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Title: Ferulic Acid Attenuates Oxidative Stress and Behavioral Alterations in a Ketamine-Induced Model of Mania in Rats

Running Title: Ferulic Acid in Ketamine-Induced Mania

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Abstract

Objective: Growing evidence implicates that oxidative imbalance may play an important role in the pathophysiology of bipolar disorder (BD) and manic episodes. Ferulic acid (FA), a plant-derived phenolic antioxidant known for its neuroprotective and free radical-scavenging activities, has not yet been investigated in an experimental model of mania. This study investigated the effects of FA on ketamine (KET)-induced mania-like behavioral and oxidative alterations in rats.

Methods: Adult male Wistar rats received FA (20, 40 or 80 mg/kg/day, p.o.), lithium chloride (45 mg/kg, p.o., twice daily) or distilled water for 14 days. From days 8 to 15, rats received daily intraperitoneal injections of either KET (25 mg/kg) or saline according to the experimental group. On day 15, locomotor activity, rearing and working memory were evaluated using the open-field and Y-maze paradigms, respectively. Oxidative stress biomarkers, including malondialdehyde, superoxide dismutase, reduced glutathione and catalase, were measured in the cerebral cortex and hippocampus.

Results: FA attenuated KET-induced hyperlocomotion, restored rearing behavior and improved working memory impairment. It also reduced lipid peroxidation and improved antioxidant defenses. Among the tested doses, FA (80 mg/kg) produced the most consistent protective effects, with efficacy broadly comparable to lithium in most behavioral and biochemical assessments.

Conclusion: FA ameliorated KET-induced behavioral and oxidative alterations in rats, supporting its neuroprotective potential in this experimental model. Additional studies are needed to elucidate its underlying mechanisms and therapeutic potential in BD.

Keywords: Ketamine, Mania, Oxidative stress, Ferulic Acid, Neuroprotection

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1. Introduction

Mood variations are a normal part of daily life; however, persistent and severe alterations in mood that impair functioning may indicate an affective disorder. Among mood disorders, bipolar disorder (BD) is a long-term affective illness marked by alternating episodes of mania, hypomania and depression. The clinical spectrum of BD includes bipolar I disorder, bipolar II disorder and cyclothymic disorder. The hallmark feature distinguishing BD from other mood disorders is the occurrence of manic or hypomanic episodes, which may alternate with depressive states. Manic episodes are typically associated with an abnormally elevated mood accompanied by increased activity, decreased sleep requirement and impulsive behaviors and in some cases, psychotic symptoms, whereas bipolar II disorder is predominantly characterized by depressive episodes accompanied by hypomania. These recurrent mood disturbances substantially affect psychosocial functioning and contribute to the considerable clinical burden of the disorder (Ropper, 2020). BD affects more than 1% of the global population and often has an early onset, with nearly half of cases developing around a mean age of 17 years. Moreover, BD is associated with considerable functional impairment and an elevated risk of premature mortality, particularly from suicide and cardiovascular disease (Oliva et al., 2025).

Evidence from post-mortem studies has demonstrated alterations in glutamatergic neurotransmission in brain regions implicated in BD, including the hippocampus and cerebral cortex. Reduced expression of NMDA receptor subunits and associated proteins has been reported in the hippocampus and dorsolateral prefrontal cortex, accompanied by a decreased density of NMDA receptor-expressing neurons in these regions. Collectively, these observations support the involvement of hippocampal and cortical dysfunction in the underlying pathophysiology of BD (Scarr et al., 2003).

In addition to glutamatergic dysfunction, accumulating evidence indicates that oxidative stress is involved in the pathophysiology of BD and manic episodes (Madireddy & Madireddy, 2022).

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Elevated lipid peroxidation products, including thiobarbituric acid reactive substances and malondialdehyde (MDA), have been consistently reported in patients with BD, particularly during mania (Siwek et al., 2016). Also, alterations in glutathione (GSH) homeostasis have been reported in BD (Rosa et al., 2014).

Among pharmacological models of BD, ketamine (KET) administration has been extensively employed to induce mania-like behavior (MLB) in rodents, reproducing several behavioral, neurochemical and oxidative stress-related alterations relevant to manic episodes. The reversal of these alterations to established mood stabilizers supports the predictive validity of this experimental model for preclinical evaluation of candidate therapeutic agents (Ghedim et al., 2012; Sharma et al., 2016).

Lithium is known as the first-line drug for the treatment of acute mania and maintenance therapy in bipolar patients. However, in some patients, lithium and other drugs show limited efficacy or side effects such as lethargy, cognitive impairment, metabolic changes and weight gain. Therefore, the identification of new drugs for the treatment of this disorder is necessary (Ferensztajn-Rochowiak & Rybakowski, 2023; Price & Heninger, 1994).

Ferulic acid (FA) ((*E*)-3-(4-hydroxy-3-methoxy-phenyl) prop-2-enoic acid), a naturally occurring phenolic compound, is abundantly present in a variety of edible plants, including cereals, fruits, and vegetables, as well as beverages such as coffee and beer. It is also isolated from several traditional medicinal herbs, notably *Angelica sinensis*, *Cimicifuga racemosa* and *Ligusticum chuanxiong*, where it is considered one of the major bioactive phenolic constituents (Kumar et al., 2025; Mancuso & Santangelo, 2014). Previous studies have demonstrated that FA exerts neuroprotective effects in both *in vitro* and *in vivo* models by attenuating oxidative stress, reducing neuronal apoptosis, and improving cognitive impairment (Kim et al., 2007). These neuroprotective effects have been associated with reduced reactive oxygen species (ROS) and MDA levels, enhancement of endogenous antioxidant defenses, including

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superoxide dismutase (SOD) and catalase (CAT), and modulation of oxidative stress-related signaling pathways (Karademir et al., 2024; Ren et al., 2017; Singh et al., 2022). In addition, FA acts as a potent free radical scavenger (Mancuso & Santangelo, 2014).

Despite the growing evidence supporting the neuroprotective and antioxidant properties of FA, its effects in experimental models of mania have not been investigated. Therefore, the present study was designed to evaluate the effects of FA on behavioral alterations and oxidative stress biomarkers in the cerebral cortex and hippocampus following KET-induced MLB.

2. Materials and Methods

2.1. Drugs

FA and lithium chloride were purchased from Merck Company, Germany. KET was purchased from Rotexmedica Company, Germany.

2.2. Animals

The study was conducted using 48 adults male Wistar rats weighing between 180 and 220 g. Following randomization, rats were assigned to eight experimental groups (n = 6 per group). Rats were housed in standard polypropylene cages under controlled environmental conditions (23 ± 2 °C, 50–70% relative humidity) with a 12-h light/12-h dark cycle. Animals had free access to a standard pellet diet and tap water throughout the experimental period. All experimental procedures were approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Approval No.IR.AJUMS.ABHC.REC.1397.057) and were conducted in accordance with institutional guidelines for care and use of laboratory animals.

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2.3. Protocol of mania induction

Mania was induced according to the protocol previously described by Ghedim et al. (Ghedim et al., 2012). All oral treatments (FA, lithium chloride or distilled water) were administered from days 1 to 14. From days 8 to 15, rats received daily intraperitoneal injections of either KET (25 mg/kg) or normal saline, depending on the experimental group. The experimental groups were as follows:

Group 1: Distilled water + Saline

Group 2: FA (80 mg/kg) + Saline

Group 3: Lithium chloride (45 mg/kg, twice daily) + Saline

Group 4: Distilled water + KET

Group 5: FA (20 mg/kg) + KET

Group 6: FA (40 mg/kg) + KET

Group 7: FA (80 mg/kg) + KET

Group 8: Lithium chloride (45 mg/kg, twice daily) + KET

The dosage levels for lithium chloride (Gazal et al., 2014) and FA (Ekhtiar et al., 2025; Sadar et al., 2016) were selected based on previous studies.

2.4. Behavioral tests

Behavioral tests were performed on day 15. Thirty minutes after the final KET or saline injection, the open-field test was performed first. After the open-field test, the Y-maze test was conducted immediately.

2.4.1. Open-field test

The open field test was used to evaluate locomotor activity and exploratory behavior following exposure to a novel environment (Gazal et al., 2014; Valvassori et al., 2017). The test was

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performed in a wooden open-field arena (72 × 72 × 33 cm). The floor of the arena was divided into 16 equal squares, and the walls prevented the animals from escaping**.** The number of crossings and rearings were recorded using a video camera and analyzed subsequently. Each rat was gently positioned in one corner of the arena and allowed to explore freely for 5 min. The apparatus was wiped with 70% ethanol between sessions to eliminate odor cues.

2.4.2. Y- maze test

This behavioral test is used to evaluate working memory. The Y-maze apparatus consisted of three identical arms measuring 40 × 25 × 6 cm, arranged at 120° intervals. At the beginning of the test, each rat was placed at the end of one arm and allowed to freely explore the maze for 8 min. The sequence of arm entries was recorded throughout the test, and an arm entry was considered complete when all four paws entered an arm.

Working memory performance was assessed by the percentage of correct alternations. A correct alternation was defined as consecutive entries into three different arms. The percentage of correct alternations was calculated as the ratio between the number of correct alternations and the total number of arm entries minus two, multiplied by 100 (Sampaio et al., 2018).

2.5. Tissue homogenization and determination of protein concentration

After behavioral tests, rats were euthanized. After decapitation, the hippocampus and cerebral cortex were dissected and homogenized in 0.1 M phosphate buffer (pH 7.4). The Bradford assay was used to measure protein concentration using Bradford reagent containing Coomassie Brilliant Blue G-250, 85% phosphoric acid, and 96% ethanol. The assay is based on the binding of Coomassie Brilliant Blue G-250 to proteins, which results in an increase in absorbance at 595 nm proportional to protein concentration (Bradford, 1976).

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2.6. Determination of oxidative stress parameters

2.6.1. MDA assay

The level of MDA was determined using the Satoh method (Satoh, 1978). In this method, a 0.67% thiobarbituric acid solution was used, and the absorbance of the resulting pink chromogen was measured at 532 nm using a spectrophotometer. The MDA concentration was determined by tetraethoxypropane as the standard.

2.6.2. GSH assay

GSH levels were measured according to previous study performed by Aksenov and Markesbery (Aksenov & Markesbery, 2001). In this method, GSH reacts with Ellman's reagent [5,5′-dithiobis-(2-nitrobenzoic acid); DTNB] to produce the yellow-colored 5-thio-2-nitrobenzoic acid (TNB), the absorbance of which was measured spectrophotometrically at 412 nm. GSH content was reported as nmol/mg protein.

2.6.3. CAT activity assay

CAT activity was quantified according to Aebi's method (Aebi, 1984). The decomposition of H_2O_2 was continuously monitored for 90 s at 240 nm using a spectrophotometer. CAT activity was reported as U/mg protein.

2.6.4. SOD activity assay

SOD activity was assessed using the method of Misra and Fridovich (Misra & Fridovich, 1972). The assay relies on inhibition of superoxide-dependent adrenaline auto-oxidation, and the absorbance was measured at 480 nm using a spectrophotometer. SOD activity was reported as U/mg protein.

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2.7. Statistical analysis

The values are presented as mean ± SD for each group and comparisons between experimental groups were performed by one-way analysis of variance (ANOVA), followed by Tukey's post hoc test when appropriate. A P-value < 0.05 was considered statistically significant. All statistical analyses were performed using the GraphPad Prism version 10.6.1 (GraphPad Software, USA).

3. Results

3.1. Behavioral tests

3.1.1. Open field test

Figure 1 summarizes the effects of KET and FA on open-field performance. One-way ANOVA demonstrated a significant group effect on the total number of crossings (Fig. 1A; $F(7,40) = 96.0280$, $P < 0.001$) and the number of rearings (Fig. 1B; $F(7,40) = 6.48319$, $P < 0.001$).

KET produced a significant increase in the number of crossings relative to the vehicle/saline group ($P < 0.001$). This effect was prevented by lithium and FA at 20, 40 and 80 mg/kg ($P < 0.001$). KET reduced the number of rearings ($P < 0.01$), while only lithium ($P < 0.01$) and FA at 80 mg/kg ($P < 0.001$) restored this parameter.

3.1.2. Y-maze test

The percentage of correct alternations differed significantly among the experimental groups (Fig. 2; $F(7,40) = 5.87402$, $P < 0.001$). KET significantly decreased the percentage of correct alternations relative to the vehicle/saline group ($P < 0.001$). This effect was improved by lithium and FA at 20 mg/kg ($P < 0.05$), whereas FA at 40 and 80 mg/kg produced a greater increase ($P < 0.01$).

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3.2. Measurement of oxidative stress markers

3.2.1. Cerebral cortex

Significant differences among the experimental groups were observed in cortical MDA levels (Fig. 3A; $F(7,36) = 9.44848$, $P < 0.001$), GSH levels (Fig. 3B; $F(7,36) = 3.26680$, $P = 0.0086$), CAT activity (Fig. 3C; $F(7,40) = 7.15106$, $P < 0.001$), and SOD activity (Fig. 3D; $F(7,40) = 9.01936$, $P < 0.001$).

KET significantly increased cortical MDA levels ($P < 0.05$) and reduced CAT and SOD activities ($P < 0.01$), whereas the decrease in GSH was not statistically significant. In comparison with the vehicle/ketamine group, lithium and FA (20, 40 and 80 mg/kg) significantly lowered MDA levels (all $P < 0.001$). Lithium significantly increased GSH ($P < 0.01$), whereas FA produced no significant effect. CAT activity was significantly increased by lithium and FA at 40 and 80 mg/kg ($P < 0.001$). SOD activity was also elevated by FA at 20 ($P < 0.05$), 40 ($P < 0.01$), and 80 mg/kg ($P < 0.001$), as well as by lithium ($P < 0.001$).

3.2.2. Hippocampus

Significant differences among the experimental groups were observed in hippocampal GSH levels (Fig. 4A; $F(7,35) = 10.2390$, $P < 0.001$), CAT activity (Fig. 4B; $F(7,40) = 3.61182$, $P = 0.0042$), and SOD activity (Fig. 4C; $F(7,33) = 16.7798$, $P < 0.001$).

KET reduced hippocampal GSH levels without reaching statistical significance, whereas CAT and SOD activities were significantly decreased ($P < 0.05$). Compared with the vehicle/ketamine group, FA at 20, 40 and 80 mg/kg significantly increased GSH levels ($P < 0.05$, $P < 0.01$, and $P < 0.01$, respectively), while lithium produced a greater increase ($P < 0.001$). CAT activity was significantly increased by FA at 40 and 80 mg/kg and by lithium ($P < 0.01$). Likewise, SOD activity was significantly elevated by FA at 20 mg/kg ($P < 0.05$), 40 and 80 mg/kg ($P < 0.001$), and lithium ($P < 0.001$).

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4. Discussion

The findings of the present study demonstrated that FA was effective in attenuating KET-induced behavioral and oxidative alterations in rats, supporting the possibility that FA may represent a promising adjunctive strategy for mania-like manifestations.

Ghedim et al. reported that KET, at subanesthetic doses, induces MLB alterations, including hyperlocomotion in rats (Ghedim et al., 2012). Enhanced mesolimbic dopaminergic neurotransmission has been proposed as one of the mechanisms underlying KET-induced hyperlocomotion. Increased glutamate release following KET administration facilitates dopamine release in the nucleus accumbens, a region that plays a pivotal role in reward processing and the regulation of locomotor activity. This dopaminergic overactivity is considered a major contributor to the hyperlocomotion and MLB changes observed in KET-treated animals (Irifune et al., 1991; Lorrain et al., 2003; Moghaddam et al., 1997).

Overactivity has been proposed as a key feature of mania and may be as important as elevated or irritable mood. Therefore, it has been suggested that overactivity should be included as a core diagnostic criteria for mania (Benazzi, 2006; Perry et al., 2010). Clinically, over-activity is characterized by increased goal-directed behavior and is often accompanied by impulsivity. To objectively quantify this behavioral domain, translational open-field paradigms have been developed for both humans and rodents. The human Behavioral Pattern Monitor (hBPM), inspired by the rodent Behavioral Pattern Monitor, has been developed as a cross-species translational paradigm that provides an objective and multidimensional assessment of locomotor and exploratory behaviors in a novel environment, facilitating direct comparison of behavioral phenotypes across humans and rodents (Rosberg et al., 2025). Using the hBPM, Perry et al. demonstrated that patients with bipolar mania increased motor activity and exploratory behavior in a novel environment, and suggested that this distinctive pattern of over-activity may represent a behavioral signature of mania (Perry et al., 2010; Perry et al., 2009).

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Consistent with these observations, KET markedly increased the number of crossings in the present study, supporting the successful induction of MLB. This effect was significantly prevented by pretreatment with FA at all tested doses and lithium. Rearing is widely considered an index of vertical exploratory behavior in the open-field test and is commonly used together with locomotor measures to characterize exploratory activity in rodents (Henry et al., 2010). In the present study, KET significantly reduced rearing behavior, whereas pretreatment with FA (80 mg/kg) and lithium restored this parameter to levels that were not significantly different from the control values. A similar behavioral profile has been reported in an ouabain-induced animal model of mania, in which increased horizontal locomotor activity was accompanied by reduced rearing behavior (El-Mallakh et al., 1995). The reduction in rearing following KET administration may be related to mild ataxia. Although KET-treated animals may still attempt vertical exploration, successful execution of rearing requires transfer of body weight to the hind limbs, maintenance of postural balance, and coordinated vertical posture, which may be impaired by KET. This interpretation is consistent with Elersič et al., who reported that racemic KET (15 and 30 mg/kg) induced ataxia while simultaneously increasing locomotor activity and reducing rearing, with ataxic effects evaluated during the first 15 min after administration and during the final 15 min of a 60-min locomotor recording period in the 30 mg/kg group. Therefore, mild ataxia effects may partly explain the dissociation between increased locomotion and reduced rearing observed in the present study (Elersič et al., 2024). Anxiety-related alterations may also have contributed to this finding (Manooki et al., 2025). Such factors may contribute to the variability of rearing responses reported across different KET-induced manic-like models.

The Y-maze spontaneous alternation test is a well-established behavioral paradigm for assessing spatial working memory in rodents. Spontaneous alternation is driven by natural preference of rodents for exploring a less recently visited arm and depends on the coordinated

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function of interconnected brain regions, particularly the hippocampus and prefrontal cortex, together with cholinergic, dopaminergic and GABAergic neurotransmission (Kraeuter et al., 2018; Lalonde, 2002). In the present study, KET significantly reduced spontaneous alternation performance. Working memory, attention and executive function are key domains of cognition that are commonly disrupted during manic episodes of BD, contributing to impaired decision-making (Daglas et al., 2015). Accordingly, reduced spontaneous alternation in the Y-maze may represent the cognitive deficits associated with mania. In contrast, pretreatment with FA at all tested doses, as well as lithium, significantly improved spontaneous alternation performance. Similar impairments in spontaneous alternation and their reversal by therapeutic interventions have also been reported in amphetamine-induced mania models (Chaves Filho et al., 2021; de Souza Gomes et al., 2015).

KET has been demonstrated to disrupt mitochondrial function, inhibit mitochondrial electron transport, and increase ROS production, resulting in oxidative damage in neural tissue (Ito et al., 2015). CAT and SOD constitute major enzymatic antioxidant defenses that detoxify superoxide radicals and hydrogen peroxide, thereby limiting oxidative injury, whereas GSH, a non-enzymatic intracellular antioxidant, helps preserve intracellular redox balance through scavenging ROS and serving as a cofactor for antioxidant enzymes (Hasanuzzaman et al., 2020; Jomova et al., 2024). On the other hand, MDA is a widely used marker of lipid peroxidation resulting from oxidative attack on membrane polyunsaturated fatty acids, a process that contributes to membrane damage and may promote inflammatory responses (Ayala et al., 2014; Jomova et al., 2024). Altered activity of these antioxidant defenses and increased lipid peroxidation have been reported in patients with BD, particularly during manic episodes, supporting the role of impaired redox regulation in the disorder (Lv et al., 2020; Ranjekar et al., 2003; Siwek et al., 2016). In the present study, KET significantly increased cortical MDA levels and reduced CAT and SOD activities in both the cortex and hippocampus, indicating

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enhanced oxidative stress and weakened antioxidant defense. These observations are in agreement with earlier studies demonstrating that repeated KET administration induces oxidative damage, increases lipid peroxidation, and decreases antioxidant enzyme activity in the cortex and hippocampus of rats (Gazal et al., 2014). Although KET produced a trend toward reduced GSH levels in both the cortex and hippocampus, these changes did not reach statistical significance. Nevertheless, pretreatment with FA significantly increased GSH levels compared with the KET group. The absence of a significant reduction in GSH may be related to the dynamic regulation of GSH homeostasis, which is maintained through continuous de novo GSH synthesis, GSH/oxidized glutathione recycling, and adaptive induction of GSH production under oxidative conditions, thereby preserving intracellular redox balance (Aquilano et al., 2014; Han et al., 2006; Kalinina et al., 2014; Lian et al., 2018). A similar pattern has been reported in an amphetamine-induced model of mania, in which no significant reduction in prefrontal cortical GSH was observed following amphetamine administration, whereas lithium treatment significantly increased GSH levels in this brain region (Macêdo et al., 2012). FA increased GSH levels compared to the KET group, suggesting a potential role in promoting GSH synthesis. Experimental evidence indicates that FA activates the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway, leading to increased expression of the glutamate-cysteine ligase (GCL) catalytic subunit, improved GSH redox status, and attenuation of oxidative stress. Since Nrf2 transcriptionally regulates both the GCL catalytic and GCL modifier subunits of GCL, the rate-limiting enzyme in GSH biosynthesis, activation of this pathway may enhance cellular GSH synthesis and antioxidant capacity (Li et al., 2020; Wang et al., 2023). Consistent with these findings, FA has also been shown to enhance GSH levels, increase SOD activity, reduce MDA accumulation, and activate the Nrf2/GCL catalytic signaling pathway in a rat model of ionizing radiation-induced oxidative injury (Chen et al., 2023).

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Overall, among the tested doses, FA (80 mg/kg) was effective across the widest range of behavioral and oxidative stress parameters. FA demonstrated efficacy broadly comparable to lithium in most behavioral and biochemical assessments, supporting its potential as a promising candidate for the management of mania-like alterations. Future investigations may provide further insight into the molecular mechanisms underlying the neuroprotective effects of FA, while also evaluating its efficacy in additional experimental models of BD and its potential as an adjunct to currently available mood stabilizers.

5. Conclusion

In conclusion, pretreatment with FA ameliorated KET-induced mania-like behavioral abnormalities and oxidative stress in rats, indicating that its neuroprotective effects may be partly attributable to its attenuation of oxidative damage (Fig. 5). Taken together, the present findings suggest that FA merits further investigation as a potential therapeutic approach for BD.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical Considerations

All experimental procedures were approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Approval No.IR.AJUMS.ABHC.REC.1397.057).

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Authors' Contribution

MA Conducted the experimental work, performed the formal analysis, wrote the first draft of the manuscript and participated in reviewing and editing the manuscript. **SM** Contributed to data interpretation, critically reviewed the manuscript for important intellectual content, reviewed and edited the manuscript. **SA** Performed the formal analysis, interpreted the data, wrote and substantially revised the manuscript and prepared the final version of the manuscript. **HK** Contributed to the methodology, supervised the experimental work, participated in data interpretation and reviewed the manuscript. **MJK** Conceived and designed the study, developed the methodology, acquired the funding, supervised and administered the project, and reviewed and edited the manuscript.

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Figure legends

Figure 1. Effects of ferulic acid and lithium on ketamine (KET)-induced alterations in open-field tests. (A) Number of crossings and (B) number of rearings. Data are expressed as mean ± SD (n = 6 rats per group). **P < 0.01, ***P < 0.001 relative to the vehicle/saline group; ##P < 0.01, ###P < 0.001 versus the vehicle/ketamine group.

Figure 2. Effects of ferulic acid and lithium on the percentage of correct alternations in the Y-maze test. Data are expressed as mean ± SD (n = 6 rats per group). ***P < 0.001 versus the vehicle/saline group; #P < 0.05 and ##P < 0.01 versus the vehicle/ketamine group.

Figure 3. Effects of ferulic acid and lithium on cortical oxidative stress markers in rats. (A) malondialdehyde levels, (B) glutathione (GSH) levels, (C) catalase (CAT) activity, and (D) superoxide dismutase (SOD) activity. Data are expressed as mean ± SD (n = 5–6 rats per group). *P < 0.05 and **P < 0.01 relative to the vehicle/saline group; #P < 0.05, ##P < 0.01, ###P < 0.001 versus the vehicle/ketamine group.

Figure 4. Effects of ferulic acid and lithium on hippocampal antioxidant markers in rats. (A) GSH levels, (B) CAT activity and (C) SOD activity. Data are expressed as mean ± SD (n = 4–6 rats per group). *P < 0.05 relative to the vehicle/saline group; #P < 0.05, ##P < 0.01, ###P < 0.001 versus the vehicle/ketamine group.

Fig. 5. The graphical abstract illustrates the experimental timeline and the effects of ferulic acid on behavioral and oxidative stress markers in a KET-induced mania-like behavior model.

Fig. 1:

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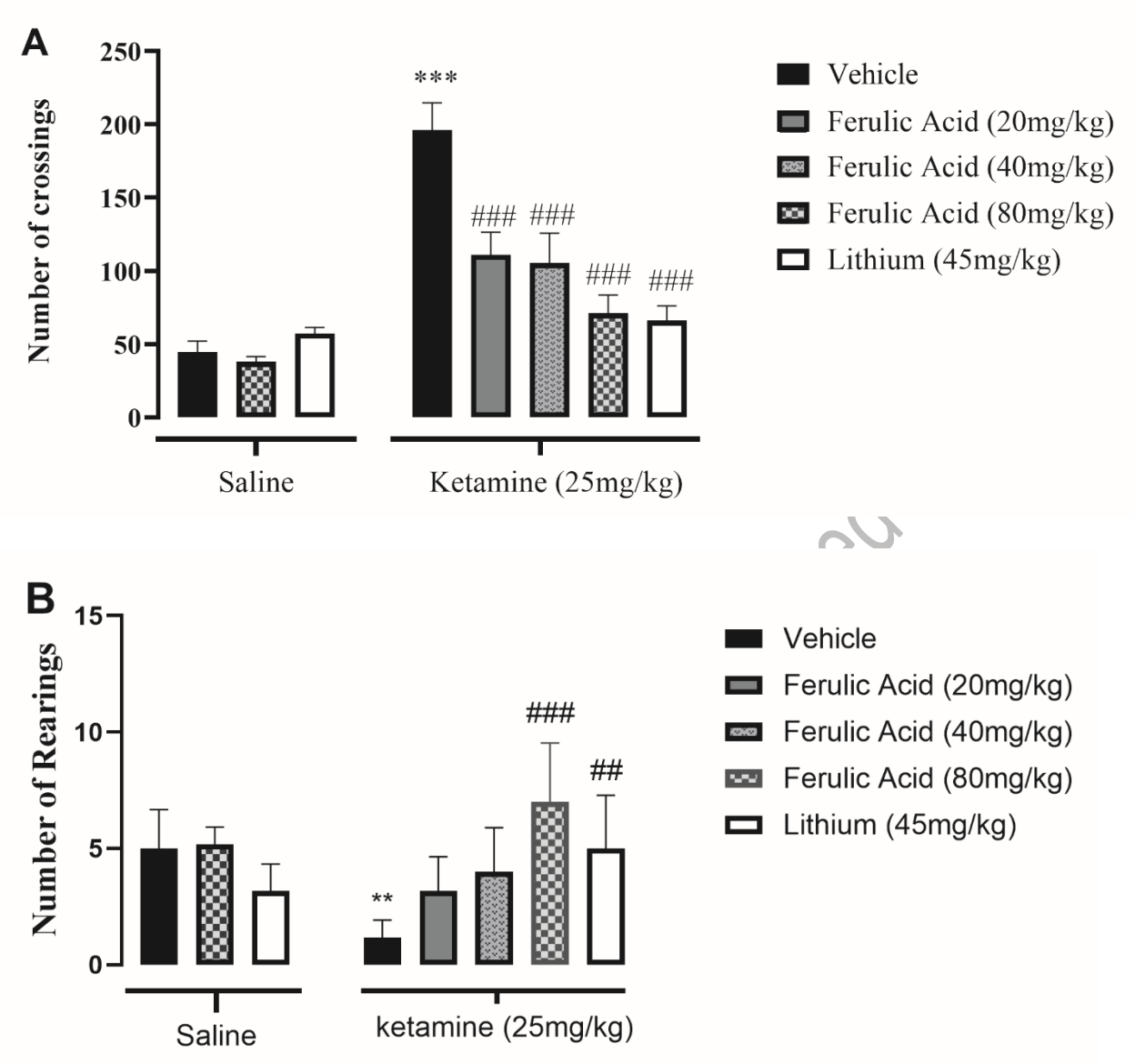


Figure 1. Effects of ferulic acid (FA) and lithium on ketamine (KET)-induced alterations in open-field tests. (A) Number of crossings and (B) number of rearings. Data are expressed as mean ± SD (n = 6 rats per group). **P < 0.01, ***P < 0.001 relative to the vehicle/saline group; ##P < 0.01, ###P < 0.001 versus the vehicle/ketamine group.

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Fig. 2:

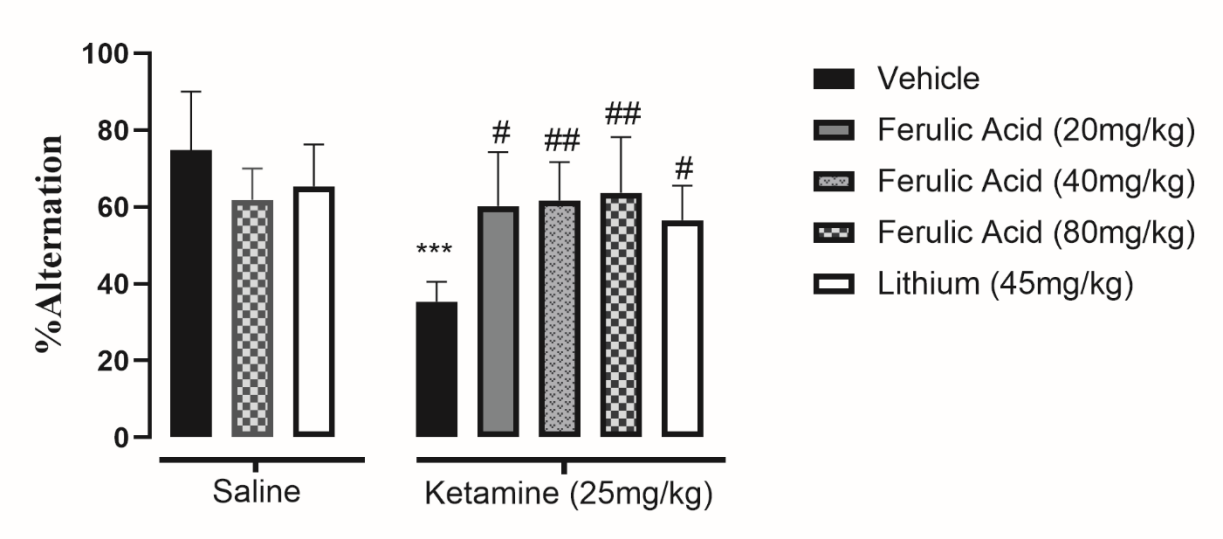
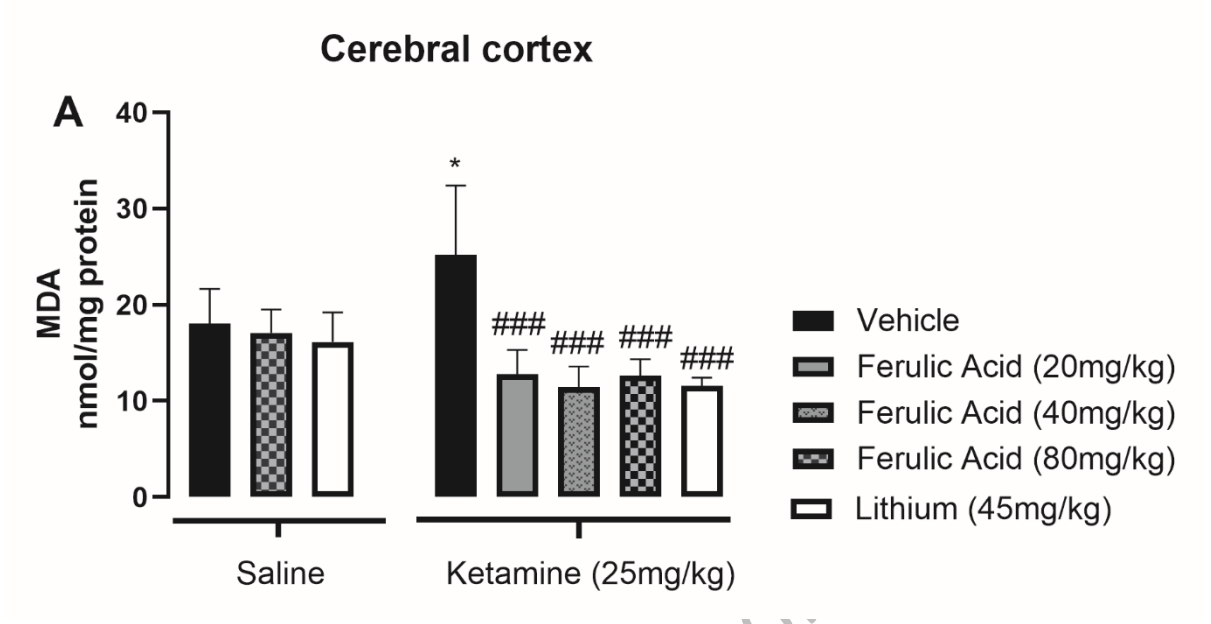
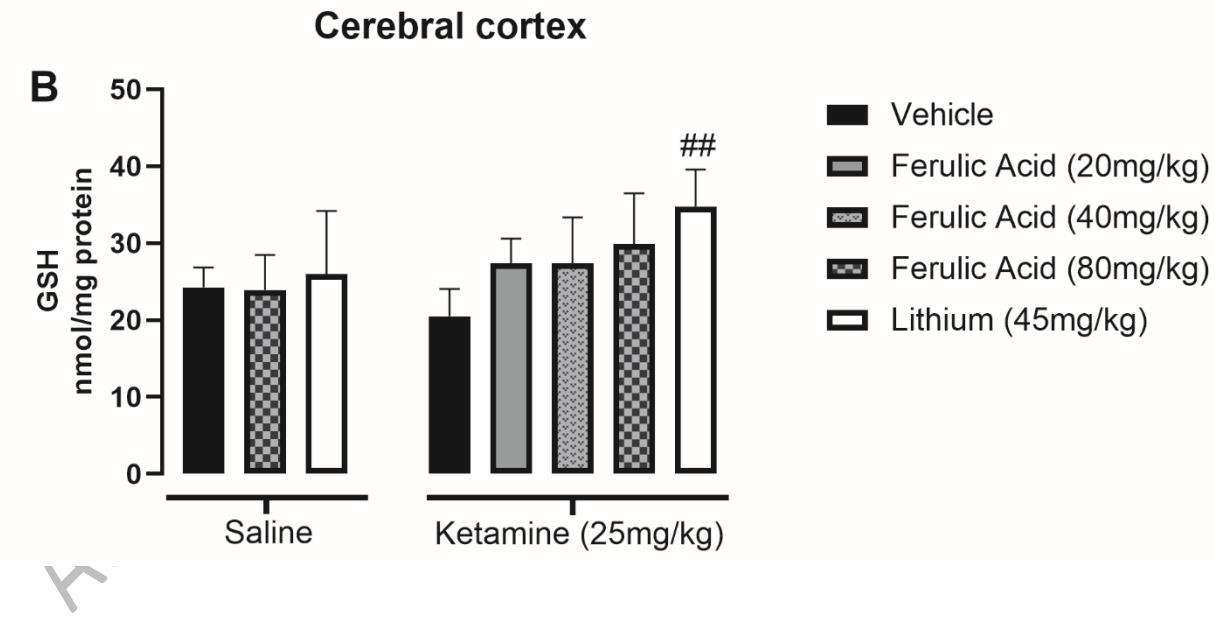


Figure 2. Effects of FA and lithium on the percentage of correct alternations in the Y-maze test. Data are expressed as mean ± SD (n = 6 rats per group). ***P < 0.001 versus the vehicle/saline group; #P < 0.05 and ##P < 0.01 versus the vehicle/ketamine group.

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Fig. 3:


Cerebral cortex
A
MDA
nmol/mg protein
40
30
20
10
0
*
###
###
###
###
Saline
Ketamine (25mg/kg)
Vehicle
Ferulic Acid (20mg/kg)
Ferulic Acid (40mg/kg)
Ferulic Acid (80mg/kg)
Lithium (45mg/kg)


Cerebral cortex
B
GSH
nmol/mg protein
50
40
30
20
10
0
##
Saline
Ketamine (25mg/kg)
Vehicle
Ferulic Acid (20mg/kg)
Ferulic Acid (40mg/kg)
Ferulic Acid (80mg/kg)
Lithium (45mg/kg)

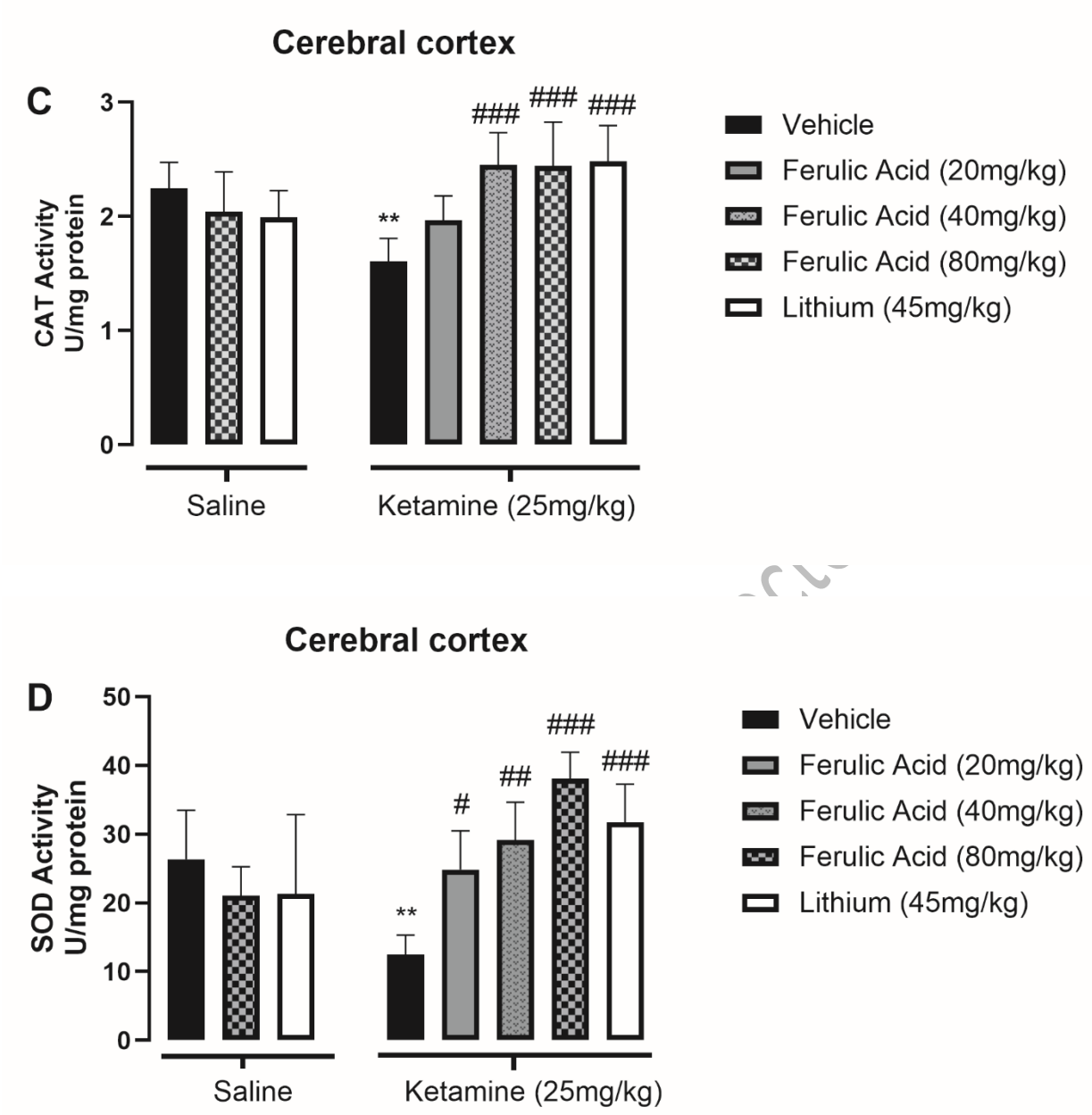
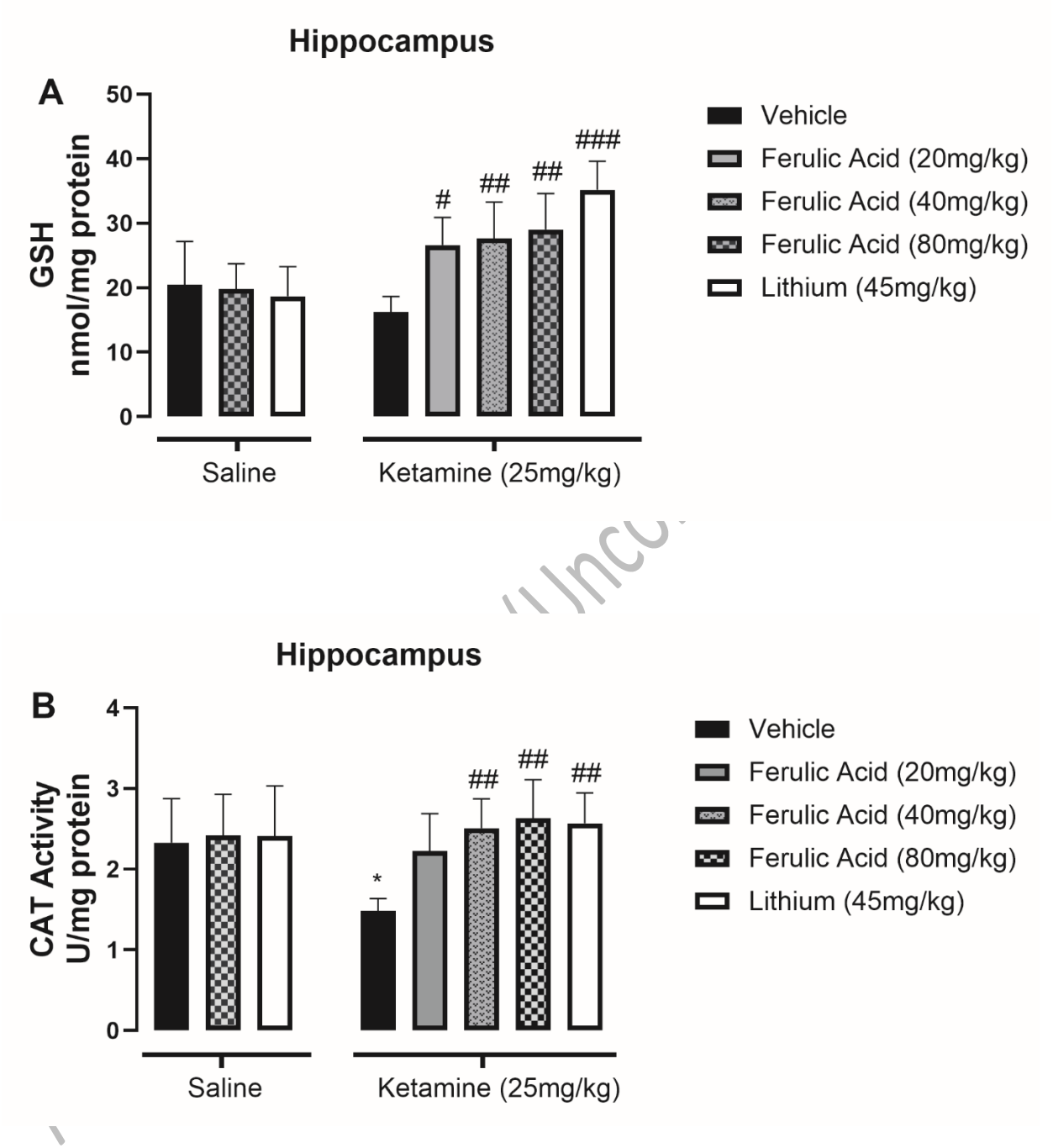


Figure 3. Effects of FA and lithium on cortical oxidative stress markers in rats. (A) malondialdehyde levels, (B) glutathione (GSH) levels, (C) catalase (CAT) activity, and (D) superoxide dismutase (SOD) activity. Data are expressed as mean ± SD (n = 5–6 rats per group). *P < 0.05 and **P < 0.01 relative to the vehicle/saline group; #P < 0.05, ##P < 0.01, ###P < 0.001 versus the vehicle/ketamine group.

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Fig. 4:


Hippocampus
A
GSH
nmol/mg protein
50
40
30
20
10
0
#
##
##
###
Saline
Ketamine (25mg/kg)
Vehicle
Ferulic Acid (20mg/kg)
Ferulic Acid (40mg/kg)
Ferulic Acid (80mg/kg)
Lithium (45mg/kg)
Hippocampus
B
CAT Activity
U/mg protein
4
3
2
1
0
*
##
##
##
Saline
Ketamine (25mg/kg)
Vehicle
Ferulic Acid (20mg/kg)
Ferulic Acid (40mg/kg)
Ferulic Acid (80mg/kg)
Lithium (45mg/kg)

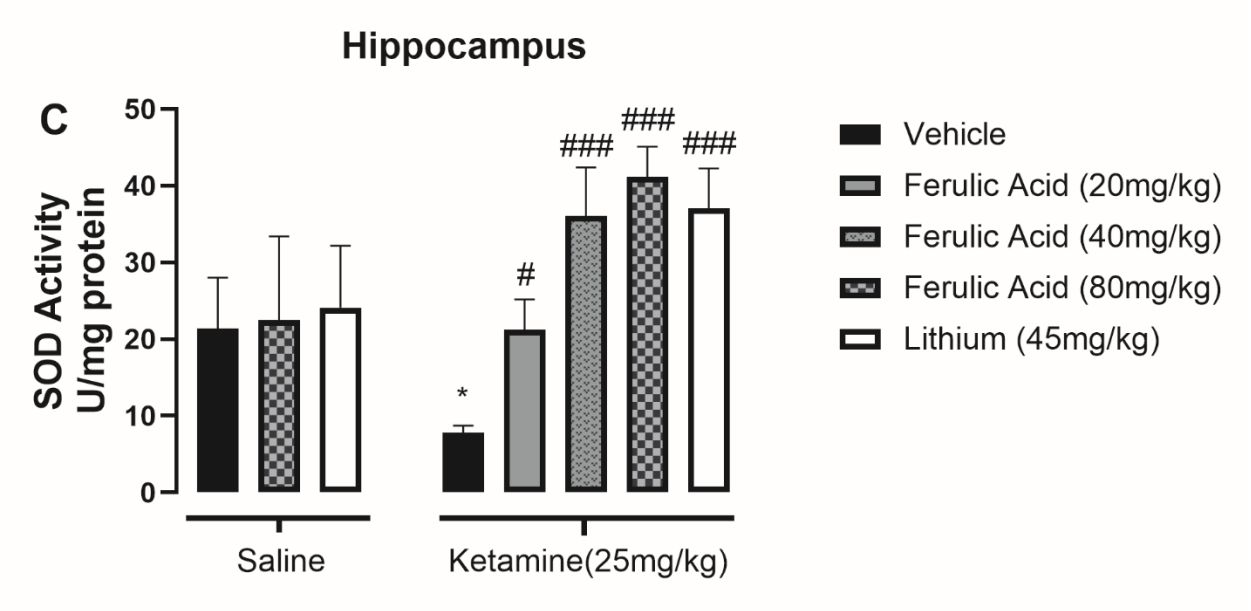


Figure 4. Effects of FA and lithium on hippocampal antioxidant markers in rats. (A) GSH levels, (B) CAT activity and (C) SOD activity. Data are expressed as mean ± SD (n = 4–6 rats per group). *P < 0.05 relative to the vehicle/saline group; #P < 0.05, ##P < 0.01, ###P < 0.001 versus the vehicle/ketamine group.

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Fig. 5:

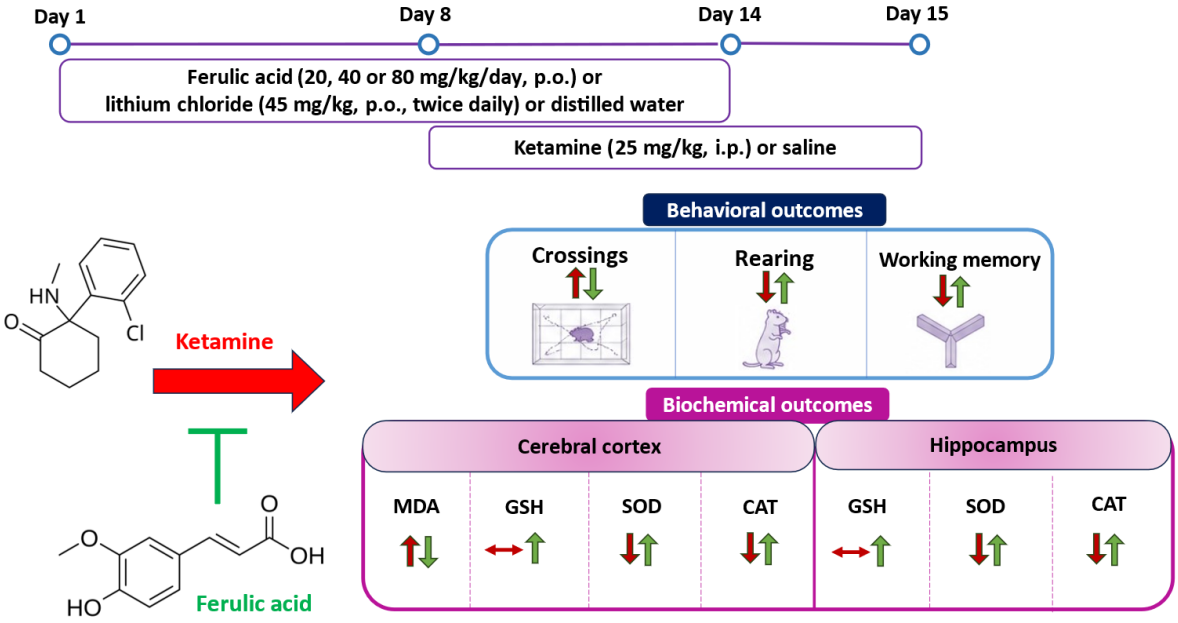


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