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Neuroprotective effect of ranolazine and famotidine in a mouse model of Alzheimer's disease

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Abstract

Introduction. The neurodegenerative disorder known as Alzheimer's disease progresses over time as it causes damage to different parts of the brain. Ranolazine, a piperazine derivative, is a treatment that is considered to be of secondary relevance for persistent aortic stenosis in individuals with stable angina who do not react to other drugs. Additionally, famotidine is a competitive H2-receptor antagonist that reduces stomach acid secretion and treats conditions such as acid reflux and ulcers. In mouse models, ranolazine may help protect the brain against Alzheimer's disease-like characteristics induced by scopolamine.

Aim. To examine the potential neuroprotective properties of the combined administration of ranolazine and famotidine in mitigating symptoms of Alzheimer's disease in a mouse model induced by scopolamine.

Materials and methods. The experiment included four groups of ten mice each: a control group, an induction group that received 1 mg/kg of scopolamine intraperitoneally once a day for seven days to mimic Alzheimer's disease symptoms, and a memory loss group that received no such medication. For the remaining two groups of mice, the following medications were given orally once daily: donepezil (5 mg/kg/d) and a combination of ranolazine (40 mg/kg/d) and famotidine (40 mg/kg/d). After 14 days of prophylactic medication, the induction was performed with scopolamine (1 mg/kg i.p. once daily), and the medication was continued for an additional week. Research on the brain tissue sample included histopathological examinations, evaluation of inflammatory cytokines and oxidative stress parameters (such as acetylcholinesterase concentration), and assessment of behavioral parameters (such as novel object recognition and Y-maze tests).

Results and discussion. Scopolamine significantly impaired behavior (Y-maze 53.72, $p \leq 0.001$), which was reversed by treatments (donepezil: 67.58, $p \leq 0.001$). Treatments significantly reduced oxidative stress (MDA 1.65, $p < 0.01$) and inflammation (TNF-α 125.91, $p \leq 0.001$) compared to the induction group. All treated groups showed no significant difference compared to controls ($p > 0.05$). In comparison to the scopolamine group, ranolazine and famotidine combination significantly improved behavioral and memory performance, oxidative stress parameters, and inflammatory cytokine levels. However, there was no significant reduction in the concentration of acetylcholinesterase in brain homogenate.

Conclusion. Ranolazine and famotidine protected mice from scopolamine-induced AD-like symptoms in this study. The recent investigation showed that ranolazine and famotidine's antioxidant and anti-inflammatory actions may explain this benefit.

Keywords: Alzheimer's disease, famotidine, donepezil, inflammatory cytokines, oxidative stress

Conflict of interest. The authors declare that they have no obvious and potential conflicts of interest related to the publication of this article.

Contribution of the authors. Mariam Hadi Sadiq – conceptualization, data curation, investigation, methodology, resources, software, visualization, writing – original draft, writing – review & editing. Adeeb Ahmed Al-Zubaidy – conceptualization, data curation, methodology, supervision, validation, visualization, writing – original draft, writing – review & editing. Nawres Lateef Wahab – conceptualization, supervision, validation, visualization, writing – original draft, writing – review & editing.

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Нейропротекторное действие ранолазина и фамотидина на мышиной модели болезни Альцгеймера

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Резюме

Введение. Нейрогенеративное расстройство, известное как болезнь Альцгеймера, прогрессирует с течением времени, вызывая повреждение различных участков головного мозга. Ранолазин, производное пиперазина, представляет собой препарат второй линии для лечения аортального стеноза у пациентов со стабильной стенокардией, не реагирующих на иные лекарственные средства. Кроме того, фамотидин является соперником Н2-рецепторов, снижающим секрецию желудочной кислоты и применяемым для лечения кислотного рефлюкса и язвы. На мышиных моделях ранолазин может способствовать защите мозга от проявлений, подобных болезни Альцгеймера и индуцированных скополамином.

Цель. Изучить потенциальные нейропротекторные свойства комбинированного применения ранолазина и фамотидина в смягчении симптомов болезни Альцгеймера на мышиной модели, индуцированной скополамином.

Материалы и методы. Эксперимент включал четыре группы по 10 мышей в каждой: контрольную группу, индукционную группу, получавшую скополамин в дозе 1 мг/кг внутрибрюшинно один раз в сутки в течение семи дней для воспроизведения симптомов болезни Альцгеймера; и группу с потерей памяти, не получавшую подобного препарата. Двум оставшимся группам мышей ежедневно перорально вводили следующие лекарственные средства: донепезил (5 мг/кг/сут) и комбинацию ранолазина (40 мг/кг/сут) с фамотидином (40 мг/кг/сут). После 14 дней профилактического приема препаратов была проведена индукция скополамином (1 мг/кг внутрибрюшинно один раз в сутки), при этом введение препаратов продолжалось ещё в течение одной недели. Исследование образцов ткани головного мозга включало гистопатологический анализ, определение воспалительных цитокинов и показателей оксидативного стресса (таких как концентрация ацетилхолинэстеразы), а также оценку поведенческих параметров (тест распознавания нового объекта и Y-образный лабиринт).

Результаты и обсуждение. Скополамин существенно ухудшил поведенческие показатели (Y-образный лабиринт 53,72, $p \leq 0{,}001$), что было изменено применяемыми препаратами (донепезил: 67,58, $p \leq 0{,}001$). Препараты значительно снижали выраженность окислительного стресса (MDA 1,65, $p < 0{,}01$) и воспаления (TNF-α 125,91, $p \leq 0{,}001$) по сравнению с индукционной группой. Все группы, получавшие лечение, не имели значимых отличий от контрольной группы ($p > 0{,}05$). По сравнению с группой скополамина, комбинация ранолазина и фамотидина значительно улучшала поведенческие показатели и память, параметры окислительного стресса и уровни провоспалительных цитокинов. Однако значимого снижения концентрации ацетилхолинэстеразы в гомогенате головного мозга не наблюдалось.

Заключение. В данном исследовании ранолазин и фамотидин защитили мышей от индуцированных скополамином симптомов, подобных болезни Альцгеймера. Проведенное исследование показало, что антиоксидантное и противовоспалительное действие ранолазина и фамотидина может объяснить этот эффект.

Ключевые слова: болезнь Альцгеймера, фамотидин, донепезил, провоспалительные цитокины, окислительный стресс

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Вклад авторов. М. Х. Садик — концептуализация, обработка данных, проведение исследования, методология, ресурсы, программное обеспечение, визуализация, написание первоначального текста, редактирование и доработка текста. А. А. Аль-Зубайди — концептуализация, обработка данных, методология, руководство, валидация, визуализация, написание первоначального текста, редактирование и доработка текста. Н. Л. Ваххаб — концептуализация, руководство, валидация, визуализация, написание первоначального текста, редактирование и доработка текста.

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LIST OF ABBREVIATIONS

Aβ	Amyloid beta.
AD	Alzheimer›s disease.
Akt	Protein kinase B.
ANOVA	Analysis of variance.
CAT	Catalase.
COVID-19	Coronavirus disease 2019.
CRP	C-reactive protein.
Cu/Zn-SOD	Copper/zinc superoxide dismutase.
ELISA	Enzyme-linked immunosorbent assay.
FDA	Food and Drug Administration.
GERD	Gastroesophageal reflux disease.
GSK-3	Glycogen synthase kinase-3.
HIF-1α	Hypoxia-inducible factor-1 alpha.
i.p.	Intraperitoneal.
IFN	Interferon.
IL-1β	Interleukin-1 beta.
IL-6	Interleukin-6.
LDH	Lactate dehydrogenase.
MDA	Malondialdehyde.
Mn-SOD	Manganese superoxide dismutase.
MTX	Methotrexate.
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells.
NOR	Novel object recognition.
PBS	Phosphate-buffered saline.
PPAR-γ	Peroxisome proliferator-activated receptor gamma.
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2.
SD	Standard deviation.
SOD1	Superoxide dismutase-1.
SPSS	Statistical Package for the Social Sciences.
TAC	Total antioxidant capacity.
T-SH	Total thiol.
TLR	Toll-like receptor.
TNF-α	Tumor necrosis factor alpha.
T2DM	Type 2 diabetes mellitus.
Y-maze	Y-shaped maze test.

INTRODUCTION

A neurodegenerative disorder, Alzheimer's disease (AD), typically begins slowly but steadily worsens as it affects more and more brain regions and new symptoms emerge. The disease is also incurable. The primary features of AD pathogenesis are the formation of extracellular beta-amyloid protein clumps and intracellular tau protein twisted strands [1].

There have been several proposed theories regarding AD, some of which include amyloid-β (Aβ), Tau, the death of cholinergic neurons, oxidative stress, inflammation, and others. There have been a lot of attempts to develop anti-AD drugs based on these concepts [2].

The FDA has authorized six medicines for Alzheimer's disease (AD) treatment. Galantamine, donepezil, rivastigmine, and memantine are the four medications that make up this list; they only provide short-term relief from Alzheimer's symptoms; they do nothing to address the disease's core brain problems [3, 4].

Famotidine is a competitive antagonist of histamine H2-receptors that diminishes stomach acid production and is utilized in the treatment of gastrointestinal illnesses related to acid, including gastroesophageal reflux disease (GERD), duodenal ulcers, gastric ulcers, and pathological hypersecretory conditions [5].

In vitro studies using SARS-CoV-2-infected cells have shown that famotidine inhibits histamine-induced toll-like receptor 3-mediated inflammatory signaling [6]. Pharmacokinetic studies suggest that famotidine may improve COVID-19 outcomes by achieving blood levels that favor its antagonism of histamine H2 receptors on neutrophils, eosinophils, and mast cells [7].

Objective of the Study

This study examines whether ranolazine and famotidine exhibit neuroprotective effects against scopolamine-induced Alzheimer's disease-like features in murine models.

MATERIALS AND METHODS

Collection of Animal Samples

Fifty male mice, aged 2–3 months and weighing 25–35 g, were maintained under conventional laboratory conditions at a temperature of 20–22 °C. Scopolamine (Hyper Chem, China), famotidine (Hyper Chem, China), and donepezil (Hyper Chem, China) were dissolved in normal saline and used in the experiment. The Y-maze and open field box were manufactured locally in Baghdad.

Preparation of Medications

In this randomized controlled animal study, mice were categorized into five groups: a control group, a scopolamine-induced group (1 mg/kg i.p. administered once daily for 7 days), and three treatment groups that received prophylactic administration for 14 days, followed by ongoing treatment during scopolamine induction: donepezil (5 mg/kg i.p. once daily), famotidine (40 mg/kg i.p. once daily), and a combination of both (donepezil 5 mg/kg + famotidine 40 mg/kg i.p. once daily). Behavioural evaluations were conducted utilizing Y-maze and novel object identification tests over three consecutive days, commencing on day 25 [8, 9].

Behavioural tests

Y-Maze Spontaneous Alternation Behaviour

The geometric shape of this apparatus resembles a Y, with the letters [A, B, and C] serving as the three equal arms. They were 15 cm tall, 6 cm broad, and 20 cm long, with a right angle joining the two arms [10].

This test lasted 10 minutes for each animal. Each animal was placed in one arm and noted for its subsequent arms. The complete arm access occurred when the hind paws fully encompassed an arm, whereas alternation involved each mouse sequentially entering three arms. The Y-maze arena was sanitized with ethanol [70 % v/v] to eliminate olfactory cues between trials. The spontaneous alternation percentage was calculated by this equation [11–13]:

$$\left[\frac{\text{Number of alternations}}{(\text{Total number of arm entries} - 2)}\right] \cdot 100.$$

Novel Object Recognition (NOR): Discrimination Index Analysis

The experimental equipment was a [40 · 40 · 20 cm] white plastic open-field box. Initial habituation allowed each mouse to become familiar with the open field box for 15 minutes without an object. On the second day of training, each mouse was allowed to investigate the two equivalent objects in an open-field test [10 min.]. 90 minutes after training, one familiar object was replaced with a novel one, and the mice ran for 5 minutes while the time spent exploring each object was recorded. [12]. Formula for determining the recognition index:

$$[TB/(TA + TB) \cdot 100].$$

Object exploration was defined as active engagement with the object, which may involve using the nose and/or forepaws to smell or touch it. TA and TB represent the duration spent investigating familiar object A and novel object B, respectively [14].

Brain Tissue Collection and Biochemical Analysis

Immediately after the behavioural testing was finished, the animals were anesthetized and sacrificed, and the brains were promptly excised. One cerebral hemisphere was homogenized for biochemical analysis after being rinsed with ice-cold phosphate-buffered saline (PBS, pH 7.2–7.4) [15]. The enzyme-linked immunosorbent assay (ELISA) kits were employed to evaluate oxidative stress markers, such as malondialdehyde (MDA) and superoxide dismutase-1 (SOD1), as well as proinflammatory cytokines (IL-1β, IL-6, and TNF-α), in the resulting brain homogenates, in accordance with the manufacturers' protocols [16].

Statistical analysis

Statistical Package for the Social Sciences (SPSS) [Version 23] was utilized in order to do the analysis of the data. We reported the data as the mean plus or minus the standard deviation. For the purpose of statistical comparisons, the independent t-test and the one-way analysis of variance ANOVA were applied, and $p < 0.05$ was considered to be significant.

RESULTS

Both behavioural tests indicated significant findings. The Y-maze test showed a highly significant decline in spontaneous alteration in the scopolamine induction group compared to the control group ($p < 0.0001$). Conversely, the donepezil and combination groups (ranolazine + famotidine) showed significant increases in spontaneous alteration compared with the induction group ($p < 0.0001$ and $p < 0.0001$, respectively). However, no significant difference was observed compared with the control group. In the NOR test, the scopolamine induction group showed a substantial decrease in recognition index compared to the control group ($p < 0.0001$), whereas the donepezil and combination groups showed highly significant improvements over the induction group ($p < 0.0001$ and $p < 0.0001$, respectively) (Table 1).

Assessment of oxidative stress

The induction group showed a significant elevation in MDA levels and a decline in SOD1 compared to the control group (MDA: $p < 0.0001$; SOD1: $p < 0.0001$). In contrast, both the donepezil and the combination (ranolazine + famotidine) groups exhibited significant reductions in MDA levels and elevations in SOD1 levels compared with the induction group (MDA: $p < 0.0001$ and $p < 0.0001$, respectively; SOD1: $p = 0.016$ and $p < 0.0001$,

Table 1. Effects of famotidine and donepezil on behavioral tests

Groups	Y maze mean Â ± SD	NOR mean Â ± SD	p-values*
Control	66.58Â ± 2.82	63.58Â ± 2.81	–
Induction (scopolamine)	53.72Â ± 4.3	50.16Â ± 4.0	Y-maze: <0.0001; NOR: <0.0001
Donepezil	67.58Â ± 4.0	64.77Â ± 5.35	Y-maze: <0.0001; NOR: <0.0001
Ranolazine + Famotidine	64.35Â ± 3.67	61.1Â ± 3.22	Y-maze: <0.0001; NOR: <0.0001

Note. * Reconstructed pairwise t-test p-values ($n = 10$/group): induction was compared with control; donepezil and ranolazine + famotidine were each compared with induction. Statistically significant of independent t-test ($p < 0.05$).

Table 2. **Effects of famotidine and donepezil on oxidative stress parameters**

Groups	MDA (ng/ml)	SOD1 (ng/ml)	p-values*
Control	1.74Â ± 0.21	16.93Â ± 2.55	–
Induction (scopolamine)	2.57Â ± 0.29	10.87Â ± 2.32	MDA: <0.0001; SOD1: <0.0001
Donepezil	1.65Â ± 0.21	14.51Â ± 3.59	MDA: <0.0001; SOD1: 0.016
Ranolazine + Famotidine	1.9Â ± 0.14	16.03Â ± 1.74	MDA: <0.0001; SOD1: <0.0001

Note. * Reconstructed pairwise t-test p-values (n = 10/group): induction was compared with control; donepezil and ranolazine + famotidine were each compared with induction. Statistically significant of independent t-test ($p < 0.05$).

respectively). However, compared with the control group, these groups showed no statistically significant differences in MDA ($p = 0.35$ and $p = 0.06$, respectively) or SOD1 ($p = 0.1$ and $p = 0.37$, respectively) (Table 2).

Assessment of inflammatory cytokines

The induction group demonstrated markedly significant increases in IL-1β, IL-6, and TNFα levels compared with the control group (TNFα: $p = 0.0002$; IL-1β: $p = 0.0001$; IL-6: $p = 0.0004$). The donepezil and combination (ranolazine + famotidine) groups showed significant reductions in IL-1β, IL-6, and TNFα levels compared to the induction group (TNFα: $p = 0.0001$ and $p = 0.0005$, respectively; IL-1β: $p < 0.0001$ and $p < 0.0001$, respectively; IL-6: $p < 0.0001$ and $p < 0.0001$, respectively). Compared with the control group, the donepezil and combination groups showed no significant differences in TNFα ($p = 0.59$ and $p = 0.53$, respectively), IL-1β ($p = 0.32$ and $p = 0.59$, respectively), or IL-6 ($p = 0.86$ and $p = 0.28$, respectively) (Table 3).

DISCUSSION

Alzheimer's disease is a progressive neurodegenerative disorder that is pervasive and causes significant distress for both patients and their families [17]. The precise pathophysiology of AD remains unknown, despite the increasing evidence that it is a complex disorder that is the result of multiple causes with distinct molecular targets. Thus, it is imperative to consider the early phases of neuroinflammation, oxidative stress, or synaptic dysfunction when developing a new medication [18].

The current study has employed scopolamine hydrochloride to promote memory impairment in a mouse model. The induction of dementia is a common practice in experimental models, such as Alzheimer's disease. Scopolamine-induced amnesia has been employed to assess the activity of medications in the experimental model of neurodegenerative conditions in an effort to find medicines that treat dementia, since it causes brain synapse loss and oxidative stress [19].

This present study tested cognitive performance (learning and memory) with the Y-maze and novel object recognition (NOR). Scopolamine (induction) groups showed reduced Y-maze activity, with fewer spontaneous alternations and fewer total arm entries than the control group, consistent with previous findings [20]. The NOR test showed that the scopolamine group's recognition index was significantly lower than that of the control group, suggesting learning and recognition impairment. Scopolamine, an anticholinergic that blocks muscarinic receptors, disrupted acquisition and short-term and long-term memory [21].

The new investigation confirmed prior findings that the brain's antioxidant defense mechanism had collapsed, as MDA levels were higher in the scopolamine group than in the control group [8]. The brain homogenate had considerably lower SOD1 than the control group. SOD1 is the most significant antioxidant, detoxifying superoxide anions that damage cell membranes via an enzymatic effect [22]. The increased MDA level and reduced SOD1 level in the neural homogenate of the induction group were the primary findings of the current study, confirming the oxidative stress state induced by scopolamine administration.

Table 3. **Effects of famotidine and donepezil on inflammatory cytokines**

Groups	TNF-α (pg/ml)	IL-1β (pg/ml)	IL-6 (pg/ml)	p-values*
Control	130.77Â ± 18.32	693.56Â ± 150.18	156.45Â ± 39.04	–
Scopolamine	189.89Â ± 33.93	983.69Â ± 109.73	227.51Â ± 35.19	TNF: 0.0002; IL-1β: 0.0001; IL-6: 0.0004
Donepezil	125.91Â ± 21.21	744.48Â ± 34.39	158.68Â ± 15.92	TNF: 0.0001; IL-1β: <0.0001; IL-6: <0.0001
Ranolazine + Famotidine	135.8Â ± 17.54	726.72Â ± 119.73	141.28Â ± 17.56	TNF: 0.0005; IL-1β: <0.0001; IL-6: <0.0001

Note. * Reconstructed ANOVA p-values (n = 10/group): scopolamine was compared with control; donepezil and ranolazine + famotidine were each compared with scopolamine. Statistically significant of independent t-test ($p < 0.05$).

Spatial memory and learning serve as indicators of the behavioral abnormalities and memory deficits induced by scopolamine. Scopolamine has been associated with elevated levels of acetylcholinesterase, oxidative stress, neuroinflammatory markers, interleukin-1 beta, tumor necrosis factor-alpha, interleukin-6, and interferon in the brain, leading to significant cognitive dysfunction [23]. Neuronal injury is defined by the abnormal production of inflammatory cytokines, which precedes the progression of Alzheimer's disease. Earlier research has demonstrated that administering scopolamine to an experimental animal model significantly increased levels of neuroinflammatory markers, which, in turn, led to neuronal injury [20]. Muhammad et al. (2019) previously reported that scopolamine administration increased inflammatory mediators and neurotoxic cytokines, including IL-1β, TNF-α, and IL-6. The present study has further demonstrated this [24].

Ranolazine markedly enhanced the recognition index and the average spontaneous alteration score, indicating its potential efficacy against scopolamine-induced cognitive impairment. The results of this investigation are consistent with those of Cassano et al. (2022), who demonstrated that rats administered metformin or ranolazine for an extended duration exhibited less cognitive deterioration [25].

Also, Cassano et al. (2022) found that ranolazine protects against cognitive decline in diabetic rats by preventing cognitive impairment (assessed by latency to access a dark compartment) and enhancing memory and cognition (as demonstrated by the NOR test). Ranolazine treatment in diabetic mice showed reduced inflammatory features, suggesting its potential to combat depression and cognitive impairment by lowering TNF-α and IL-6 levels [26].

In this study, ranolazine significantly reduced MDA and increased SOD1, demonstrating its antioxidant properties. These findings match earlier research. This study also showed that ranolazine reduces MTX-induced oxidative damage in cardiomyocytes. Reduced oxidative stress by lowering MDA activity, keeping CAT, TAC, and T-SH levels stable, and regulating HIF-1α inflammatory pathway growth. Thus, ranolazine prevents oxidative injury and hypoxia [27].

The current findings demonstrated that ranolazine significantly decreased proinflammatory cytokines (TNF-α, IL-1β, and IL-6). Therefore, a study corroborates these findings, indicating that in diabetic rats, ranolazine markedly reduced the levels of proinflammatory cytokines, including TNF-α, IL-1β, IL-6, p-IKKα, and NF-κB in the hippocampal regions. The evidence for ranolazine derives from its ability to mitigate neurodegeneration of hippocampal neurons after the introduction of type 2 diabetes mellitus (T2DM) [28].

In primary astrocyte cultures, Aldasoro et al. (2016) found that ranolazine increased the production of Mn-SOD and Cu/Zn-SOD antioxidants and decreased the proinflammatory cytokines IL-1β and TNF-α. It also increased PPAR-γ expression, an anti-inflammatory Receptor [29]. Ranolazine also reduced LDH and increased astrocyte survival and proliferation. Ranolazine may protect the central nervous system by boosting astrocyte survival, preventing necrosis and apoptosis, decreasing inflammation, and promoting antioxidant and anti-inflammatory effects. Astrocytes play a vital role in safeguarding neurons from oxidative and inflammatory damage. They do this through mitochondrial cell biogenesis [30].

The present study demonstrated famotidine significantly enhanced the measure of recognition and the mean number of unplanned changes, suggesting that the drug may confer a protective effect against scopolamine-induced cognitive impairment. The findings of the current study align with those of Unal et al. (2020), who showed that famotidine pretreatment mitigated ketamine's disruptive impact on sensorimotor gating in rodents and improved the recognition index in the NOR test. Moreover, administering famotidine alone to rats did not alter their memory performance [31].

A study by Nikiforuk et al. (2016) demonstrated that famotidine therapy corrected the majority of behavioral impairments involving visual recognition memory, learning and memory, and social performance in a rat model of schizophrenia-like behavior induced by ketamine. It proposed its molecular effects on the signaling pathways Akt/GSK-3/-Catenin [32].

One case report found that a young patient's neuropsychiatric problems, which had emerged after COVID-19, were relieved by 20 mg of oral famotidine administered twice daily; the anti-inflammatory effect of famotidine was attributed to stimulation of the vagus nerve inflammatory reflex [33].

The results of the current investigation demonstrated that famotidine exhibited a substantial decline in MDA levels and a substantial increase in SOD1 levels, suggesting that it has potent antioxidant properties. These results align with the findings of Kurt et al. (2011), who demonstrated famotidine's preventive effect against ischemia-reperfusion-induced ovarian damage in rats by reducing an oxidative stress marker (MDA) and maintaining tGSH and SOD levels, suggesting that famotidine prevents a drop in enzymatic and nonenzymatic antioxidation levels [34].

In the present study, famotidine significantly reduced proinflammatory cytokines (TNF-α, IL-1β, and IL-6). This aligns with our results, as shown in the studies, that in severe viral infections such as COVID-19, famotidine has a potential role in reducing inflammation by lowering TNF-α and IL-6 and preventing a cytokine storm. Because it inhibits histamine synthesis, it might worsen immune responses and trigger a cytokine storm [35].

Furthermore, by stimulating the immunological response, famotidine stimulates the activity of specific immune cells, including T cells and natural killer cells. In SARS-CoV-2-infected cells, famotidine decreased the

levels of specific proteins involved in the NF-κB, interferon, and TLR signaling pathways [6]. Another study indicated that famotidine could prevent cytokine storms and lower inflammatory biomarkers, including IL-6, TNF-α, ferritin, CRP, and procalcitonin, supporting our current findings [36].

CONCLUSION

The neuroprotective effect of the combination (ranolazine + famotidine) in response to scopolamine-induced Alzheimer's disease-like characteristics in a mouse model was a subject of the current study. The reason for this beneficial effect is likely that both drugs have substantial antioxidant and anti-inflammatory effects, albeit through distinct mechanisms of action, as demonstrated in the current study.

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