treatment on active and passive memory, oxidant–antioxidant balance, and TNF-α level after STZ induced AD in the male rats.

2. Materials and methods

2.1. Materials

All reagents were of analytical purity. The assay kits for total antioxidant capacity (TAC) and malondialdehyde were purchased from Teb Pazhouhan Razi Institute (Tehran, Iran). The TNF-α kit were purchased from Diaclone (France).

2.2. Animals

Thirty-two adult male Wistar rats (220–250 g) were obtained from animal care and breeding center, Zahedan University of Medical Sciences (ZAUMS), Zahedan, Iran. They were maintained under

standard condition, temperature-controlled room (20 ± 2 °C), and a 12/12 h light/dark cycles (lights on 6:00 a.m.–6:00 p.m.). Animals were allowed ad libitum access to water and standard lab chow. All experimental protocols were carried out in agreement with the regulations set by the ethics committee of the Zahedan University of Medical Sciences, Zahedan, Iran (IR. ZAUMS. REC.1397.341).

2.3. Experimental design

Animals were kept in standard cages (four rats per cage) and divided randomly into four main groups: 1) Sham: animals received normal saline (NS) for twenty-one consecutive days, 2) BC: Rats received coffee for twenty-one consecutive days before test days, 3) ICV-STZ: animals received STZ, then treated with NS similar to the above time, 4) BC-STZ: Rats received BC for twenty-one consecutive days before STZ induced AD. Experimental schedule and intervals for the estimation of various parameters are shown in Fig. 1. During the light phase, all procedures were performed between 8:00 and 12:00 a.m.

2.4. Preparation of coffee

A filtered BC was prepared with the technique described by Vitaglione et al. [41] as follows: 10 g of the coffee powder was added in filter paper; then, 100 mL of water at 90 °C was poured into the coffee. The BC was always prepared at the gavage time. The BC was gavaged once daily for twenty-one days and the dose used was 5.7 mL kg^{-1} per day, which is comparable to an adult human drinking eight 50 mL cups of BC (10%) per day [23].

2.5. Morris water maze

Spatial learning and memory were investigated using Morris water maze (MWM) task. MWM is made from a circular pool (180 cm in diameter and 60 cm in height) with a smooth dull inner surface. The circular pool was filled with water (26 ± 1 °C). The tank was placed in a dimly light, sound insulation room with various constant extra-maze cues. The pool was practically divided into four quadrants. The movable hidden escape platform (12 cm in diameter and 38 cm in height) was located in the center of the pool quadrants and submerged 2 cm below the water surface so that it was not visible at water level. During the 4 subsequent days, the rats were allowed training sessions four times per day with the platform in place. For each training trial, rats were placed in the water facing the pool wall in different pool quadrants, with a variable order on each day. When a rat located the platform, it was permitted to remain on the platform for 30 s. If the rat failed to reach the platform within 90 s, it was placed on the platform for 30 s. The animal was taken to its home cage and was allowed to dry under an infrared lamp after each trial. During each trial, the time taken to find the hidden platform (latency) was recorded using a video camera-based Ethovision System (Nodulus, Wageningen, Netherlands). On the fifth day, rats were subjected to a probe trial session in which the platform was removed from the pool and rats were allowed to swim for 90 s to explore it. The time spent by a rat in the target quadrant searching for the hidden platform was recorded as the index of retrieval [34].

2.6. Passive avoidance test

The two shuttle box instrument is a well-established experimental procedure used to assess short-term reference memory, which is dependent on cortical and hippocampal circuitries [29]. The step-through passive avoidance test was performed in identical illuminated and dark chambers (ST-5500, Borj Sanat Co, Tehran, Iran). The illuminated chamber was lightened by a 5 W Lamp, and the floor of the non-illuminated compartment was composed of stainless steel bars separated by 1 cm distance. These compartments were separated by a guillotine door. The procedure was performed in 4 days; on the first and second days, the rats were adapted for recognition of chamber. For 10 min rats were free to move in light and dark chambers. On the third day, rats were initially located in the illuminated chamber and the door between the two chambers was opened 20 s later for the acquisition trial. When

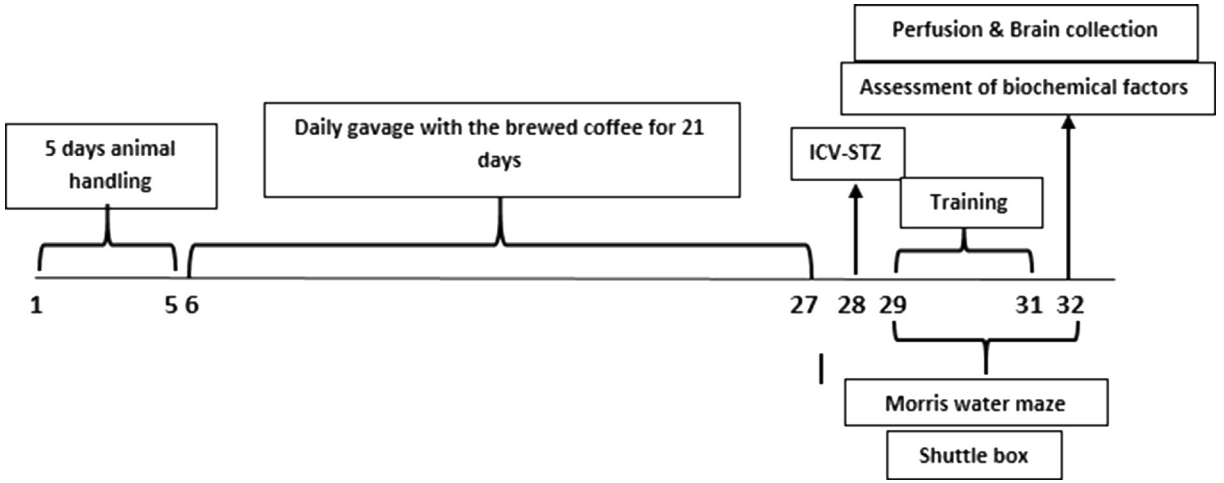

Fig. 1. Various parameters measured and the time intervals are presented in a scheme of experimental schedule.

the rats entered the dark chamber, the door closed automatically and an electrical foot shock (0.5 mA, 3 s) was delivered through the stainless steel rods. Twenty-four hours (fourth day) after the acquisition trial, the rats were again placed in the illuminated chamber for the retention trials. The time taken for a rat to enter the dark chamber after the door opened and the time spent in the dark chamber were recorded. The cut-off time was 300 s [34].

2.7. Tissue sampling

24 h following MWM probe test and shuttle box, the rats were euthanized with ketamine (100 mg/kg) and decapitated. The brains were quickly dissected. Hippocampi were isolated and blotted dry, then weighed and prepared as a tissue homogenate in ice-cold (10% w/v) phosphate buffer (pH 7.4). After centrifugation (1000×*g*, 4 °C, 10 min), the supernatant was removed and stored at −70 °C until assayed.

2.8. Biochemical analysis

The hippocampal content of TNF-α, TAC, and MDA were measured using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. The quantities of these biochemical factors present in the hippocampal were determined using their respective standard curve [3]. Tissue MDA was measured using thiobarbituric acid reactive substances (TBARs) test, as described by Shabani and Mirshekar [34]. The final concentrations of TNF-α, TAC, and MDA were expressed as pg/mg protein, unit/mL (U/mL) and μM/mL as previously reported [20].

2.9. Statistical analysis

Statistical analysis was done using the Graph Pad Prism 7.0 software. Data from MDA, TAC, and TNF-α concentration were analyzed by one-way ANOVA but shuttle box and MWM data were analyzed by Two-way ANOVA repeated measurements, respectively, and followed by Tukey's post hoc test. The Results of this research are presented as the Mean ± SEM and reflected at p values less than 0.05.

3. Results

All measurements were done by an experienced observer uninformed of the different groups identified for the study. BC supplement, as compared to the control group, had no effect on the rats' food consumption and body weight gain. The effect of BC supplement on the rats' learning and memory was evaluated by an MWM and shuttle box tests.

3.1. Neurobehavioral observations

3.1.1. Effect of BC on mean escape latency of rats with ICV-STZ in MWM task

The spatial memory functions were studied using MWM task. The mean escape latencies of ICV-STZ induced Alzheimer for animals significantly increased [F (9,63) = 2.314; $p < 0.01$] compared to sham animals starting from the first day of training trial of MWM test. Interestingly, a significant decrease was observed in the mean escape latency of animals pre-treated with BC (BC + STZ) compared to that of the animals which were administered ICV-STZ [F (9,63) = 2.314; $p < 0.01$]. Progressive decrements of mean escape latency indicated significant amelioration of impaired memory functions in BC + STZ compared to ICV-STZ rats on training trials [F (9,63) = 2.314; $p < 0.001$] (Fig. 2A).

3.1.2. Effect of BC on mean path length of rats with ICV-STZ in MWM task

ICV-STZ injection displayed a significant increase in path length on day 2, 3, and 4 during the training trial [F (6,63) = 1.170; $p < 0.001$] of MWM compared to the sham-operated animals. Pre-treatment with BC elicited a significant decrease in path length [F (6,63) = 1.170; $p < 0.01$] compared to that of animals administered ICV-STZ. Furthermore, the reduced path length on the

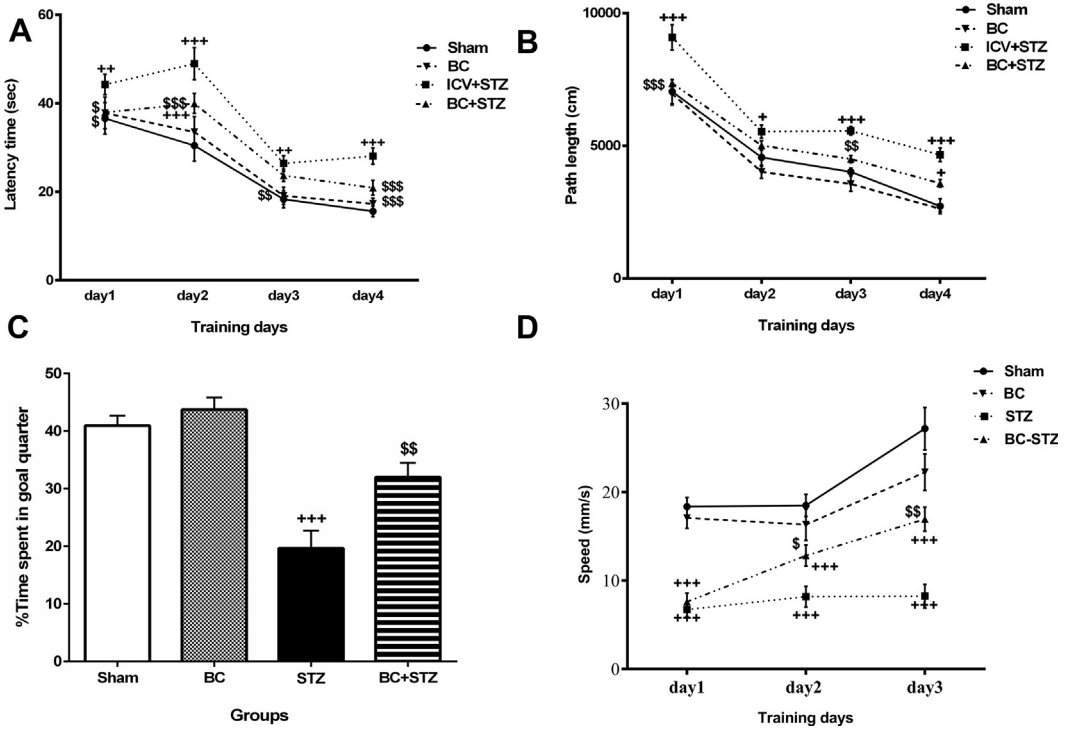

Fig. 2. The Effect of brewed coffee on A: escape latency, B: Path length, C: Percent of total time spent by each one of the rats at goal quarter in probe trial and D: speed in the STZ-induced memory impairments in sham, BC, ICV-STZ, and BC-STZ groups, during spatial memory test (+ $p < 0.05$, ++ $p < 0.01$, +++ $p < 0.001$ vs. sham, and \$ $p < 0.05$, \$\$ $p < 0.01$ and \$\$\$ $p < 0.001$ vs ICV-STZ, mean ± SEM ($n = 8$) two-way ANOVA repeated measurements, followed by Tukey's post hoc tests).

second, third, and fourth days of the acquisition trial in BC + STZ compared to the ICV-STZ animals indicates the improvement in the memory performance ($p < 0.01$) (Fig. 2B).

3.1.3. Time spent in goal quadrant (TSGQ) in probe trial

TSGQ, as well as passing time across the goal quadrant, is a putative measure of spatial learning and memory performance. ICV-STZ animals spent considerably less time in the goal quadrant compared to the sham animals [($F(3,28) = 20.50$ $p < 0.001$]. In addition, the amount of time BC pre-treated STZ rats spent in the goal quadrant increased significantly compared to that spent by animals administered ICV-STZ [$F(3,28) = 20.50$ $p < 0.01$]. The same results were observed for the passing times across the goal quadrant (Fig. 2C).

3.1.4. Pretreatment with BC improved swimming speed in ICV-STZ rats

As shown in Fig. 5 the swimming speeds (cm/s) in ICV-STZ rats were decreased significantly [$F(3,21) = 114.3$; $p < 0.001$] compared with the sham group and increased significantly after oral administration of coffee in BC-STZ compared with the ICV-STZ group [$F(3,21) = 114.3$; $p < 0.01$] (Fig. 2D).

3.1.5. Passive avoidance memory

Fig. 6 demonstrated the preventative effect of chronic treatment of BC on the initial latency (IL) and step-through latency (STL) in different group. There were no differences regarding IL times between the groups (Fig. 2). Throughout memory trials, STL time reduced [$F(9.63) = 2.314$; $p < 0.001$] in the ICV-STZ group (17.12 ± 2.1 S) compared with the sham (50.62 ± 2.5 S) a day after the delivery of the shock to the foot paw significantly. Also, spent time increased in a dark chamber in the ICV-STZ group compared with the sham group [$F(9.63) = 2.314$; $p < 0.001$]. STL augmented in the BC + STZ group (40.87 ± 0.97 S) against ICV + STZ group significantly [$F(9.63) = 2.314$; $p < 0.001$] (Fig. 3). Meanwhile, administration of the sham group with the BC led to made a little role on the learning and memory in the passive avoidance test (45.63 ± 2.1 S).

3.1.6. Effect of BC on TAC levels in HDG tissue

Compared with the Sham group, TAC concentration in the HDG tissue gradually decreased to a remarkably low level due to ICV-STZ injection. Pre-treatment with BC significantly reversed the decreased TAC activity in HDG [$F(3,28) = 8.719$; $p < 0.05$]. Moreover, enhanced TAC concentration with pre-treatment of BC indicates the improved endogenous anti-oxidant defense [$F(3,28) = 8.719$; $p < 0.05$] (Fig. 4).

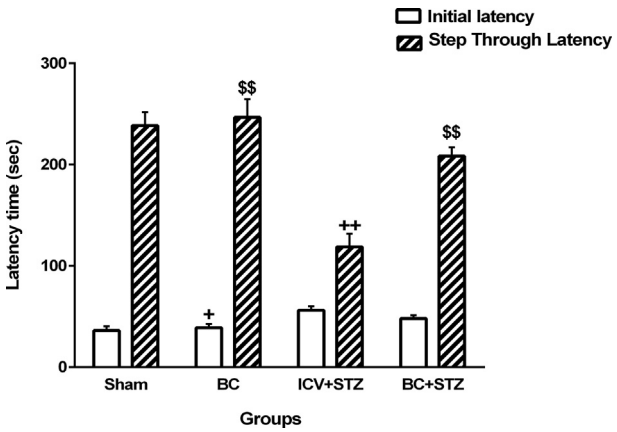

Fig. 3. The effect of the administration of brewed coffee (BC) on latency times in sham, BC, ICV-STZ, and STZ-BC groups post Alzheimer induction. Data represent mean ± SEM ($n = 8$) (+ $p < 0.05$, ++ $p < 0.01$ vs. sham, $$ $p < 0.01$ vs ICV-STZ. One-way ANOVA, followed by Tukey's post hoc tests, $n = 8$).

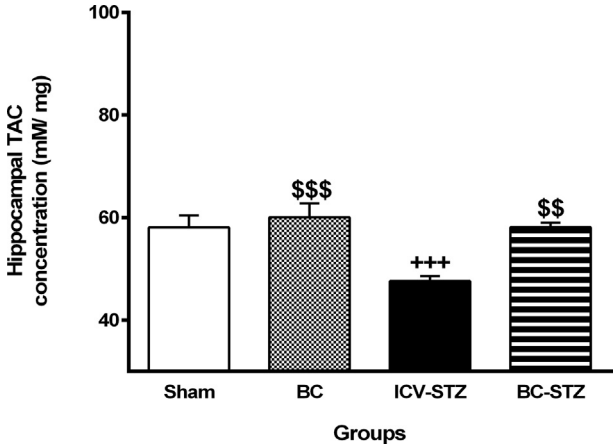

Fig. 4. Changes in TAC concentrations of rats' hippocampus. All values are expressed as mean ± S.E.M ($n = 8$ per group). Comparisons were made with a one-way ANOVA, followed by a post hoc Tukey test. +++ $p < 0.001$ as compared with sham group. $$ $p < 0.01$, $$$ $p < 0.001$ as compared with ICV-STZ treated group.

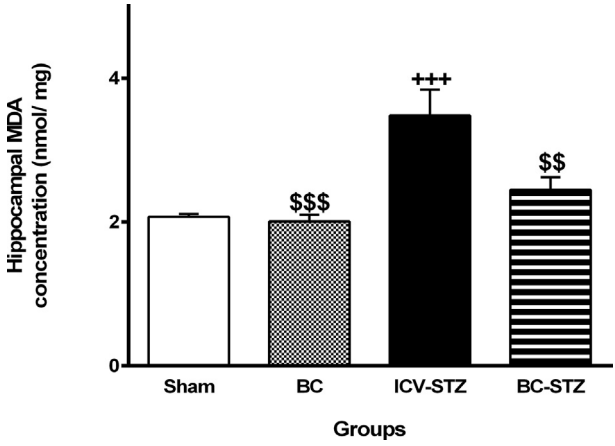

Fig. 5. Changes in MDA contents of rats' hippocampus. All values are expressed as mean ± S.E.M ($n = 8$ per group). +++ $p < 0.001$ as compared with sham group. $$ $p < 0.01$, $$$ $p < 0.001$ as compared with ICV-STZ treated group. One-way ANOVA repeated measurements, followed by Tukey's post hoc tests).

3.1.7. Effect of BC on MDA levels in HDG tissue

The injection of STZ into the cerebral ventricles resulted in significantly increased MDA concentration in HDG [$F(3,28) = 10.99$; $p < 0.001$] compared with the concentration in the sham group. Pretreatment with BC significantly reversed the enhanced MDA activity in HDG ($p < 0.05$) compared to that of ICV-STZ animals (Fig. 5).

3.1.8. TNF-α level in hippocampus region

As shown in Fig. 6, TNF-α level in ICV-STZ (805.87 ± 19.34 pg/mL) was significantly higher than sham group (568.87 ± 11.82 pg/mL) [$F(3,28) = 10.01$; $p < 0.001$]. BC pretreatment caused a significant decrease in TNF-α level (695.26 ± 11.73 pg/mL) [$F(3,28) = 10.01$; $p < 0.01$] as compared with ICV-STZ group.

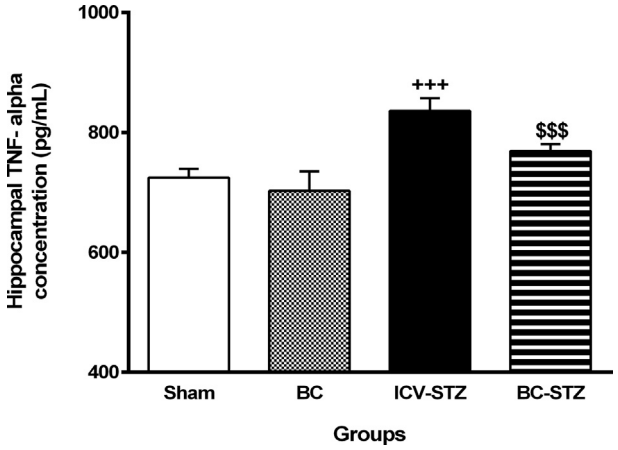

Fig. 6. Changes in the TNF-α content of rats' hippocampus. All values are expressed as mean ± S.E.M ($n = 8$ per group). +++ $p < 0.001$ as compared with sham group, $$$ $p < 0.001$ as compared with ICV-STZ treated group. One-way ANOVA repeated measurements, followed by Tukey's post hoc tests).

4. Discussion

The present study intended to evaluate the preventive effects of sub-chronic pretreatment of BC from roasted coffee beans on brain functions such as memory and cognition, cerebral hippocampal tissue antioxidant, and inflammation after AD-induced by STZ in rats.

In ICV-STZ group, the mean swim path length and escape latency to find the hidden platform during training trials increased gradually. This, accompanied by the decreased number of entries and time spent in the target quadrant, verifies the impaired retention memory elicited by AD rats during the spatial navigation in MWM task. The mean escape latency and discovering time in the hidden platform decreased significantly for the BC pre-treatment group compared to what were observed for AD animals. Our results revealed that BC pre-treatment improved spatial learning, and memory functions in MWM [37]. Moreover, BC protective effects enhanced the STL time into the dark compartment, eliciting improved retention memory compared to ICV-STZ animals.

Based on previous studies, 5.7 mL kg^{-1} of coffee in the daily diet is capable to produce physiological and metabolic effects in different biological systems of rats such as weight reduction, without toxic effects [18]. According to our pilot studies, the addition of coffee to the rats' diet did not alter water and food consumption nor did it have any observable effect on the body weight of all groups studied.

ICV injection of STZ, an ordinarily experimental method used for AD induction, can lead to cerebral inflammation as one of the classical features of AD [30]. In AD, the activated microglia are immunopositive for inflammatory cytokines, e.g. interleukin-1 (IL-1), TNF-α, and complements system proteins. Studies suggest that the enhanced level of neuro-inflammatory cytokines induce neuronal death and AD progression [2]. Consequently, we studied the effect of BC on TNF-α concentration as one of the main pro-inflammatory cytokines in cerebral tissue. ICV injection of STZ produced a marked impairment in active and passive memories, which was associated with a significant increase in hippocampal MDA, as well as TNF-α and dropped levels of TAC in HDG tissue [35]. The main findings of this study indicate that pretreatment with BC: 1) significantly enhanced spatial and passive avoidance memories; 2) meaningfully reversed the elevated concentrations of TNF-α and MDA toward Control; 3) significantly restored TAC concentrations to the normal level.

Our data indicated that BC preventive effects could increase of TNF-α and MDA contents of brain which may prevent the increase of time latencies in MWM and shuttle box, restoration of other neurological behaviors, and the increase in the TAC. These findings are consistent with Chang et al.'s about the effect of coffee, i.e. its effectively decreasing the expression of inflammatory cytokines, including TNF-αin hamsters, and showing anti-inflammatory activity [6].

Studies have shown that there is a negative correlation between coffee intake and neurodegenerative diseases such as MS and Parkinson's disease [28].

Caffeine is a CNS stimulant and is related to the methyl xanthine class [9]. It is well-known for its psycho-stimulating effects and ability to cross the blood–brain barrier due to its high lipid solubility. There are several identified mechanisms to explain the effects of caffeine. The most noticeable is that it reversibly blocks the action of and, consequently, prevents the onset of lethargy induced by adenosine [32]. Adenosine A2A receptors (A2AR) are generally located in the synapses controlling synaptic plasticity. The adenosine A2A receptors (A2AR) up-regulation can cause memory shortages and with blockage of this receptors AD be prevented [8]. Consequently, repeated caffeine intake mimics the impact of A2AR antagonists on the preservation of memory stultifications in different animal models of AD.

In the learning and memory formation, the role of long-term potentiation is noticeable. STZ triggers neurotoxicity via forming ion channels on cell membranes, and subsequent Ca^{2+} influx and inflammatory cascades via the activation of microglia in the hippocampus [24]. More importantly, the modification of intracellular Ca^{2+} homeostasis happens sooner than many of the histopathological markers seen in the AD brain [10]. Ryanodine receptors (RyRs) are a family of Ca^{2+} release channels found in intracellular Ca^{2+} storage/release organelles. Caffeine by binding to RyRs and activating these, can increase endoplasmic reticulum calcium [14]. In summary, one of the mechanisms of the occurrence of memory impairment is that the influx of calcium into the cells by altering the ryanodine receptor leads to up-regulation of tau protein expression [25]. Studies have also shown that Tau protein hyper-phosphorylation may leads to breakdown of intracellular transport and degeneration of neurons, which is the cause of Alzheimer's incidence [13]. According to the results of previous studies, caffeine from BC consumption could prevent tau protein phosphorylation in neurofibrillary tangles in Alzheimer's induced dementia [17].

The effects of chronic coffee on the cognitive function and antioxidant system of rat brains have been studied. In this study, the increment of TNF-α concentration in hippocampus following STZ injection is probably linked to tau phosphorylation [36].

Increased neuronal oxidative stress worsens the structure of lipids membrane through MDA generation, which, in turn, amplifies neuronal damage, severely affecting key cellular biomolecules. It is commonly used as biomarkers of oxidative damage. In the present study, the overproduction of free radical triggered MDA-mediated hippocampal oxidative damage. Our findings were in agreement with the pieces of evidence offered by earlier studies, suggesting the imperfect anti-oxidant defense system potentiating oxidative damage. Furthermore, ICV-STZ administration decreased plasma and tissue TAC levels, which provoked reactive oxygen species (ROS) arbitrated neuronal damage and compromised normal brain functions [39]. Moreover, BC administration mitigated TNF-α. Also, TNF-α and MDA generation due to the injection of STZ into the cerebral ventricles displayed neurobehavioral dysfunction. Therefore, it is imperative to consider the anti-oxidant properties of BC in attenuating ICV-STZ-induced neurotoxicity and cognitive impairment. Interestingly, some reports have reported that Javamide-II found in coffee may have anti-inflammation activity greater than caffeine, but this part of coffee decreases ERK phosphorylation, ergo reducing TNF-α mRNA expression in the cells [27]. Especially TNF-α, as a potent inflammatory cytokine, is significantly involved in the initiation or progression of acute systemic inflammation because it is critically involved in inflammation processes [11]. Deregulation is considered to be a major cause for the progression of several human chronic diseases such as diabetes, liver disease, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and cancer. Prior studies of coffee drinking and systemic inflammation were concerned with a small number of inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 (IL-6). Coffee consumption has reduced the increased levels of CRP and IL-6 concentrations [12].

One of the hypotheses that may explain the various relations of coffee drinking with health outcomes is that the constituents of coffee, such as polyphenols, have antioxidant and anti-inflammatory properties. For example, decaffeinated coffee consumption has been shown to reduce TNF-α concentrations in nonalcoholic steatohepatitis animal model, which is marked by a chronic inflammatory state [4]. Chlorogenic acid, one of the constituents of coffee, has been shown to strengthen insulin resistance by reducing gluconeogenesis and inflammation in the liver and glucose absorption in the gut [40]. The intake of caffeine, a naturally occurring compound in coffee, has been shown to improve

endothelial function and reduce inflammation in patients with and without coronary artery disease [5]. BC has significant antioxidant properties; it also has additional effects which may be relevant in the context of AD pathogenesis. BC can counter the oxidative stress in multiple ways, for instance, through radical scavenging, reduction of disulfide linkages of oxidized proteins, and upregulation of intracellular levels of reduced glutathione and antioxidant enzymes [16]. This study was designed to investigate the beneficial effects of BC on active and passive learning, TAC and MDA, and pro-inflammatory cytokines concentrations.

In conclusion, the present study demonstrated that the BC consumption, before the administration of ICV-STZ, disrupted neuronal circuitries in the hippocampus and improved the memory (passive avoidance and spatial memories) and biochemical assays. Thus, BC could be considered as a potential candidate for prophylaxis targets. However, further studies needed to clarify the neuroprotective mechanism of BC.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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