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Research Article

Protective Effects of Maropitant in Chemotherapy-Induced Cognitive Impairment Caused by Methotrexate

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Abstract

Objectives: This study aimed to investigate whether prophylactic maropitant (MAR) administration can attenuate methotrexate (MTX)-induced cognitive impairment and related hippocampal molecular alterations.

Methods: Twenty-eight 10-week-old male BALB/c mice were randomly assigned to four groups (n=7): control, MTX, MTX+MAR, and MAR. MTX was administered intraperitoneally at 40 mg/kg 24 hours before behavioral testing. Maropitant was given subcutaneously at 10 mg/kg two days before and one hour before MTX administration. Cognitive function was evaluated using the novel object recognition (NOR) test. After behavioral assessment, animals were sacrificed, hippocampal tissues were collected, and levels of TLR4, amyloid beta (Aβ1–42), tau, and brain-derived neurotrophic factor (BDNF) were quantified using ELISA.

Results: MTX administration significantly impaired cognitive performance, evidenced by reduced hippocampal BDNF levels and increased TLR4, tau, and Aβ1–42 levels ($p<0.001$), along with a marked decrease in the NOR discrimination index ($p<0.001$). Maropitant treatment effectively prevented these MTX-induced molecular and behavioral alterations, maintaining all parameters near control levels and significantly improving outcomes compared to the MTX group.

Conclusion: Prophylactic maropitant administration protected against MTX-induced acute cognitive impairment by modulating hippocampal inflammatory and neurodegenerative pathways, suggesting NK1 receptor antagonism as a promising preventive strategy for chemotherapy-related cognitive dysfunction.

Keywords: Cognitive Impairment, Maropitant, Methotrexate

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Chemotherapy-induced cognitive impairment (CICI), commonly referred to as "chemotherapy brain," is a clinically significant neurological sequela that affects a significant proportion of cancer survivors. CICI is a neurobehavioral syndrome characterized by impairments in cognitive domains such as learning, memory, and attention, as well as emotional symptoms such as anxiety and depression.[1] Clinical observations show that 70-75% of patients undergoing chemotherapy may experience cognitive dysfunction after treatment, and that this dysfunction can persist for years after treatment ends.[2–4] This situation seriously negatively impacts patients' quality of life and functional independence.

Methotrexate (MTX), one of the commonly used chemotherapeutic agents, is a structural analogue of folic acid and inhibits tetrahydrofolate synthesis by exhibiting high affinity for the dihydrofolate reductase enzyme.[5] This inhibition disrupts purine and thymidylate biosynthesis, leading to significant impairments in DNA synthesis and cellular pro-

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liferation.[6] Due to these pharmacological properties, MTX is widely used in the treatment of hematological and solid tumors, as well as autoimmune and inflammatory diseases. However, MTX exhibits pronounced neurotoxic effects associated with permanent cognitive impairment in both adult and pediatric patients.[7,8] Its widespread use in the treatment of childhood acute lymphoblastic leukemia makes MTX-induced neurocognitive side effects clinically even more important.[9]

The pathophysiology of MTX-induced CICI is multifactorial and involves cellular and molecular changes occurring within the hippocampus, which is critical for learning and memory processes.[10,11] Chronic neuroinflammation, oxidative stress, disruption of the blood-brain barrier, and direct damage to neural stem cells and oligodendrocytes play important roles in this process. These pathological changes contribute to cognitive impairment by resulting in decreased neurogenesis and white matter dysfunction.[12–14] Furthermore, MTX has been shown to trigger endoplasmic reticulum stress by increasing microglial activation,[12] reduce brain-derived neurotrophic factor (BDNF) levels, and disrupt the metabolism of amyloid-beta 1–42 (Aβ1–42) and tau.[15,16] Toll-like receptor 4 (TLR4)-mediated signaling also plays a central role in initiating and sustaining chemotherapy-induced neuroinflammatory responses, establishing a critical link between systemic inflammation and central nervous system damage.[17]

Despite increasing understanding of the underlying mechanisms of CICI, effective pharmacological interventions to prevent or alleviate these cognitive impairments remain limited. Therefore, identifying new therapeutic strategies that can target the fundamental pathophysiological components of chemotherapy-induced neurocognitive impairment represents an important unmet clinical need.[18]

Neurokinin-1 (NK1) receptors play an important role in regulating neuroinflammation and stress responses, and it has been reported that blocking these receptors exhibits anti-inflammatory and neuroprotective effects in various preclinical models.[19,20] Maropitant (MAR) is a non-peptide NK1 receptor antagonist with high selectivity for substance P, developed to inhibit NK1-mediated signaling at central and peripheral levels.[21,22] MAR has been shown to inhibit neurogenic inflammation, stress-related neurotransmission, and emetic signaling within the central nervous system by suppressing substance P activity.[23] Although used as an antiemetic in veterinary medicine, aprepitant, an NK1 receptor antagonist structurally and pharmacologically closely related to MAR, has widespread clinical use in humans for the prevention of chemotherapy-induced nausea and vomiting.[24] Preclinical studies suggest that NK1 receptor blockade may have potential beneficial effects on cognitive functions, including learning and memory.[25]

Maropitant's ability to cross the blood-brain barrier and its well-established safety profile make it a potential therapeutic candidate for modulating methotrexate-associated neurotoxic effects.[26,27] However, the effects of NK1 receptor blockade in the context of MTX-induced CICI, particularly on TLR4-mediated neuroinflammation, BDNF dysfunction, and Aβ/tau-related pathological changes, have not yet been systematically evaluated.

In this study, a mouse model was used to assess the neuroprotective effects of maropitant against methotrexate-induced cognitive impairment. Acute cognitive dysfunction was induced by a single dose of methotrexate, with learning and memory evaluated using the novel object recognition test. Hippocampal levels of TLR4, Aβ1–42, tau, and BDNF were analyzed to characterize associated molecular changes. The aim of this study is to demonstrate the potential of prophylactic MAR administration to modulate MTX-induced cognitive impairment and associated molecular pathologies.

Methods

Experimental Design and Experimental Animals

In this study, a total of 28 male BALB/c mice (10 weeks old; body weight 30–35 g) obtained from the KONÜDAM accredited Experimental Medicine Application and Research Center at Necmettin Erbakan University (Konya, Türkiye) were used. All animals were free from any prior experimental procedures. Mice were housed under standard laboratory conditions with an ambient temperature of 22±2 °C, relative humidity of 50±5%, and a 12-hour light/dark cycle. Animals had ad libitum access to standard laboratory chow and drinking water.

The study was conducted in accordance with national legislation, ARRIVE 2.0 guidelines, and the European Union's Directive 2010/63/EU on the protection of animals used for scientific purposes. Ethical principles in the experimental design process were determined based on the Reduction principle of the 3Rs approach (Directive 2010/63/EU).[28]

Grouping and Sample Size

Following the acclimatization period, the animals were randomly divided into four experimental groups (n=7 per group) using Random Allocation Software. Sample size was determined using the Resource Equation Meth-

od to ensure statistical adequacy while minimizing animal use.[29]

Experimental Groups and Applications

The experimental flow of the study is presented schematically in the graphic summary.

Control Group (CON): Animals received an equivalent volume of saline administered intraperitoneally or subcutaneously in parallel with the other groups.

Methotrexate Group (MTX): MTX (Metoart®, Koçak Farma, Turkey) was administered as a single intraperitoneal injection at a dose of 40 mg/kg 24 hours before the behavioral tests. An equivalent volume of saline was injected subcutaneously at the time of MAR administration.

Methotrexate + Maropitant Group (MTX+MAR): MTX was administered intraperitoneally at a dose of 40 mg/kg 24 hours before the behavioral test, as in the MTX group. MAR (Cerenia®, maropitant citrate; Zoetis, USA) was administered subcutaneously at a dose of 10 mg/kg twice; the first dose was administered 2 days before MTX administration, and the second dose was administered 1 hour before MTX injection.

Maropitant Group (MAR): MAR was administered according to the protocol used in the MTX+MAR group; however, an equivalent volume of saline injection was administered instead of MTX.

Behavior Test

Novel Object Recognition Test

The novel object recognition (NOR) test was performed in a sound-isolated behavior laboratory under constant lighting conditions (100 lux). The open-field arena was cleaned between trials to eliminate olfactory cues, and all behaviors were recorded by video. Animals were randomly assigned to experimental groups, and the order of testing was randomized to minimize potential confounding effects. During the training phase, mice were allowed to explore two identical objects placed equidistantly in the arena. The position of the novel object (left or right side of the arena) was randomized across animals to prevent side preference bias. After 1.5 hours, one object was replaced with a novel object, and exploration behavior was recorded for 5 minutes. Exploration was defined as direct contact or nose-oriented investigation within 2 cm of the object. The discrimination index was calculated as the difference between time spent exploring the novel and familiar objects divided by total exploration time. A habituation session was conducted one day before testing. All behavioral tests were conducted by different investigators who were blinded to the experimental groups to minimize observer bias. The discrimination index was calculated using the formula ((time spent interacting with the new object-time spent interacting with the familiar object) / total exploration time). A practice test was conducted one day before the test day.

Collection of Tissue Samples

All animals were anesthetized using a combination of ketamine and xylazine (90 and 50 mg/kg, respectively) and euthanized by cervical dislocation. After euthanasia, the brains were quickly removed and the hippocampal tissues were carefully dissected on ice. Tissue samples were homogenized in pH 7.4 phosphate buffer and centrifuged at 4000 rpm for 10 minutes at 4 °C. The resulting supernatants were stored at −80 °C for use in biochemical analyses.

Biochemical Analysis

Toll-like receptor 4, Aβ1–42, tau, and BDNF levels in hippocampal tissue were determined using the ELISA method. For this purpose, tissue samples were homogenized in cold phosphate-buffered saline and centrifuged. Target protein concentrations in the supernatants were measured using mouse-specific commercial ELISA kits (Bioassay Technology Laboratory, Shanghai Korain Biotech Co., Ltd., Shanghai, China). Measurements were performed according to the manufacturer's protocols, and absorbance values were determined using a microplate reader at the recommended wavelengths. Concentrations were calculated based on standard curves.

Statistical Analysis

All compliant analyses were performed using SPSS (version 27.0, IBM Corp., Armonk, NY, USA) and GraphPad Prism (version 10.0, GraphPad Software, San Diego, CA, USA) software on a Windows operating system. Quantitative data are presented as mean ± standard deviation (SD). The control of parametric test applications was assessed using the current Shapiro-Wilk test for normality and Levene test for homogeneity of variances. One-way analysis of variance (ANOVA) was performed for data group comparisons. If a significant difference was detected as a result of the ANOVA, Tukey multiple comparison post-hoc test variations were used to determine specific differences between groups. In all tests, a $p<0.05$ value was considered a persistence value.

Results

Hippocampal BDNF Levels

Hippocampal BDNF levels showed significant differences between groups ($p<0.001$). BDNF levels in the MTX group were significantly reduced compared to the control group. BDNF levels in the MTX+MAR and MAR groups were similar to the control group and significantly higher than in the MTX group ($p<0.001$) (Fig. 1)

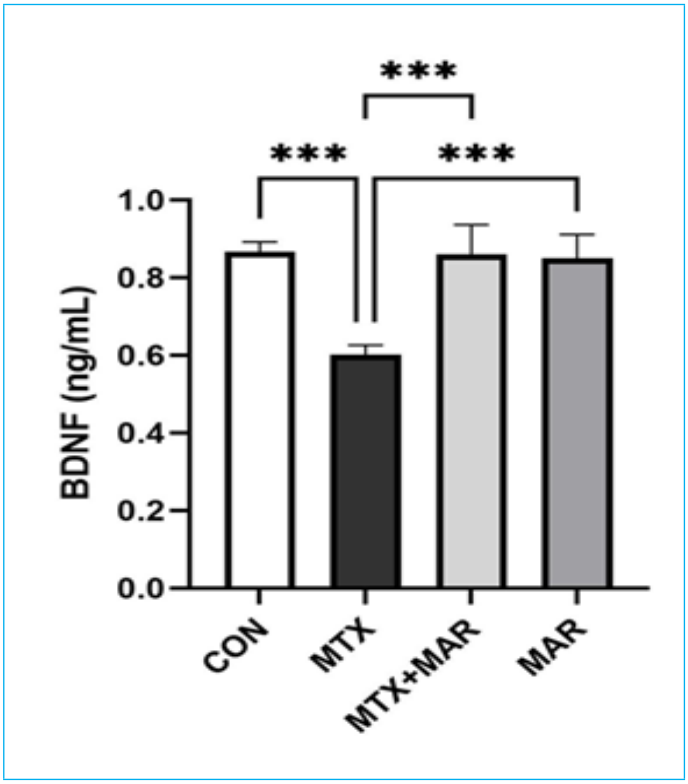

Figure 1. Effects of MTX and MAR administration on hippocampal BDNF levels. Hippocampal Brain-derived neurotrophic factor (BDNF) (ng/mL) in the control (CON), methotrexate (MTX), methotrexate + maropitant (MTX+MAR), and maropitant (MAR) groups. The data are presented as the mean ± SD. Intergroup differences were evaluated using one-way ANOVA and the Tukey post-hoc test. ***p<0.001.

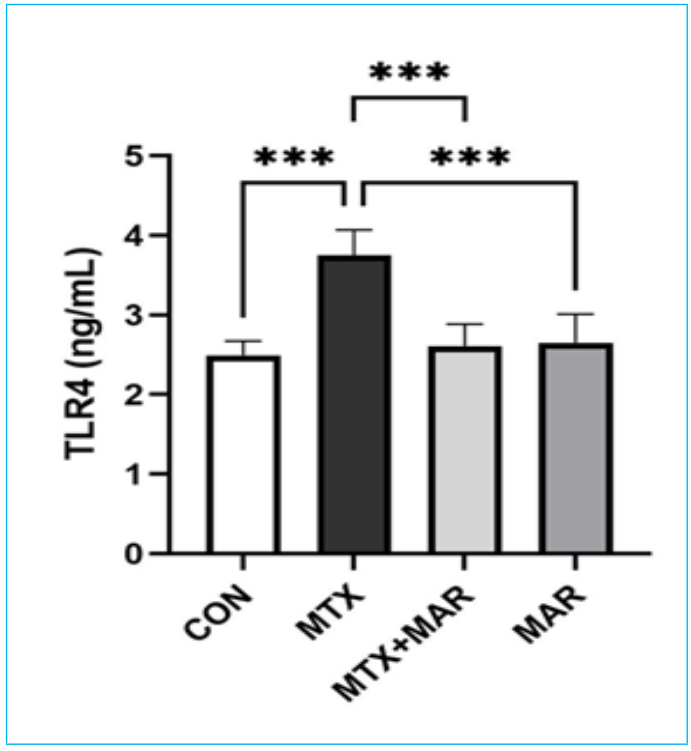

Figure 2. Effects of MTX and MAR administration on hippocampal TLR4 levels. Hippocampal Toll-like receptor 4 (TLR4) (ng/mL) in the control (CON), methotrexate (MTX), methotrexate + maropitant (MTX+MAR), and maropitant (MAR) groups. The data are presented as the mean ± SD. Intergroup differences were evaluated using one-way ANOVA and the Tukey post-hoc test. ***p<0.001.

Hippocampal TLR4 Levels

A significant difference was found in hippocampal TLR4 levels between groups (p<0.001). The MTX group had much higher levels of TLR4 than the control group. The TLR4 levels in the MTX+MAR and MAR groups were similar to those in the control group and much lower than those in the MTX group (p<0.001) (Fig. 2)

Hippocampal Tau Levels

A significant difference was observed between groups in terms of tau levels (p<0.001). Tau levels in the MTX group increased compared to the control group. Tau levels in the MTX+MAR and MAR groups remained similar to the control group and were significantly lower than in the MTX group (p<0.01) (Fig. 3a)

Hippocampal Aβ1–42 Levels

A significant difference was found between groups in terms of hippocampal Aβ1–42 levels (p<0.001). MTX administration caused a marked increase in Aβ1–42 levels, while levels in the MTX+MAR and MAR groups were similar to the control group and significantly lower than the MTX group (p<0.001) (Fig. 3b)

Learning and Memory Performance (Discrimination Index)

Discrimination index values for the NOR test showed significant differences between groups (p<0.001). Giving MTX led to a big drop in the discrimination index, while the index values in the MTX+MAR and MAR groups were close to those in the control group and much higher than in the MTX group (Fig. 4)

Discussion

This study demonstrates that prophylactic administration of MAR prevents methotrexate-induced acute cognitive impairment and significantly normalizes the accompanying hippocampal molecular changes in a mouse model. Acute MTX exposure led to increased levels of TLR4, Aβ1–42, and tau in the hippocampus and decreased levels of BDNF; these molecular changes paralleled a marked impairment in recognition memory. In contrast, MAR pretreatment largely prevented both behavioral deficits and these biochemical alterations. These findings suggest that targeting neuroinflammatory signaling pathways early on may be effective in reducing MTX-induced cognitive vulnerability.

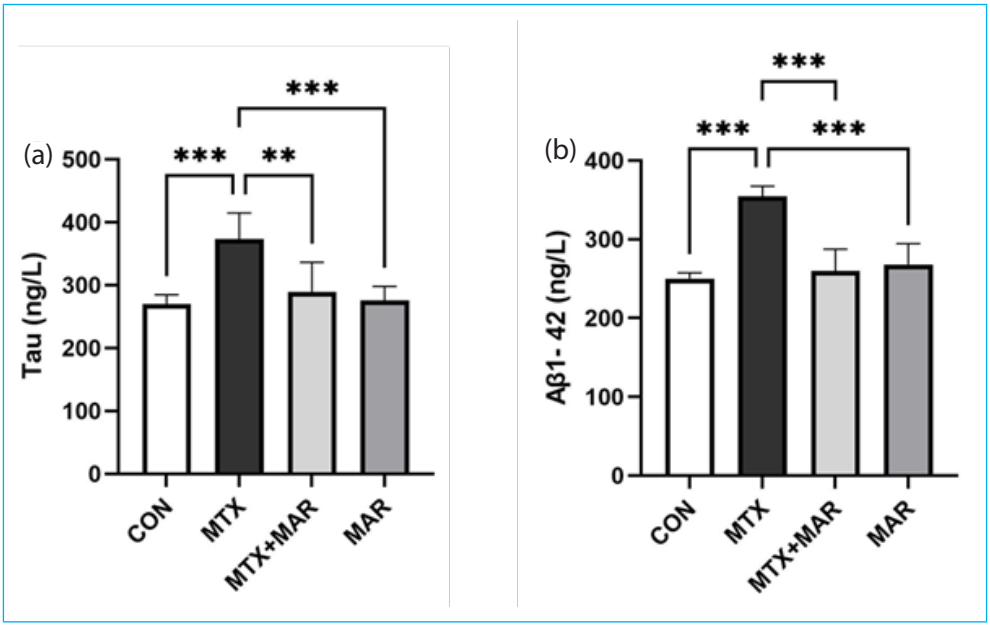

Figure 3. Effects of MTX and MAR administration on hippocampal tau and Aβ1–42levels. Hippocampal tau (a) and Amyloid beta 1–42 (Aβ1–42) (b) levels (ng/L) in the control (CON), methotrexate (MTX), methotrexate + maropitant (MTX+MAR), and maropitant (MAR) groups. The data are presented as the mean ± SD. Intergroup differences were evaluated using one-way ANOVA and the Tukey post-hoc test. **p<0.01, ***p<0.001.

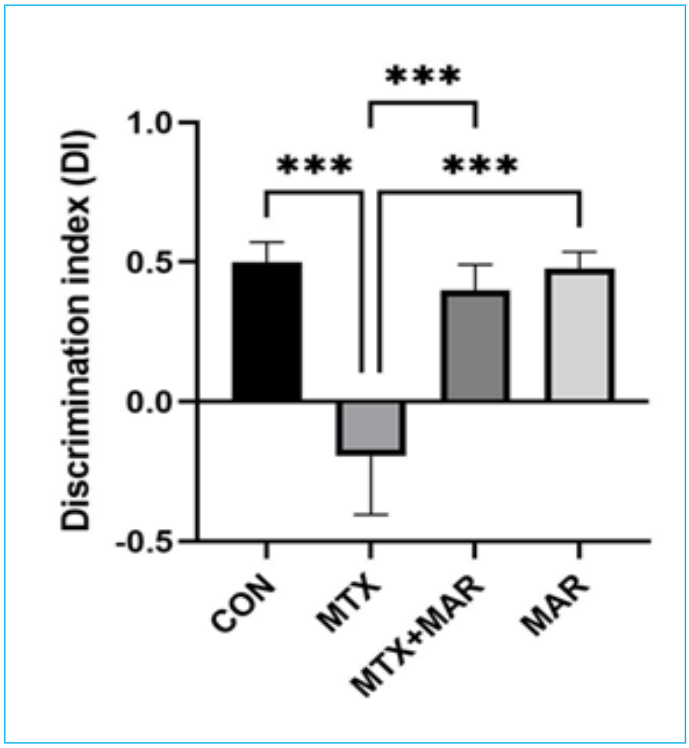

Figure 4. Effects of MTX and MAR administration on learning and memory performance. Discrimination index (DI) values for the NOR test in the control (CON), methotrexate (MTX), methotrexate + maropitant (MTX+MAR), and maropitant (MAR) groups. The data are presented as the mean ± SD. Intergroup differences were evaluated using one-way ANOVA and the Tukey post-hoc test. ***p<0.001.

Accumulating preclinical evidence indicates that MTX can lead to rapid cognitive impairment, particularly in tasks dependent on hippocampal integrity such as NOR, associated with impairments in neurotrophic support and inflammatory homeostasis.[30–32] The marked decrease in the discrimination index observed 24 hours after MTX administration in the current study is consistent with these reports and supports that even a single high dose of MTX can trigger acute cognitive dysfunction. The concomitant decrease in hippocampal BDNF levels is consistent with previous preclinical findings showing that chemotherapeutic agents impair learning and memory processes by suppressing neurotrophic signaling, pointing to an important underlying mechanism of chemotherapy-induced cognitive impairment.[33] In this context, the return of BDNF levels in the MTX+MAR group to levels close to control values is mechanistically important. Considering BDNF's fundamental role in synaptic plasticity, long-term potentiation, and memory consolidation, MAR's preservation of BDNF levels may be one of the potential mechanisms underlying its protective effect on recognition memory.[34]

Parallel to these neurotrophic changes, MTX exposure has also been shown to affect innate immune signaling. TLR4 is expressed in various cells in the central nervous system, primarily microglia, and its activation triggers NF-κB-mediated inflammatory pathways. Increased TLR4 expression has been shown to be associated with neuroinflammation

and neurodegenerative processes in conditions such as Alzheimer's disease.[35,36] The hippocampal TLR4 increase detected in the MTX group in the current study suggests that MTX may activate the innate immune response directly or indirectly within the hippocampus. The prevention of this TLR4 upregulation by MAR pretreatment indicates that early immune modulation may be a potential mechanism for protecting hippocampal function under chemotherapeutic stress. NK1R antagonists are considered to be potential alternatives to traditional anti-inflammatory agents due to their good tolerability, ability to target chronic inflammation without impairing the acute immune response, and ability to cross the blood-brain barrier.[19,37] The fact that MAR alone does not alter hippocampal TLR4 levels compared to the control group supports the safety profile of the drug in the absence of inflammatory damage.

Current findings also show that acute MTX administration causes significant increases in hippocampal tau and Aβ1–42 levels, while prophylactic treatment with MAR effectively prevents these molecular changes. These results indicate that MTX exposure can trigger molecular changes associated with neurodegenerative processes in a short time. There is growing evidence that chemotherapeutic agents, including MTX, may increase the accumulation of tau and amyloid-β peptides through neuroinflammation, oxidative stress, and impaired protein clearance. Acute inflammatory signaling has been shown to increase tau phosphorylation and amyloidogenic protein processing even in the absence of a distinct neurodegenerative disease state.[11,38] The high hippocampal tau and Aβ1–42 levels observed in the MTX group in the current study are consistent with these findings and support that MTX exposure can lead to molecular changes reflecting neurodegenerative processes within a short time. Experimental studies have shown that increases in tau load and amyloid-β levels impair synaptic plasticity and contribute to cognitive dysfunction, even if the changes are mild or transient.[36] The fact that MAR pretreatment prevents MTX-induced increases in tau and Aβ1–42, maintaining these protein levels at levels similar to those in control animals, suggests that the drug may exert an indirect modulatory effect on upstream processes contributing to pathological protein accumulation.

At the behavioral level, recognition memory assessed by the NOR test is largely dependent on hippocampal integrity and synaptic plasticity. Previous preclinical studies have shown that MTX can cause rapid cognitive impairment shortly after administration, particularly in tasks related to learning and memory.[30,31] The marked decrease in the discrimination index observed in the MTX group in this study is consistent with these reports. In contrast, prophylactic administration of MAR prevented this behavioral impairment, and discrimination index values in the MTX+MAR group were maintained at levels similar to those in the control group. The fact that MAR alone did not affect NOR performance suggests that the drug does not enhance basic learning and memory processes in a non-specific manner, and that its cognitive benefits arise under MTX-induced neurotoxic stress conditions. Substance P–NK1 signaling has been reported to be associated with stress- and inflammation-related cognitive impairments, and inhibition of this pathway has been shown to attenuate neuroinflammatory signaling in experimental models.[19]

Limitations

While this study provides important findings regarding the potential neuroprotective effects of MAR, it has some limitations. First, only acute effects were evaluated following a single dose of MTX, and the long-term course of cognitive and molecular changes and the persistence of MAR's protective effects could not be determined. Furthermore, although TLR4, Aβ1–42, tau, and BDNF provide important mechanistic insights, the lack of assessment of microglial activation, synaptic integrity, and oxidative stress markers limits the comprehensive validation of the proposed mechanisms. Finally, the differences between the experimental dosing and exposure models and clinical chemotherapy regimens necessitate caution in extrapolating the findings to clinical practice.

Conclusion

In conclusion, the current findings suggest that prophylactic MAR administration can effectively prevent MTX-induced acute cognitive impairment by normalizing hippocampal inflammatory and neurodegenerative-like molecular alterations. These results emphasize that innate immune signaling is a critical early target in MTX-induced cognitive dysfunction and support further investigation of NK1 receptor antagonism as a potential strategy to prevent chemotherapy-induced cognitive impairment.

Disclosures

Ethics Committee Approval: The study was conducted in accordance with national legislation, ARRIVE 2.0 guidelines, and the European Union's Directive 2010/63/EU on the protection of animals used for scientific purposes. It was approved by the Necmettin Erbakan University Local Ethics Committee on Animal Experiments (Approval No: 2025-080/24.07.2025).

Informed Consent: As the study involved experimental animals rather than human participants, informed consent was not required.

Author's contributions: Concept – DAA; Design – DAA; Supervision – DAA, FNB; Materials – DAA, FNB; Data collection &/or processing – DAA, FNB; Analysis and/or interpretation – DAA,

FNB; Literature search – DAA, FNB; Writing – DAA; Critical review – DAA, FNB.

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