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Research Article

The Water Extract of *Dendropanax morbiferus* Ameliorates Scopolamine-Induced Cognitive Impairment in Mice

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Abstract

Dendropanax morbiferus (DM) has been used in oriental medicine for various diseases such as inflammation, diabetes, and cancer. Several effects of DM have been known by researchers, but there have been no reports of the effects of cognitive impairment. Therefore, in this study examined anti-amnesic activity with its potential mechanism of action using scopolamine induced amnesic C57/BL6N mice. The effect of DM on cognitive impairment improvement on scopolamine-induced memory impairment in mice was evaluated using passive avoidance test and y-maze test. Besides, ELISA and Western Blot analysis were performed to examine several molecular markers such as inflammatory markers, oxidative stress markers, and BDNF signaling that occur in memory damage caused by scopolamine. The administration of DML (100 or 200 mg/kg, p.o.) significantly ameliorated the scopolamine-induced cognitive impairment in the passive avoidance task, the Y-maze. Also, the administration of DM suppressed increased brain inflammatory markers (iNOS, cox-2, IL-1α, IL-6, IFN-α), lipid peroxidation (MDA), and BDNF expression. Current research suggests that DM improves cognitive dysfunction by regulating molecules caused by neuroinflammatory and oxidative damage leading to nerve damage and may have therapeutic potential for cognitive dysfunction.

Keywords: Cognitive dysfunction; Scopolamine; Anti-neuroinflammation; *Dendropanax morbifera*

Introduction

Cognitive dysfunction is memory impairment and behavioral disorders that occur in various neurodegenerative disease from dementia to Alzheimer's disease [1]. The pathological characteristic of these diseases is that neural cell death occurs slowly, leading to irreversible deterioration of brain function over time, and there is no clear treatment [2]. There may be a number of factors for this cognitive impairment, but in particular, there are oxidative stress, and neuroinflammatory reactions, that cause damage to nerve cells [3,4]. Damage to the hippocampus of the brain due to inflammatory reactions and oxidative stress causes cognitive impairment. These hippocampus injuries are also consistent with the pathological characteristics of dementia and Alzheimer's disease [5]. The hippocampus is structurally and functionally important for learning and memory, and is located between the hypothalamus

and the inner temporal lobe of the brain [6]. Scopolamine is used in animal testing of cognitive functions, which nonselectively blocks of muscarinic cholinergic receptors in the hippocampus and cortex, leading to cognitive impairment [7]. In addition, it has been confirmed by several researchers that scopolamine induced animal models increase the biomarkers of neuroinflammatory and oxidative damage, and that inhibited cAMP response factor binding (CREB)/brain-derived neurotrophic factor (BDNF) pathways [8]. These molecular marker changes are similar to the pathological characteristics of Alzheimer's disease and other neurocognitive disorders in the human brain [2]. Therefore, scopolamine has been used to therapeutic investigations for neurodegenerative diseases that cause cognitive impairment.

Dendropanax morbiferus (DM) is a endemic plants to Korea and has been traditionally used as a treatment for various diseases and has now been revealed by several scientific studies for its efficacy such as antioxidant, anti-inflammatory, anti-cancer, anti-bacteria, and anti-diabetes. [9,10]. In particular, the leaves of this plant contain relatively many phenolic-flavonoids such as kaempferol, quercetin, apigenin, coumaric acid, and caffeic acid et al, showing this efficacy, and in several studies, it seems that these phenolic-flavonoids show the efficacy of DM [10,11]. The ethanol extracts of DM have been also reported to improve oxidative damage to the hippocampus by neurotoxins [12]. Although the medicinal properties of DM have been reported through several studies, the efficacy of cognitive function improvement efficacy is not clear. In this study, we are the first investigated cognitive impairment inhibition mechanisms in scopolamine animal models using the water extract of DM.

Materials and Methods

Reagents

Scopolamine hydrochloride and tacrine hydrochloride hydrate were purchased from Sigma-Aldrich (St. Louis, MO, USA). Tween 80 was purchased from Calbiochem (Gibbstown, NJ, USA). A protease and phosphatase inhibitor cocktail in tablet form was obtained from Roche (Indianapolis, IN, USA). A RIPA buffer was procured from Millipore (Milford, MA, USA). All the other chemicals used were of high analytical grade obtained from Sigma, unless mentioned otherwise. Antibodies raised against inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), β-actin and horseradish peroxidase-conjugated appropriate IgG secondary antibodies were purchased from Cell Signaling Technology, Inc. (Danvers, MA, USA). Specific antibodies raised against BDNF were obtained from Abcam (Cambridge, UK). The polyvinylidene difluoride (PVDF) membrane was acquired from Millipore (Bedford, MA, USA)

Plant extraction of Dendropanx morbiferus

The water extracts of dendropanx morbiferus leaves and branches was obtained as described previously [11]. DM were purchased from Hanna arboretum, Republic of Korea. The obtained fresh DM were washed in running tap water, oven-dried (50-60 ˚C) for 3-5 days, and it is crushed manually to obtain the leaf flakes. The flakes were subjected to heat-maceration in 1L of distilled water at 100˚C for 2h, and the extract was filtered through Whatman® filter paper No. 2. The obtained filtrate was further concentrated using rotary evaporator (EYELA N-1000, Tokyo), for 2 h, 3 times. The DM extract (DM) residual was freeze-dried for 7 days and stored in an airtight container at -20˚C.

Animal and treatment

Male C57BL/6N mice strains (8–9 weeks; 24–27 g) were procured from the Deahan Bio Link (Eumseong, Korea). All the animals were housed in a controlled environment (23 ± 1°C; 50% ± 5% humidity; 12 h dark-light cycle) and allowed water and food ad libitum. After a week of acclimatization, the animals were randomly divided into experimental groups (n = 5 per group). In brief, the animals were divided into five groups - Control group (0.9% saline, i.p.), Scopolamine 2 mg/kg, (Scopolamine in 0.9% saline, i.p.), DM 100 mg/kg, p.o. + Scopolamine 2 mg/kg i.p. DM 200 mg/kg, p.o. + Scopolamine 2 mg/kg i.p. and Tacrine (10 mg/kg, p.o. + Scopolamine 2 mg/kg i.p.). DM and tacrine were administered by oral gavage dissolved in 0.9% saline containing 1% Tween 80 and 0.9% saline, respectively, for 7 days prior to Scopolamine injection. All the experiments were accomplished in accordance with the Principles of Laboratory Animal Care (NIH publication no.85-23, revised 1985) and approved by Konkuk University Institutional Animal care and Use Committee (KU21217).

Passive avoidance test

The step-through passive avoidance test (PAT) was conducted using a Gemini active and passive avoidance instrument (San Diego Instruments, San Diego, CA) linked with a computerized system as described earlier [8], with slight modifications. In brief, on the day of acquisition, animals were individually habituated in the lighted compartment for 30 s, followed by a computer-operated opening of the guillotine door and holding of the trial for 300 s. On the entry of the animal to the dark compartment, the programmed door was automatically closed, after which the animal received a single low intensity foot shock of 0.5 mA for 5 s, followed by recording of the time latencies (LT). Subsequently, the exact same procedure was performed on the next day to record the retention time, except for the shock punishment, however, the time taken

for the animal to enter the dark compartment (LT) was recorded. The criterion for learning was taken as an increase in the LT on the retention trial compared to the acquisition trial.

Y-maze test

The memory functioning and exploratory behaviors of the animals were determined using a spontaneous alternation Y-maze test as described previously [8]. In brief, after 30 min of PAT experiments, the animals were naively introduced to one wing of the clean Y-maze and allowed to explore freely. The arm entry was considered when the hind paws of the animal were completely moved into the arm. When the animal entered three arms in a consecutive pattern, it was considered spontaneous alternation behavior on overlapping triplets. The total number of arm entries was recorded visually by a person unaware of the experimental groups. The percentage of alternation was calculated using the following formula. Percentage alternation = [(number of alternations) / (total number of arm entries −2)] x 100.

Lipid peroxidation

The level of lipid peroxidation activity in the homogenates of the hippocampus and cerebral cortex was determined by measuring the level of malonaldehyde (MDA) generated using a lipid peroxidation colorimetric/fluorometric assay kit (BioVision, USA, CA) according to the manufacturer's procedure, as described earlier [8]. The absorbance was measured at 410 nm using a UV spectrophotometer**.**

ELISA

The level of pro-inflammatory (TNF-α, IL-1β, IL-6) and anti-inflammatory (IL-10) cytokines in the hippocampus were quantified using commercially available ELISA kits (R&D systems, Minneapolis, MN) according to the manufacturer's procedure, as described earlier [8].

Western blot analysis

The protein level expressions of iNOS, COX-2, CREB/phospho-CREB and BDNF in the hippocampus were measured using western blot analysis as described in previously [8]. In brief, the homogenates accumulated with equivalent proteins levels were separated in 10% polyacrylamide gels and transferred to PVDF membranes (Millipore, Bedford, MA, USA). Then, the membranes were blocked with 5% Bovine-serum Albumin (BSA) and subsequently incubated overnight at 4°C with primary antibodies: anti- iNOS (1:2000), anti-COX-2 (1:2000), anti-CREB (1:1000), anti-p-CREB, (1:1000), anti-BDNF (1:1000) and anti-β-actin (1:1000). After 24 h, the membranes were washed and incubated with respective HRP-con- jugated secondary antibodies (1:10000). The blots were visualized with a Davinch-Chemi & Fluoro Imaging System (Seoul, Korea), and their relative band densities were analyzed by ImageJ software (version- 1.47).

Statistical analysis

All the data were analyzed using Graph Pad Prism software ver. 5.01 (GraphPad, Inc., Lajolla, CA, USA). All data are expressed as mean ± standard deviation of at least three independent experiments. The statistical analysis was performed with a one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison tests. The P-values < 0.05 were significant.

Results

DM ameliorated scopolamine inflicted cognitive and behavioral impairment in C57/BL6N mice

To investigate the effects of DM on cognition and behavioral impairments, passive avoidance test and Y-maze test were conducted with 100, 20 mg/kg of DM administered orally for 7 days. As shown in Figures 1A and B, the latency times of the acquisition stage of the passive avidity test were found to be a non-significant pattern in all groups. However, it was confirmed that the latency times in the retention stage were significantly($P<0.001$) reduced from 300 seconds in the control group to 32±10.2 seconds in the group administered scopolamine, and increased dose-dependent in the group administered DM (195.46±21.23s; 100mg/Kg DM treated group; 282.08 ± 29.83s; 200mg/Kg DM treated group). In Y-maze experiments, Total arm entries were found to decrease in the scopolamine-treated group, but were not significant (Figure 1C), and spontaneous alternation percentage was significantly ($P<0.001$) decreased to 70±2.44% in the control group and 27.5±3% in the scopolamine-treated group, and dose-dependent increased in the DM-treated group. In addition, 56.1±5.16% of the 200 mg/Kg DM treated group was found to be almost similar to 58.75±5.18% of positive control tacrine-treated groups (Figure 1D).

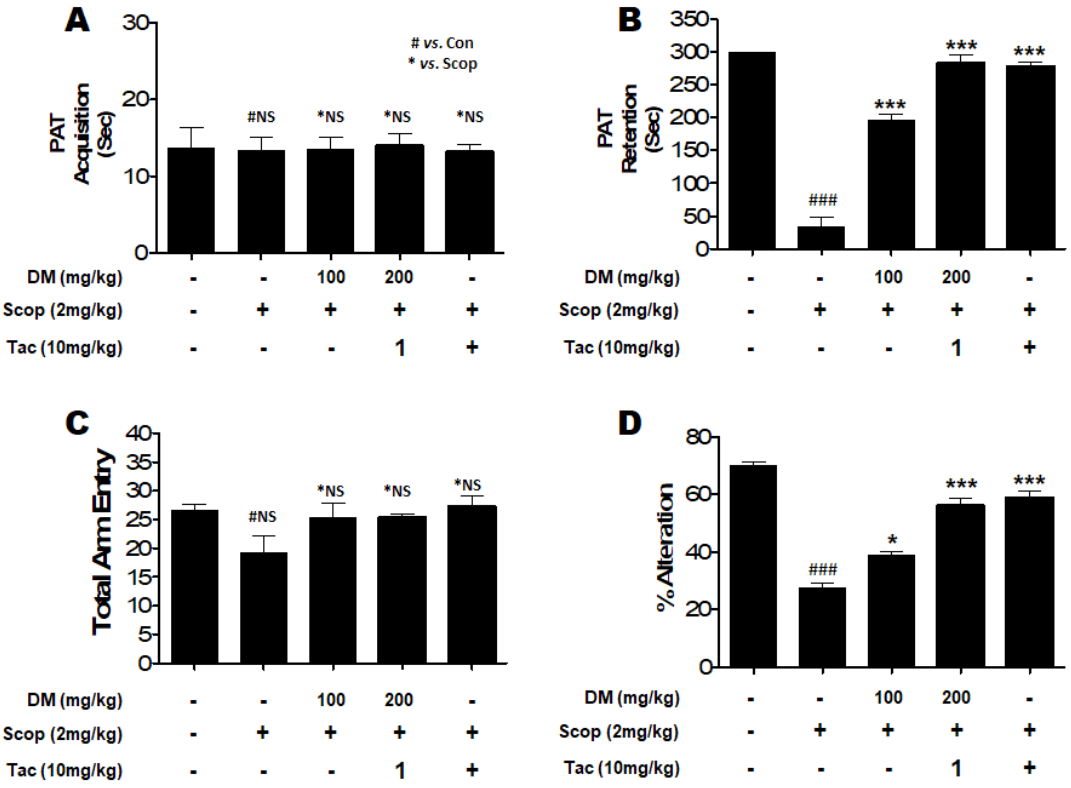

Figure 1: Effects of DM on scopolamine-inflicted cognitive and behavioral impairment in C57/BL6N mice. In the passive avoidance test, the latency variance in the acquisition(a) and retention(b) phase was acquired; In the spontaneous alternation performance (Y-maze test), e) the total arm entry and f) percentage of alternation was acquired. Data are expressed as the mean ± SEM (n = 5). One-way ANOVA-Tukey's multiple comparison test was performed. #: $p < 0.05$ compared with the control group; *: $p < 0.05$ other treated groups compared with the scopolamine group.

Anti-neuroinflammatory potential of DM in the hippocampus of scopolamine-treated mice

Neuroinflammation is one of the major factors in several neurodegenerative diseases, including Alzheimer's disease, which causes cognitive impairment. We used ELISA kit to analyze the protein amounts of TNF-α, IL-1, IL-6 and IL-10, which are pro- and anti-inflammatory cytokines, and inflammatory mediators iNOS and cox-2 using Western bolt, that occurring in hippocampus of scopolamine animal models. As a result of analyzing the ELISA assay results (figure 2), it was confirmed that TNF-α, IL-1, and IL-6 significantly($p<0.001$) increased, and IL-10 levels, decreased in the scopolamine administered group, with values of 1296.41 ± 81.13 pg/mg, 1465.66 ± 63.28 pg/mg, 1464.33 ± 45.43 pg/mg and 561.29 ± 40.44 pg/mg protein compared to the control group with values of 662 ± 38.41pg/mg, 795.66 ± 23.21 pg/mg 637.67 ± 24.30 pg/mg and 1000.45 ± 52.26 pg/mg, respectively. In the group administered with the highest concentration of 200 mg/kg DM, the levels of TNF-α, IL-1, and IL-6 were inhibited to 653.25 ± 24.30 pg/mg, 974 ± 119.05 pg/mg, and 953.33 ± 17.08 pg/mg, respectively, and it was confirmed that IL-10 was increased to 889.21 ± 30.35 pg/mg. However, the group administered with DM significantly inhibited the levels of TNF-α, IL-1, and IL-6 in a dose-dependent manner, and it was confirmed that IL-10 also increased in a dose -dependent manner. As shown in Figure 3, because of analyzing the expression levels of inos and cox-2, the scopolamine administered group significantly($p<0.001$) increased the expression by about 2 times compared to the control group. And it was confirmed that the expression levels of inos and cox-2 were significantly ($p<0.05$) suppressed in the group administered with 200 mg/kg DM.

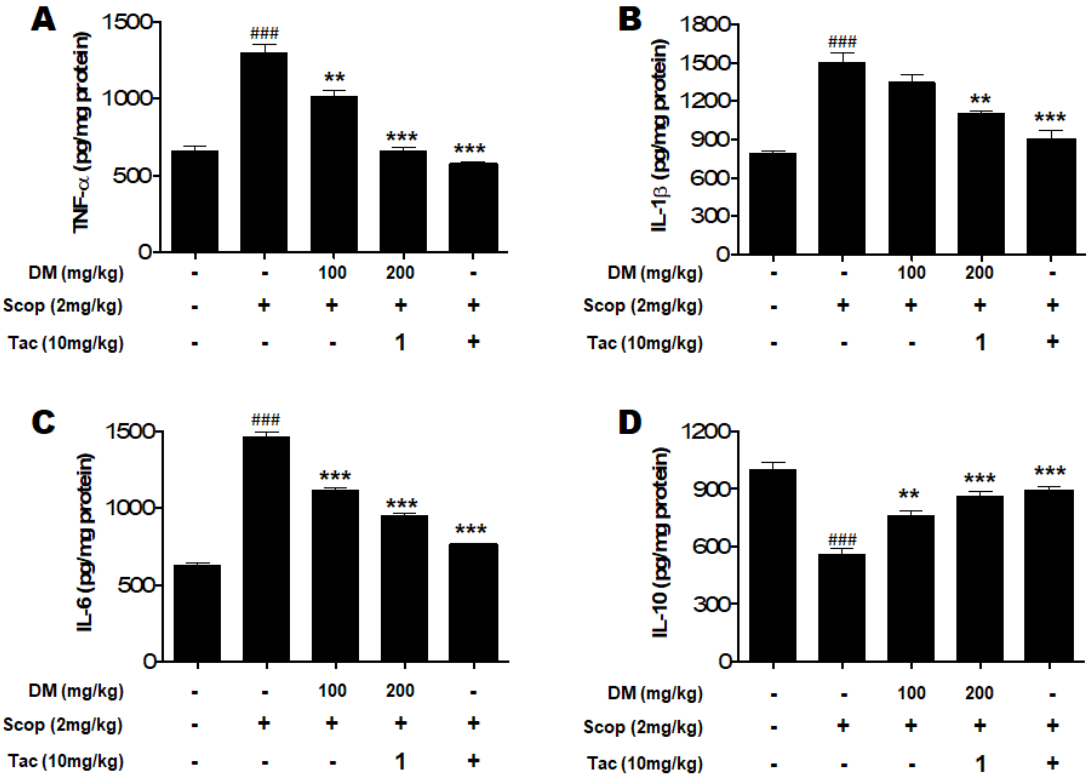

Figure 2: Effects of DM on inflammatory cytokines (A)TNF- α (B) IL-1β, (C) IL-6, and (D) IL- 10 protein in the hippocampus of C57BL/6 mice with scopolamine-induced memory impairment. Data are expressed as the mean ± SEM(n=5). A one-way ANOVA-Tukey's multiple comparison test was performed. #: $p < 0.05$ compared with the control group; *: $p < 0.05$ other treated groups compared with the scopolamine group.

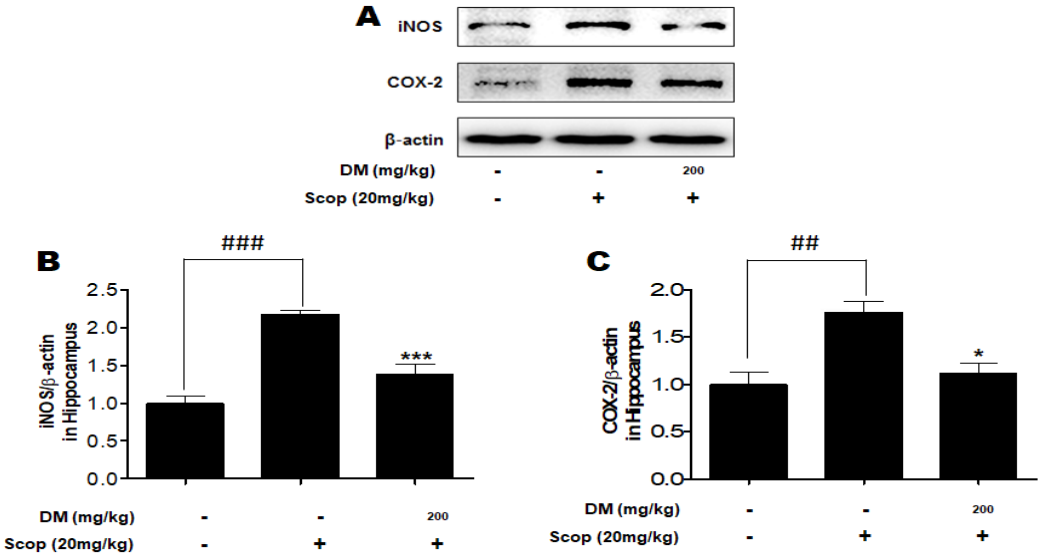

Figure 3: Effect of DM on inhibiting inducible nitric oxide (iNOS) and cyclooxygenase (COX)-2 production in scopolamine-induced neuroinflammation in C57/BL6N mice. a) iNOS and COX-2 protein expressions in the hippocampus (n = 3) was determined by western blotting analysis, and b), c) represents the quantification of inflammatory protein expression relative to β-actin, which was achieved using ImageJ software.

Effects of DM on lipid peroxidation in hippocampus and cerebral cortex of scopolamine-treated mice

There is strong evidence that free radical generation by scopolamine causes oxidative stress in the brain. We measured the amount of malondialdehyde (MDA) produced by lipid peroxidation in the hippocampus and cortex to confirm the inhibition of oxidative damage by DML. The level of MDA significantly ($p<0.001$) increased by 30.15 ± 6.56 nmol/mg and 26.66 ± 3.50 nmol/mg in both hippocampus and cortex in the scopolamine administered group, compared to the control group (17.15 ± 1.69 nmol/mg and 12.89 ± 1.53 nmol/mg). As a result, it was confirmed that the level of MDA was significantly($p<0.001$) suppressed to 22.78 ± 3.58 nmol/mg and 19.86 ± 4.08 nmol/mg, respectively, in the group administered with 200 mg/kg DM (Figure 4).

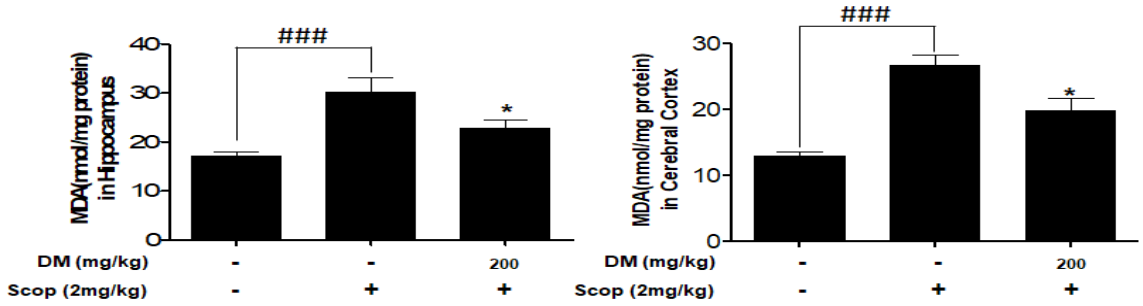

Figure 4: Effects of DM on scopolamine-inflicted lipid peroxidation(MDA) levels in C57/BL6N mice: Endogenous levels lipid peroxidation - a) MDA levels in the hippocampus, b) MDA levels in the cerebral cortex. The data are expressed as the mean ± SEM (n = 3). One-way ANOVA-Tukey's multiple com- parison test was performed. #: $p < 0.05$ compared with the control group; *: $p < 0.05$ other treated groups compared with the scopolamine group.

Effects of DM on BDNF expression levels in scopolamine-treated mice

Hippocampal BDNF (brain-derived neurotrophic factor) are known to play important roles in synaptic plasticity, memory, and neurodegenerative diseases [13,14]. To verify the molecular mechanisms underlying DM preventing scopolamine-induced cognitive impairment, the expression of memory-related proteins was measured by Western blot analysis. As shown in Figure 5, scopolamine administration significantly ($p<0.05$) decreased BDNF expression levels in the hippocampus (Figure 5). However, in the DM-administered group, it was confirmed that the expression of BDNF was increased two-fold compared to the scopolamine -administered group, and on the contrary, it was confirmed that the expression was 1.5 fold higher than that of the control group

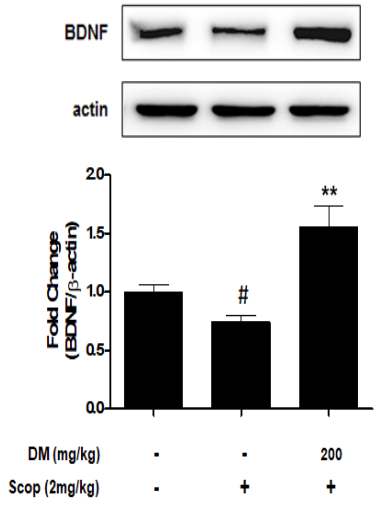

Figure 5: Effects of DM on BDNF expression in the hippocampus of C57/BL6N mice. One-way ANOVA-Tukey's multiple comparison test was performed. #: $p < 0.05$ compared with the control group; *: $p < 0.05$ other treated groups compared with the scopolamine group.

Discussion

Dendropanax morbiferus (DM) are reported to have several effects, such as inhibiting the proliferation of microorganisms, whitening action by reducing melanin content, inhibiting the proliferation of cancer cells, anti-stress by reducing stress hormones, and immunomodulation through immune activation activity. It is due to the antioxidant, anti-inflammatory, neuroprotective, anti-cancer, and immune-modulating effects of various phenolic-flavonoids contained in the leaf and branches [10]. Recently, our research team confirmed the neuroprotective potential of DM from MPTP-induced dopaminergic nerve damage [11]. In addition, another research team reported that DM showed acetylcholine esterase inhibitory activity and antioxidant activity in the hippocampus [12,15]. However, studies on the efficacy of DM for its potential as an inhibitor of cognitive impairment are scarce. Thus, we investigated the effect of DM extract on cognitive impairment in a scopolamine mouse model using Y-maze and passive avoidance tests. These two behavioral tasks are commonly used to check for impairments in learning and memory [16]. The mechanism by which DM improves memory was evaluated in terms of anti-inflammatory and antioxidant properties of the hippocampus. We also further evaluated the effect of DM on BDNF expression levels.

Scopolamine, a cholinergic muscarinic receptor antagonist, effects is used to induce cognitive impairment in humans and animals that impair learning and memory [17]. Therefore, scopolamine has been commonly used to evaluate the effectiveness of therapeutic candidates for the treatment of neurodegenerative diseases such as Alzheimer's disease that induce cognitive dysfunction [18]. Moreover, scopolamine may increase hippocampal and cortical neuroinflammation, oxidative stress and acetylcholinesterase levels, which may lead to cognitive impairment [18, 19]. Acetylcholinesterase inhibitors for suppressing cognitive impairment have several side effects along with symptom reduction. Acetylcholinesterase inhibitors for the inhibition of cognitive impairment show various side effects along with symptom reduction [20], so it is necessary to develop a multi-target drug to treat and prevent memory-related diseases without side effects.

To investigate the efficacy of DM on cognitive impairment, we evaluated a scopolamine-treated mouse model using the Y-maze and passive avoidance test. Two behavioral models assess different types of memory. The passive avoidance test is used to assess long-term memory, and the Y-maze test is used to assess working or short-term memory [21,22]. DM treatment significantly reduced scopolamine-induced learning and memory impairments in the Y-maze and passive avoidance tests. These results suggest that DM may be useful in the treatment of cognitive impairment inhibition.

The increase in proinflammatory cytokines, such as TNF-α IL-1β, and IL-6, and inflammatory mediators' cytokines, such as iNOS, and COX-2, from cognitive impairment to increased inflammation in the brain still plays an important role in explaining the pathogenesis of cognitive impairment [4]. Since scopolamine administration increases proinflammatory cytokines and inflammatory mediators due to the induction of neuroinflammation, inflammation has been proposed as a rationale for scopolamine-induced cognitive impairment [23]. As expected, scopolamine administration increased inflammatory mediators (iNOS and COX-2) and pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) levels in the hippocampus of mice. However, DM inhibited

scopolamine-induced neuroinflammatory mediators/cytokines and significantly restored anti-inflammatory cytokine (IL-10) levels in the hippocampus of scopolamine-administered mice. These results correlate with the anti-inflammatory efficacy of DM by several researchers and support the anti-neuroinflammatory potential of DML.

Next, we assessed the effect of DM on scopolamine-induced MDA levels in the hippocampus and cortex. Scopolamine increases levels of MDA, a marker of lipid peroxidation, and may generate reactive oxygen species (ROS) in the hippocampus and cortex [24]. Previous reports have shown that lipid peroxidation correlates with oxidative stress and is considered a process of cognitive dysfunction [25]. Reduced lipid peroxidation may be a therapeutic strategy for improving cognitive function. Our data show that scopolamine significantly increased MDA levels in the hippocampus and cortex, but DM treatment effectively restored this activity. Our findings suggest that DM ameliorates scopolamine-induced memory impairment through its lipid peroxidation inhibitory properties in the hippocampus and cortex of mice.

To further evaluate the memory-enhancing mechanism of DM, we investigated BDNF expression levels in the hippocampus. BDNF is a growth factor in the hippocampus [26]. This growth factor is essential for neuronal protection, synaptic transmission, learning, and memory [27]. Scopolamine down-regulated hippocampal BDNF protein expression in mice, resulting in memory impairment [28]. According to our results, similar to previous researchers, scopolamine was observed to decrease hippocampal BDFN expression, and it was found to restore the expression of BDNF protein by DM. Therefore, we believe that DM can improve scopolamine-induced learning and memory impairments by enhancing BDNF protein expression in the hippocampus of mice.

Conclusions

These results suggest that DM ameliorates scopolamine-induced cognitive impairment in mice. These effects of ISO may be related to anti-neuroinflammatory, antioxidant defense, and enhanced BDNF expression in the hippocampus. To the best of our knowledge, this is the first study to provide evidence that the cognitive impairment inhibitory effect of DM is due to its diverse efficacy in animal models. Therefore, this study clearly showed that DM could be a potential medicinal food for preventing or treating cognitive impairment caused by neurodegenerative diseases.

Disclosure

Author Contributions: Conceptualization, I-S.K. and S-Y.P.; validation, I-S.K., S-Y. P and Y-G.K.; formal analysis, I-S.K. and S-Y.P.; writing—original draft preparation, I-S.K.; writing—review and editing, D-K.C.; supervision, D-K.C. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: All data is presented in the manuscript.

Conflicts of Interest: None.

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