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Estimating The Role Of Bromalain In The Protection Effect Of Alzheimer's Disease Induced By Scopolamine

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Abstract
The current study was aimed to estimate the role of bromalain in the Protection Effect of Alzheimer's Disease induced by scopolamine via evaluating the antioxidant activity and anti-inflammatory activity of bromalain. For the study, 25 adult female rats were used, which were obtained from the animal house at the Veterinary Medicine College of Tikrit University. Between 10 and 12 weeks of age, the animals weighed an average of 207 grams, with a range of 181 to 204 grams. Between August 29, 2024, and September 11, 2024, the experiment was conducted at the College of Veterinary Medicine's animal home at Tikrit University. Animals were divided into five main groups (each group consisted of 5 adult female). The findings showed that the levels of AChE in positive group demonstrated a significant (P≤0.05) increased compared to the control group. in the treated groups, the AChE and ABE1 – 42 levels continue to show elevation compared to the control group, but less than positive group. The levels of ACH showed significant decreased in G2 group (P≤0.05) in contrast to the untreated group. in the treated groups, the ACH levels showed non-significant (P≤0.05) differences compared to the control group. The findings showed that the levels of GSH in positive group demonstrated a significant (P≤0.05) decreased in G2 group in contrast to the untreated group. in the treated groups, the GSH levels showed significant (P≤0.05) increased in contrast to the untreated group. The levels of IL–1 and BCS showed significant increase in positive group (P≤0.05) in contrast to the untreated group. in the treated groups, the IL–1 levels showed significant (P≤0.05) decreased in contrast to the untreated group. It is concluded that bromalain has an effective and protective role against the harmful effects of scopolamine, which causes Alzheimer's disease in mice.
Keywords: *bromelain, Scopolamine, AchE, Alzheimer's Disease.*

INTRODUCTION

Alzheimer's disease (AD) is a neurological illness that develops slowly. Synapse loss (1), The three primary features of AD are intracellular neurofibrillary tangles (NFTs), extracellular amyloid-beta (Aβ) accumulation, and (2). An anticholinergic medication called scopolamine (SCM) exhibits competitive antagonism at muscarinic acetylcholine receptors (mAChRs) and interferes with cholinergic transmission in the central nervous system (CNS) (3). Scopolamine is a belladonna alkaloid that is non-polar and is 9-methyl-3-oxa-9-azatricyclo non-7-yl ester of α- (hydroxymethyl) benzeneacetic acid. The structural formula is L-(2)-scopolamine, a tertiary amine, and the empirical formula is C17H21NO4. It is a viscous liquid with a pKa of 7.55–7.81 and a molecular weight of 303.35. Scopriamine is a high-affinity selective competitive antagonist of the G protein-coupled muscarinic receptor for acetylcholine that has both peripheral and central antimuscarinic effects, including sedative, antiemetic, and amnesic properties (4). It affects the central nervous system (CNS) by preventing cholinergic transmission from the reticular formation to the vomiting center and from vestibular nuclei to higher CNS centers (5,6,7). Glycoprotein is a proteolytic enzyme that includes bromelain (8). Numerous advantageous applications for bromelain as a phytomedical molecule have been demonstrated (9,10). Numerous therapeutic properties, including anti-inflammatory properties, anti-rheumatoid, anticarcinogenic (11), immunomodulatory agents, cardioprotective, and anti-adipogenic effects, have been found for bromelain. In the brains of mice given dichlorvos, bromelain has been shown to repair cholinergic deficiencies and reduce oxidative stress (12). Additionally, it has been noted that bromelain increases the BBB's permeability to nutrients (13). The treatment potential for AD may be shown by this evidence. Additionally, in vitro research revealed that bromelain breaks down Aβ1–42 monomer and soluble aggregate in AD patients' cerebrospinal fluids, which may provide evidence for additional research on the

effects of bromelain on Aβ1–42 monomer and soluble aggregate in a laboratory model of AD (14). the current study was aimed to evaluating the antioxidant activity and anti-inflammatory activity of bromalain, and evaluates the effectiveness of bromalain in inhibiting acetyl cholinesterase (AChE) activity and increasing AChE to improve memory.

MATERIALS & METHODS

The animals

Twenty-five adult female rats were used for the study; they were obtained from the animal house at Tikrit University's Veterinary Medicine College. The animals, which ranged in weight from 181 to 204 grams, were between 10 and 12 weeks old. Their average weight was 207 grams. The experiment was carried out in the animal home of Tikrit University's College of Veterinary Medicine from August 29, 2024, until September 11, 2024.

Blood Collection

Both the experimental and control rat groups had their blood drawn within 24 hours after the therapy's end. The thirty-first day following the start of the blood collection procedure, blood was extracted by heart puncture using three milliliter disposable syringes. Serum separation was performed on the blood using a tube, which has an average volume of around 1.5 ml. The blood was allowed to clot on its own for no more than fifteen minutes. Before the separated serum was utilized for the enzymatic assay, it was frozen in a deep freezer at -20 oC for five minutes at 1500 RPM using a microfuge.

Animal grouping

The rats utilized in this study were between 10 and 12 weeks old, and at the start of the investigation, their average body weight was 207 grams. The animals were separated into the following five major groups, each of which had five adult females:

1. The first group (negative control): received normal saline only for 14 days.
2. The second group (positive control): received Scopolamine 0.02 mg/kg (intra peritoneal) during 8–14 days.
3. The third group (Bromelain → Scopolamine + Donepezil): Pre-treated with Bromelain from 1–7 days, then from 8–14 days received scopolamine 0.02 mg/kg + donepezil 4.5 mg/kg concurrently.
4. The fourth group (Bromelain → Scopolamine + Bromelain): Pre-treated with Bromelain from 1–7 days, then from 8–14 days, received Scopolamine 0.02 mg/kg + Bromelain 3 mg/kg concurrently.
5. The fifth group: Pre-treated with Bromelain from 1–7 days, then from 8–14 days, Scopolamine 0.02 mg/kg + combination of Bromelain + Donepezil (5 mg/kg) concurrently.

Serological study

- **Acetylcholinesterase (AchE) kit**: The AchE ELISA Kit (SUNLONG, China) uses Sandwich-ELISA to measure the amount of AchE in human serum.
- **Acetylcholine (Ach) kit**: The Ach ELISA Kit (SUNLONG, China) uses Sandwich-ELISA to measure the amount of Ach in human serum.
- **β-amyloid (1-42) (AB1-42) kit**: The AB1-42 ELISA Kit (SUNLONG, China) uses Sandwich-ELISA to measure the amount of AB1-42 in human serum.
- **Glutathione (GSH) kit**: The GSH ELISA Kit (SUNLONG, China) uses Sandwich-ELISA to measure the amount of GSH in human serum.
- **Interlukin-1beta (IL-1β) kit**: The IL-1β ELISA Kit (SUNLONG, China) uses Sandwich-ELISA to measure the amount of IL-1β in human serum.
- **B-secretase (BSC) kit**: BSC The BSC ELISA Kit (SUNLONG, China) uses Sandwich-ELISA to measure the amount of BSC in human serum.

Statistical analysis

Microsoft Excel XP and SPSS were used to do statistical analyses on the data using a statistical Minitab application. The data were displayed using the mean ± standard deviation (SD), as well as the lowest and greatest values. To determine the significance of the differences between the treatment and control groups, the results were statistically examined using the Analysis of Variance (ANOVA) test. To compare data means, Duncan's Multiple Range test was used.

RESULTS & DISCUSSION

Table (1) showed the levels of AChE, ACH, and ABE1–42 in studied groups. Where, the levels of AChE showed significant (P≤0.05) increased in G2 group (506.5 ± 51.7) in contrast to the untreated group (338.0 ± 38.2). in the treated groups, the AChE levels continue to show elevation in contrast to the untreated group, but less than G2 group. The levels of ACH showed significant (122.4 ± 23.1) decreased in G2 group (P≤0.05) in contrast to the untreated group (181.2 ± 28.2). in the treated groups, the ACH levels showed non-significant (P≤0.05) differences in contrast to the untreated group. The levels of ABE1 – 42 showed significant (1461.2 ± 130.4) increased in G2 group (P≤0.05) in contrast to the untreated group (1230.0 ± 124.2). in the treated groups, the ABE1 – 42 levels revealed significant (P≤0.05) reduced in contrast to the untreated group.

Table (1): the levels of AChE, ACH and ABE1 – 42 in studied groups

Group	AChE	ACH	ABE1 – 42
G1	338.0 ± 38.2 c	181.2 ± 28.2 a	1230.0 ± 124.2 b
G2	506.5 ± 51.7 a	122.4 ± 23.1 b	1461.2 ± 130.4 a
G3	398.8 ± 39.4 b	187.9 ± 26.5 a	1103.0 ± 108.6 c
G4	388.0 ± 32.5 b	184.1 ± 24.8 a	1110.0 ± 103.4 c
G5	378.2 ± 37.1 b	205.3 ± 29.3 a	1080.0 ± 102.8 c
P-Value	0.003**	0.031*	0.002**

The same letters mean there are non-significant (P≤0.05) differences between groups, while different letters mean there are significant (P≤0.05) differences between groups.

Table (4-2) showed the levels of GSH, IL–1 and BCS in studied groups. Where, the levels of GSH showed significant (P≤0.05) decreased in G2 group (21.408 ± 0.399) compared to control group (26.056 ± 0.711). in the treated groups, the GSH levels showed significant (P≤0.05) increased in contrast with untreated group. The levels of IL–1 showed significant (156.8 ± 26.4) increased in G2 group (P≤0.05) in contrast with untreated group (128.6 ± 23.6). in the treated groups, the IL–1 levels showed significant (P≤0.05) decreased in contrast with untreated group. The levels of BCS revealed significant (121.200 ± 25.20) elevated in G2 group (P≤0.05) compared to control group (112.020 ± 20.09). in the treated groups, the BCS levels showed significant (P≤0.05) decreased in contrast with untreated group.

Table (2): the levels of GSH, IL–1 and BCS in studied groups

Group	GSH	IL–1	BCS
G1	26.056 ± 0.711 b	128.6 ± 23.6 b	112.020 ± 20.09 b
G2	21.408 ± 0.399 c	156.8 ± 26.4 a	121.200 ± 25.20 a
G3	25.741 ± 0.821 a	106.8 ± 22.7 c	104.210 ± 18.93 c
G4	25.847 ± 0.471 a	108.4 ± 20.1 c	101.311 ± 14.88 cd
G5	25.732 ± 0.522 a	102.7 ± 21.9 c	96.81 ± 16.14 d
P-Value	0.042*	0.001**	0.046*

Biochemical markers test for AD-induction group over the total period of the study: The current study revealed that the effects of scopolamine on biochemical markers (Acetylcholinesterase, B-secretase, IL-1B, GSH, and AB1-42) were consistent throughout the study (6 months). These results suggested that scopolamine has a prolonged effect, which will strengthen the impact of the study's medications and these

findings have not been reported in other previous studies because all other studies focused on the short-term effects of Scopolamine. Scopolamine causes cholinergic neuronal damage in the hippocampus by enhancing DNA damage and inhibiting the mRNA expression of many genes encoding neuronal factors that are crucial for cell survival as well as increasing oxidative stress by enhancing lipid peroxidation and decreasing the antioxidant system capacity (15). Since AChE is the primary enzyme that breaks down ACh, it is essential for healthy cholinergic transmission. Several studies have shown that inhibiting AChE improves memory and slows cognitive loss in AD and other dementia patients (16,17). Moreover, mounting data indicates that AChE has an extra non-cholinergic function that may worsen AD pathogenesis. In particular, it has been found that AChE colocalizes with Aβ deposits in the brains of AD patients and the elderly (18). The AChE-Aβ complex has been shown to have a more lethal effect in neuronal cells than Aβ fibrils alone, and AChE has been reported to speed up the aggregation of Aβ in solution (19). Furthermore, AChE-Aβ complexes potentiate the neurodegenerative alterations brought on by the Aβ peptide in hippocampus cells by causing prolonged elevations in intracellular Ca^{2+} and the loss of mitochondrial membrane potential (20). Aβ, in turn, improves the availability and activity of AChE by enhancing its catalytic efficiency and reducing its degradation (21). Our results demonstrated that scopolamine dramatically enhances AChE activity in the hippocampus and cortex while decreasing ACh levels, which is consistent with earlier scientific reports (22, 23). The observed relevance of those alterations in the hippocampus is especially noteworthy, since this area of the brain is essential for memory functions (24). Further exacerbating oxidative stress, scopolamine also promotes Aβ deposition (25). Furthermore, scopolamine interferes with the expression of neurofilaments, which are essential for axonal transport in neurons. The loss of cholinergic function in the hippocampus is associated with serious cognitive impairments which may last for a long time (26). The results of the current study also showed an increase in Aβ 1-42 levels after scopolamine administration. Aβ levels in the plasma of AD patients have been found to rise (27), fall (28), or remain unchanged (29) in earlier research. The fluctuation in the fraction of antibody-antigen complexes is probably what determines the reported variability. Reproducible results are obtained by dissociating the antigen-antibody complexes, and AD patients' Aβ 1-42 levels are significantly higher than those of age-matched controls (30). However, scopolamine (1 mg/kg) IP for 14 days significantly increased MDA levels, decreased GSH levels, decreased BDNF expression, and decreased short- and long-term memory, according to Aykac et al. (31). Furthermore, scopolamine single administration (2 mg/kg) elevated oxidative stress in the hippocampus by raising thiobarbituric acid-reactive substances (TBARS), which indicate lipid peroxidation, and lowering GSH and catalase levels, according to Anand et al. (32). Also, a recent study conducted by Cheedella et al. (25) found that SCM (5mg/kg) for 7 days reduced catalase activity and H&E-stained histological sections of the brain showed severe blood capillary congestion with perivascular edema (scars), along with edema and deposition of amyloid plaques in the hippocampus when compared with normal mice. In the present study, both bromelain and donepezil were found to have a positive effect against the harmful effects of scopalamine on some physiological parameters (AChE, ACH, ABE1-42, GSH, IL-1 and BCS). The current study's findings concurred with a study by Kumar et al. (33) that identified the function of bromelain, a bioactive substance derived from pineapple. where the neuroprotective effects of treatments in $AlCl_3$ and D-galactose-induced mice were shown to be significant ($p<0.05$) by the results of biochemical estimation (antioxidant enzymes, Nitrite, and AChE) and ELISA tests (mouse BACE, Aβ1–42, TNF-α, IL-6, and BDNF). Bromelain decreased hippocampus AChE levels in a mouse model of Alzheimer's disease, which is in line with our findings (34). The antioxidant bromelain can modulate the molecular targets involved in brain cholinergic signaling (35). Adu et al. (36) showed that treatments of 6-OHDA lesioned rats with bromelain decreased the plasma concentration of TNF-α and IL-1β. Also, the anti-inflammatory role of bromelain via a reduction in the sciatic levels of TNF-α and IL-1β in a rat model of neuropathic pain has been documented (37). In the cerebral cortex and its deep regions, bromelain reversed the observed increases in IL-1β concentrations. The inhibition of IL-1β and PGE2 may therefore be the cause of bromelain's anti-anxiodepressive-like actions. Possible explanations for the observed decreases in glutamate concentration include bromelain's pro-inflammatory inhibitory actions. An excitatory

neurotransmitter called glutamate mediates the feeling of pain. Glutamate is released in the afferent neurons by pro-inflammatory cytokines such IL-1β, and its release mediates central sensitization (38).

CONCLUSIONS

It is concluded from the current study that bromalain has an effective and protective role against the harmful effects of scopolamine, which causes Alzheimer's disease in mice.

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