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Therapeutic effects of Acetyl-11-Keto-Beta-Boswellic Acid (AKBA) on autism-like behaviours and oxidative stress in a valproic acid-induced mouse model

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Abstract
Objective: To evaluate the effects of AKBA on behavioural abnormalities and oxidative stress markers in a valproic acid (VPA)-induced mouse model of ASD.
Methods: Pregnant mice received a single intraperitoneal injection of VPA (600 mg/kg) on gestational day 12 to induce ASD-like behaviours in offspring. Postnatal mice were treated orally for 20 days with AKBA (5 mg/kg or 15 mg/kg), risperidone (1 mg/kg), or saline. Behavioural assessment was performed using the open field test. Brain tissues were analysed for oxidative stress biomarkers, malondialdehyde (MDA), reduced glutathione (GSH), and the proinflammatory cytokine interleukin-6 (IL-6).
Results: VPA-exposed mice exhibited significantly increased anxiety-like behaviour, grooming, and oxidative stress compared to controls ($p \leq 0.001$). AKBA treatment significantly reduced line crossings and grooming behaviour while increasing latency in the central zone, suggesting anxiolytic effects. Biochemically, AKBA significantly decreased MDA and IL-6 levels and increased GSH concentrations compared to VPA-only mice. These effects were dose-dependent and comparable to or exceeded those of risperidone.
Conclusion: AKBA demonstrated significant anxiolytic, antioxidant, and anti-inflammatory effects in a mouse model of autism. These findings suggest that AKBA may represent a potential therapeutic candidate for managing ASD-related behaviours and oxidative stress.

Keywords: Autism Spectrum Disorder, AKBA, Oxidative stress, Risperidone, Valproic acid, IL-6, Mouse model

Plain English summary

This study looked at how a natural compound called acetyl-11-keto-beta-boswellic acid (AKBA) affects autism-like behaviours in mice. Autism Spectrum Disorder (ASD) is a brain development condition that affects how people communicate, behave, and interact with others. It usually starts in early childhood and is difficult to treat, with only a few medications currently approved for managing symptoms. To model autism, researchers gave pregnant mice a substance called valproic acid (VPA), which is known to cause autism-like traits in the offspring. After birth, the young mice showed behaviours similar to those seen in human autism, such as anxiety, repetitive actions, and reduced interest in exploring. The researchers then treated these mice with either AKBA or a standard drug called risperidone, and compared their behaviour and brain chemistry to untreated mice. They used a test called the open field test to observe movement, anxiety, and

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grooming behaviours. They also measured markers of oxidative stress and inflammation in the brain, which are often linked to brain disorders. The study found that AKBA improved behaviour, reduced anxiety-like symptoms, and lowered harmful chemical levels in the brain. It also reduced a key inflammation marker called IL-6. These effects were similar to or even better than those seen with the standard drug risperidone. This suggests that AKBA may be a promising natural compound for improving autism-related symptoms and reducing brain inflammation. More research is needed, but these results are encouraging.

Introduction

Autism spectrum disorders (ASD) are developmental diseases characterised by deficits in communication, social interaction, and rigid behaviour, often shown via limited and repetitive activities and reduced adaptation to environmental changes (1). The disease is affected by a combination of epigenetic, environmental, and genetic variables throughout early prenatal and postnatal infancy (2).

At least 70% of individuals with autism spectrum disorder exhibit co-occurring symptoms, making this occurrence expected rather than the exception. The chemical basis suggests that many brain neurotransmitters, including dopamine (DA), serotonin (5-HT), gamma-aminobutyric acid (GABA), acetylcholine (ACh), glutamate (Glu), and histamine (HA), have a role in the development and evolution of ASD (3).

The current evidence-based therapy for autism spectrum disorder in children mostly focuses on behavioural interventions to alleviate the core symptoms of the disorder. The importance of pharmacological therapies escalates with age and mostly addresses comorbid diseases linked to ASD. Risperidone and aripiprazole are the only medications approved by the Food and Drug Administration (FDA) for addressing irritability associated with autism spectrum disorder (ASD) (4).

We will use the mouse model owing to the significant evolutionary affinity between mice and humans, along with their same genetic makeup, biological mechanisms, neurological pathways, and, to some extent, behaviours. While ASDs are exclusive to humans, extensive behavioural research on mice may clarify several fundamental deficits linked to these diseases (5).

This investigation used acetyl-11-keto-beta-boswellic acid (AKBA) as a potent neuroprotective drug, since previous studies have shown its considerable antioxidant and anti-inflammatory properties concerning neurological disorders. Thus, AKBA demonstrated its use in our investigation.

ASD includes a range of problems classified into two primary categories: Genetic illnesses, characterised by features linked to autism spectrum disorder, including fragile X syndrome, intellectual disabilities, and tuberous sclerosis complex. Idiopathic, indicating that the causes are unidentified. Idiopathic forms of autism spectrum disorder (ASD) have been referred to by several labels throughout the years, including persistent developmental problems and Asperger syndrome. Regarding gender, there was a significant difference between males and females (autistic children) in the concentration of copper in saliva (6).

Materials and Methods

Experimental animals

This experimental study was conducted at the animal house of the College of Medicine, University of Babylon. Sixty healthy albino mice (40 females and 20 males), aged 12 weeks and weighing 25–40 g, were used. The animals were housed under standard laboratory conditions (temperature 25 ± 5 °C, humidity 60 ± 5%, and a 12-hour light/dark cycle) and given free access to food and water. The study was conducted between October 1, 2024, and March 1, 2025, and received approval from the Institutional Ethics Committee following international guidelines.

Mating and Induction of Pregnancy

Following a two-week acclimatisation period, 20 mating groups were formed, each consisting of one male and two females. Successful mating was confirmed the next morning by the presence of a vaginal plug, examined visually and using a cotton-tipped swab. Detection of the plug indicates successful copulation and is a standard method for determining gestational timing in rodent studies (7).

Induction of Autism

On gestational day 12 (GD12), a critical window for neurodevelopmental processes such as neural tube formation and synaptogenesis, autism was induced in the experimental groups by administering a single intraperitoneal injection of sodium valproate (600 mg/kg body weight). This dosage has been shown to reliably produce autism-like phenotypes in rodent offspring without inducing teratogenic effects (8, 9). Control pregnant females received an equivalent volume of normal saline via the same route.

Drug Preparation and Administration
Valproic acid (VPA) (Depakine®, Sanofi) was diluted in 0.9% normal saline to achieve the desired concentration and administered intraperitoneally on GD12.
Acetyl-11-keto-β-boswellic acid (AKBA) was prepared by dissolving the powdered compound in distilled water to a final concentration of 1 mg/10 mL. The dosages used (5 mg/kg and 15 mg/kg) were selected based on prior studies demonstrating the compound's neuroprotective and antioxidant properties, as well as its safety profile in CNS models (10, 11). Oral administration was performed by gavage once daily for 20 consecutive days, starting on postnatal day (PND) 45.
Risperidone (Risperdal®, Janssen), a commonly used antipsychotic agent for treating irritability in autism, was administered orally at 1 mg/kg once daily for the same duration as AKBA (12).

Experimental Grouping
Offspring from both VPA- and saline-exposed dams were weaned at PND21 and housed in standard cages. On PND45, a total of 50 offspring were randomly assigned to the following five groups (n = 10 per group):
Healthy Control Group: Offspring of saline-injected dams, receiving distilled water
VPA Group: Offspring of VPA-injected dams, receiving distilled water
Risperidone Group: VPA-exposed offspring receiving risperidone (1 mg/kg)
AKBA Low-Dose Group: VPA-exposed offspring receiving AKBA (5 mg/kg)
AKBA High-Dose Group: VPA-exposed offspring receiving AKBA (15 mg/kg)

Behavioural Assessment
Behavioural evaluation was conducted on PND65 using the open field test, a validated method for assessing exploratory behaviour, locomotor activity, and anxiety-like behaviour in rodents (Vorhees & Williams, 2006). The test was conducted between 8:00 and 14:00 hours in a quiet, temperature-controlled room under uniform lighting. Parameters assessed included the number of line crossings, time spent in the centre zone, latency to enter the centre, and frequency of grooming behaviour. All observations were recorded and scored by an investigator blinded to the treatment groups (Figures 1, 2, 3, and 4).

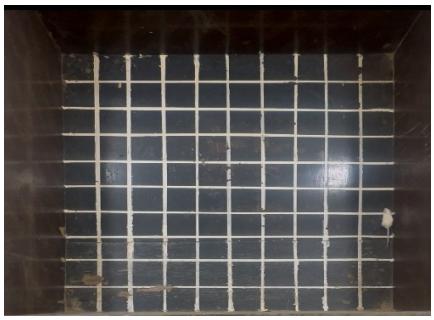


Figure 1: Open field test (by the researcher during the method)

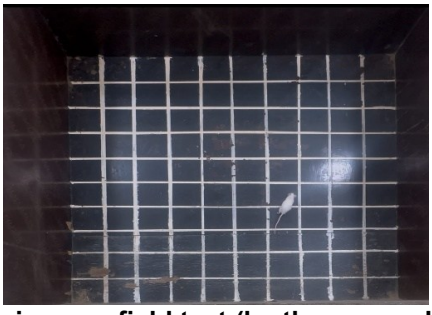


Figure 2: Line crossing in open field test (by the researcher during the method)

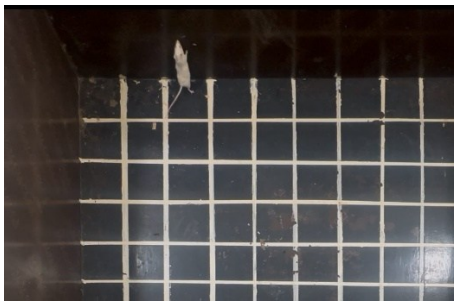


Figure 3. Rearing in an open field test (by the researcher during the method)



Figure 4: Grooming in open field test (by the researcher during the method)

Biochemical Analyses

On PND66, mice were euthanised, and whole brains were collected, immediately cooled on ice, and homogenised in phosphate-buffered saline. The homogenates were centrifuged, and the supernatants were stored at –80 °C until analysis. The following biomarkers were measured using commercially available assay kits:

Malondialdehyde (MDA) – as a marker of lipid peroxidation

Reduced Glutathione (GSH) – to assess antioxidant capacity

Interleukin-6 (IL-6) is a pro-inflammatory cytokine relevant to autism pathophysiology (13, 14).

All assays were conducted following the manufacturers' protocols and previous literature describing neurochemical analysis in ASD models (9, 14).

Statistical Analysis

All data were analysed using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA). Results are presented as mean ± standard error of the mean (SEM). Before analysis, data were assessed for normality using the Shapiro–Wilk test. For comparison among multiple groups, one-way analysis of variance (ANOVA) was used, followed by Tukey's post hoc test for pairwise group comparisons. A value of $p < 0.05$ was considered statistically significant. Specific comparisons of interest (e.g., treatment vs. VPA group) were reported with corresponding p-values in figure legends. Behavioural and biochemical parameters, including line crossings, grooming frequency, latency time, MDA, GSH, and IL-6 levels, were all evaluated using this statistical framework. The number of animals per group (n = 10) was based on prior studies using similar behavioural and biochemical endpoints in rodent models of ASD.

Results

Behavioural Assessment

Line crossing

The number of line crossings was highly significantly elevated ($p \leq 0.001$) in the VPA-saline group in comparison with other groups, and the number of line crossings was highly significantly reduced ($p \leq 0.001$) in both high and low-dose VPA-*AKBA* and VPA-risperidone groups as compared with the VPA-saline group.

The number of line crossings significantly declined ($p = 0.015$) in the control-risperidone group, in contrast to the control-saline group (Figure 5).

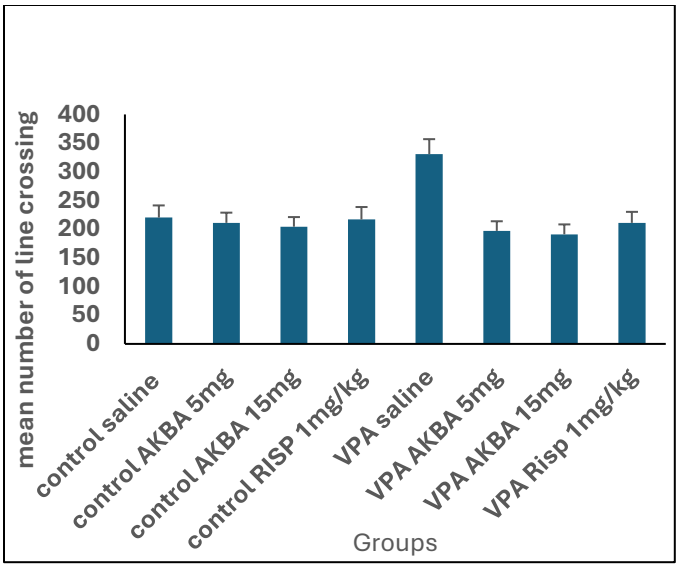


Figure 5: Effect of *AKBA* and risperidone on the number of line crossings in the open field test
The results are expressed as (Means ± SEM). No. of mice = 10 for each group. *p≤0.05 (significant), **p≤ 0.001 (highly significant). A: as compared with other groups, B: as compared to the VPA-saline group, and D: in comparison with the control-saline group

Latency time in the central zone
Latency time on the central zone was highly significantly declined (p≤ 0.001) in the VPA-saline group in comparison with other groups, while latency time on the central zone was highly significantly raised (p≤ 0.001) in both high and low-dose VPA-*AKBA* and VPA-risperidone groups as compared with the VPA-saline group. Latency time on the central zone was significantly elevated in low-dose control- *AKBA* as compared to the control-saline group (Figure 6).

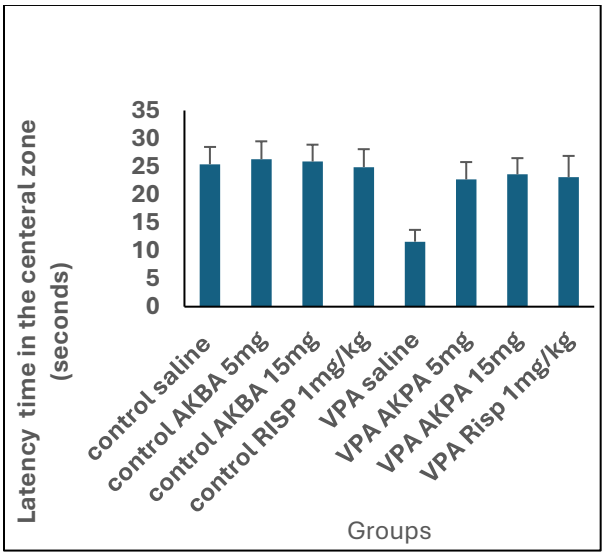


Figure 6: Effect of *AKBA* and risperidone on the latency time in the central zone in the open field test
The results are expressed as (Means ± SEM). No. of mice = 10 for each group. *p≤ 0.05 (significant), **p≤ 0.001 (highly significant). A: as compared with other groups, B: as compared to the VPA-saline group, and D: as compared to the control-saline group

Grooming

The number of grooming was highly significantly elevated (p≤ 0.001) in the VPA-saline group as compared with other groups and was highly significantly decreased (p≤ 0.001) in VPA-risperidone and both high and low-dose VPA-*AKBA*. Grooming frequency significantly decreased in high dose VPA-*AKBA* (p= 0.01) and (p= 0.027) in contrast to low dose VPA-*AKBA* and VPA-risperidone groups, respectively (Figure 7).

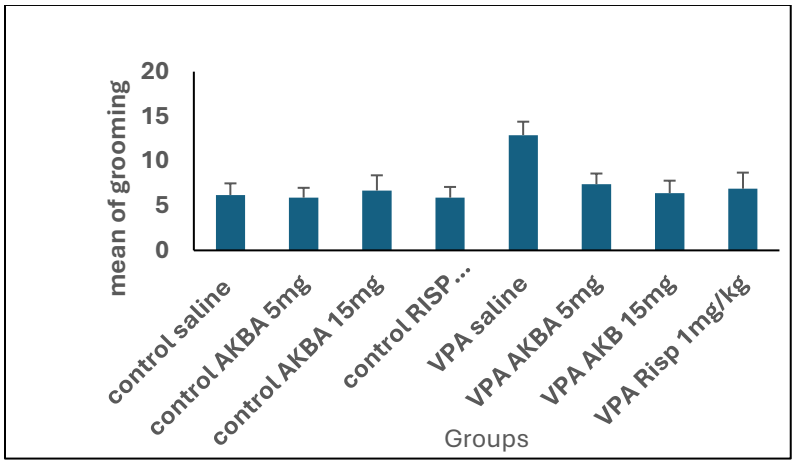


Figure 7: Effect of *AKBA* and risperidone on the number of grooming in the open field test

The results are expressed as (Means ± SEM). No. of mice = 10 for each group. *p≤ 0.05 (significant), **p≤ 0.001 (highly significant). A: as compared with other groups, B: as compared to the VPA-saline group, and C: in comparison with the VPA-risperidone group

Biochemical Analyses

Malondialdehyde (MDA)

The concentration of malondialdehyde was significantly raised (p≤ 0.001) in the VPA-saline group in contrast to other groups. The concentration of MDA was significantly declined (p≤ 0.001) in both low and high-dose VPA-*AKBA* and VPA-risperidone groups as compared to the VPA-saline group.

In the VPA-risperidone group, the level of malondialdehyde significantly declined (p= 0.003) in comparison to the high-dose VPA-*AKBA* group, while the level of malondialdehyde significantly declined (p= 0.031) in the high-dose control-*AKBA* group as opposed to the control-saline group (Figure 8).

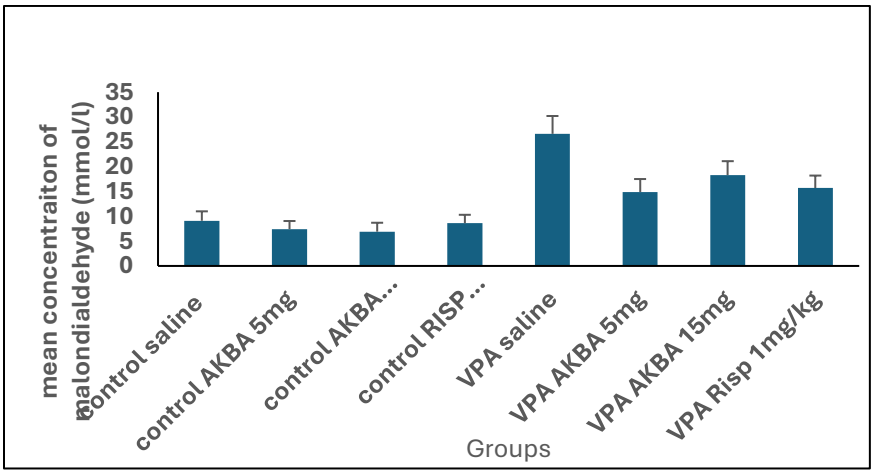


Figure 8: Effect of *AKBA* and risperidone on malondialdehyde concentration

The results are expressed as (Means ± SEM). No. of mice = 10 for each group. *p≤ 0.05 (significant), **p≤ 0.001 (highly significant). A: as compared with other groups, B: as compared to the VPA-saline group, D: in comparison with the control-saline group and C: in comparison with the VPA-*AKBA* 15mg/kg group

Reduced glutathione (GSH)

The level of reduced glutathione was significantly reduced (p≤ 0.001) in the VPA-saline group as compared with other groups, while the level of reduced glutathione was significantly raised (p≤ 0.001) in VPA-risperidone and both low and high VPA-*AKBA* groups as compared with the VPA-saline group. The concentration of reduced glutathione in the high-dose VPA-*AKBA* group was significantly elevated (p= 0.002) and highly significantly elevated (p≤ 0.001) in comparison with VPA-risperidone and low-dose VPA-*AKBA* groups, respectively. The level of GSH was highly significantly elevated (p= 0.001) in the high-dose control-*AKBA* and significantly increased in low-dose control-*AKBA* (p= 0.007) and control-risperidone (p= 0.027) groups as opposed to the control-saline group (Figure 9).

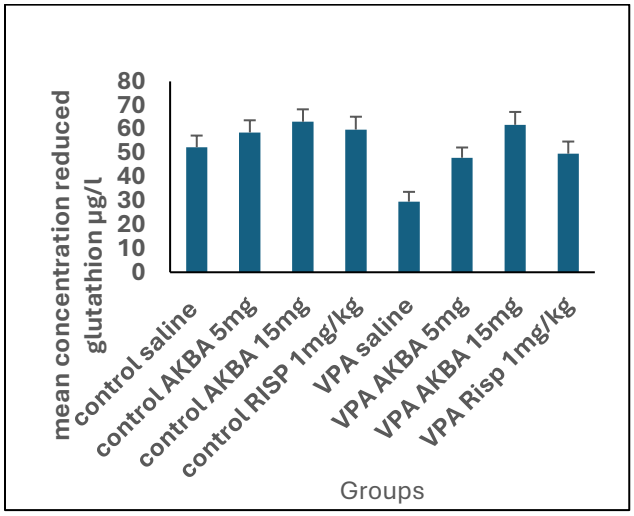


Figure 9: Effect of *AKBA* and risperidone on the concentration of reduced glutathione

The results are expressed as (Means ± SEM). No. of mice = 10 for each group. *p≤ 0.05 (significant), **p≤ 0.001 (highly significant). A: as compared with other groups, B: as compared to the VPA-saline group, D: in comparison with the control-saline group, and C: in comparison with the VPA-risperidone group

Interleukin-6 (IL-6)

The level of IL-6 was significantly reduced (p≤ 0.001) in the high-dose control-*AKBA* group in contrast to the control-saline group, while the level of IL-6 was significantly decreased (p= 0.024) and (p= 0.018) in the low-dose control-*AKBA* and control-risperidone groups, respectively, as compared with the control-saline group.

The concentration of IL-6 was significantly increased (p≤ 0.001) in the VPA-saline group as opposed to other groups, and the concentration of IL-6 was significantly decreased (p≤ 0.001) in VPA-risperidone and both high and low dose VPA-*AKBA* groups as compared with the VPA-saline group (Figure 10**).**

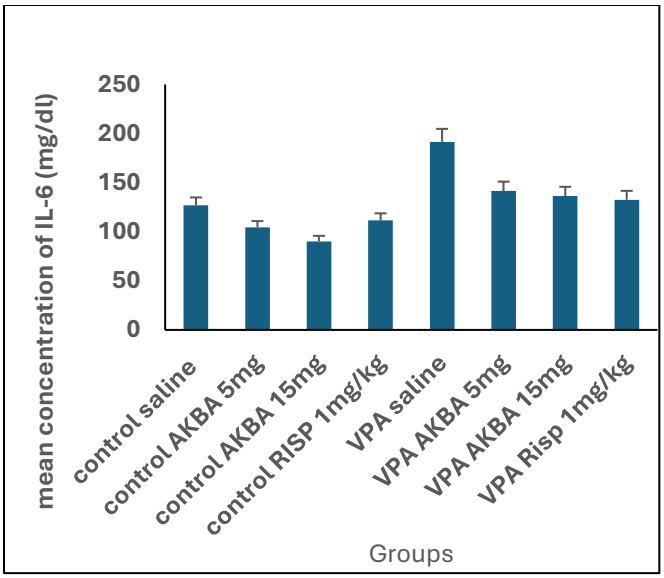


Figure 10: Effect of *AKBA* and risperidone on the concentration of IL-6
The results are expressed as (Means ± SEM). No. of mice = 10 for each group. *p≤ 0.05 (significant), **p≤ 0.001 (highly significant). A: as compared with other groups, B: as compared to the VPA-saline group, and D: in comparison with the control-saline group

Discussion

The present investigation is the first to investigate whether AKBA has an impact on ASD. By injecting sodium valproate into the peritoneal cavity of pregnant mice on gestational day 12, the researchers seek to create an animal model of autism. Mice given sodium valproate during prenatal development showed the following behavioural changes: (i) decreased sociability and social creativity; (i) increased locomotor activity, including higher anxiety scores and decreased explorative action; (ii) increased oxidative stress; and (iv) increased release of inflammatory cytokines. In contrast, AKBA and risperidone treatment increased the offspring's behavioural difficulties while decreasing oxidative stress and neuroinflammation.

While this study did not measure NF-κB, TNF-α, or antioxidant enzyme levels, previous reports suggest that AKBA's anti-inflammatory and antioxidant properties may involve these pathways, warranting further mechanistic studies

AKBA and risperidone's effects on the results of the open field test

The findings of this study revealed an elevated level of anxiety in VPA-saline offspring when they were subjected to an open-field test. When compared with the control group, the offspring that were exposed to VPA had higher mean values for Line crossing, grooming, rearing and a lower mean value of Latency time on the central zone. These findings agree with the findings of the previous research (15).

When compared with the VPA-risperidone group, the open field test of the VPA-AKBA group revealed a significant reduction in the amount of line crossings, rearing, and grooming, as well as a significant increase in latency time in the central zone.

On the other hand, the open field test of the control-AKBA group demonstrated a decrease in the number of line crossings as well as an increase in latency time in the central zone when compared with the control-saline and VPA-risperidone groups. These findings agree with the findings of the previous research, which showed that AKBA reduced anxiety in an open field test in other CNS disorders (16).

Effects of risperidone and AKBA on oxidative stress assessed by MDA and GSH levels

The overproduction of ROS, which can come from both endogenous and external sources such as inflammation, regular metabolism, weakened antioxidant defences, or a combination, causes oxidative stress. In this study, oxidative stress was evaluated by measuring the levels of lipid peroxidation (MDA; a product of lipid peroxidation) and the antioxidant enzyme activity, such as GSH, which is a major cellular radical scavenger (17).

The findings of this research showed that the VPA-saline group in comparison to the control group, had a highly significant rise in the level of lipid

peroxidation (MDA) and a highly significant decline in the level of reduced glutathione (GSH), indicating oxidative stress. These outcomes were in line with the previous research.

After administration of risperidone and *AKBA* therapy to the control and VPA groups for 20 days, the level of MDA significantly declined in the VPA-*AKBA* and VPA-risperidone groups as compared to the VPA-saline group and the level of lipid peroxidation significantly reduced in the VPA-risperidone group when compared with the VPA-AKBA 15mg group. These findings indicate that both risperidone and *AKBA* are powerful antioxidants by decreasing lipid peroxidation with superior efficacy for AKBA at a low dose. Regarding the control groups, the level of MDA significantly declined in the high-dose control-*AKBA* group in contrast to the control-saline group. These results are consistent with prior research (18).

Anti-inflammatory activity of AKBA and risperidone assessed by IL-6 levels

Neuropathology is described by the generation of inflammatory cytokines, such as IL-6, among other inflammatory cytokines. When the values of the VPA-saline group were compared to the values of the control group, the results showed that there was a significant rise in the IL-6 levels in the VPA-saline group (19).

Inflammatory reactions can be caused by IL-6 acting as a trigger in the nuclear factor kappa B (NF-kB) signal transduction pathway, which stimulates the transcription and release of subsequent inflammatory mediators. It is possible for pro-inflammatory cytokines to trigger the production of reactive oxygen species (ROS), which in turn may activate the transcription factor NF-kB and result in an inflammatory response. NF-kB is then moved into the nucleus, where it activates several genes involved in the inflammatory response (20).

Study Limitations

While this study provides encouraging evidence for the therapeutic potential of acetyl-11-keto-beta-boswellic acid (AKBA) in a valproic acid-induced mouse model of autism, several limitations must be acknowledged.

First, although the inclusion of interleukin-6 (IL-6) as a biomarker of inflammation represents a meaningful step toward understanding the underlying mechanisms of AKBA's effects, the study did not investigate additional inflammatory or oxidative stress-related molecular pathways. Key signalling molecules such as nuclear factor-kappa B (NF-κB), tumour necrosis factor-alpha (TNF-α), and antioxidant enzymes like superoxide dismutase (SOD) and catalase (CAT) were not assessed. Including these markers in future work would provide more comprehensive insight into the neuroprotective and anti-inflammatory mechanisms of AKBA.

Second, although sex differences are well-documented in both clinical presentations of autism spectrum disorder and animal models, this study did not perform sex-disaggregated analyses. While both male and female offspring were included, the sample size did not permit subgroup analysis. As such, potential sex-specific responses to VPA exposure and AKBA treatment could not be evaluated. Future studies with larger cohorts and balanced group sizes are needed to explore sex-dependent variations in behavioural and biochemical outcomes.

Lastly, the study did not include histological or immunohistochemical analyses, which could have provided structural or cellular-level evidence of AKBA's effects on the brain. Incorporating such analyses, along with long-term behavioural tracking, would strengthen the translational relevance of the findings.

Acknowledging these limitations is essential in framing the results appropriately and guiding future investigations toward more robust mechanistic and translational conclusions.

Conclusions

In this study, we investigated the potential therapeutic effects of acetyl-11-keto-beta-boswellic acid (AKBA) in a valproic acid-induced mouse model of autism. The results demonstrated that AKBA administration led to improvements in behavioural parameters commonly associated with autism-like features, such as anxiety and repetitive grooming. These behavioural changes were accompanied by a significant reduction in oxidative stress and inflammation, as evidenced by decreased levels of malondialdehyde (MDA) and interleukin-6 (IL-6), and increased glutathione (GSH) levels in brain tissue.

Importantly, the effects of AKBA were dose-dependent and in some cases comparable to the standard antipsychotic risperidone, highlighting its potential as a complementary or alternative therapeutic agent. While these findings are promising, it is important to interpret them with caution. The study did not directly assess molecular markers of neurogenesis, synaptic plasticity, or long-term behavioural outcomes. Moreover, sex-specific differences, which are known to play a role in autism spectrum disorder,

were not analysed separately in this model and should be considered in future research.
Overall, AKBA shows potential as a neuroprotective compound with antioxidant and anti-inflammatory properties in the context of autism-like behaviours. Further studies involving a broader range of biomarkers, histological analysis, and sex-disaggregated data are needed to validate and expand upon these findings, particularly before considering clinical translation.

List of Abbreviations

AKBA: Acetyl-11-keto-beta-boswellic acid
5-HT: 5-hydroxytryptamine
VPA: Valproic acid
Ach: Acetylcholine
ADHD: Attention-deficit hyperactivity disorder
ANOVA: Analysis of variance
ASD: Autism spectrum disorders
BBB: Blood-Brain Barrier
CNS: Central nervous system
COX-2: Cyclooxygenase-2
Glu: Glutamate
GSH: Reduced glutathione
GSSG: Glutathione disulfide
I.p.: Intraperitoneal
IFN-Y: Interferon-gamma
IL-6: Interleukin-6

Declarations

Ethics Approval and Consent to Participate
All experimental procedures involving animals were approved by the Institutional Ethical Committee of the College of Medicine, University of Babylon (Approval No. 1449) and conducted following international guidelines for the care and use of laboratory animals.

Consent for Publication
All authors have reviewed and approved the final version of the manuscript and consent to its publication under the terms of the Creative Commons Attribution Non-Commercial 4.0 International License.

Availability of Data and Materials
The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request.

Competing Interests
The authors declare that they have no competing interests.

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Authors' Contributions
JAW conceived and designed the study. SRH performed the experiments. JAW analysed the data and interpreted the results. SSM wrote the manuscript. All authors read and approved the final manuscript.

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