Research Article

The Journal of Anatomical Sciences
Email: journalofanatomicalsciences@gmail.com

J. Anat Sci 17(3) Sept.

Submitted: July 18th, 2026
Revised: September 7th, 2026
Accepted: September 14th, 2026

DOI: https://dx.doi.org/10.4314/jans.v17i3.10

Antidepressant- and Anxiolytic-like Effects of Nicotinamide in a Chronic Unpredictable Mild Stress Mouse Model

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ABSTRACT

Depression and anxiety are common stress-related neuropsychiatric disorders associated with impaired neuroplasticity, oxidative stress, neuroinflammation, and altered cellular energy metabolism. Nicotinamide, a precursor of nicotinamide adenine dinucleotide (NAD^+), has emerged as a potential neuroprotective agent, although its behavioral effects in chronic stress models remain incompletely characterized. This study investigated the antidepressant- and anxiolytic-like effects of nicotinamide in mice exposed to chronic unpredictable mild stress (CUMS). Thirty adult Swiss albino mice were allocated to six groups: distilled water control, CUMS, fluoxetine (20 mg/kg), and nicotinamide-treated groups (100, 200, and 400 mg/kg). Following CUMS induction, behavioral assessments were performed using the forced swim test (FST), open field test (OFT), and elevated plus maze (EPM). CUMS significantly increased immobility time in the FST, confirming the induction of depressive-like behavior. Nicotinamide at 200 and 400 mg/kg significantly reduced immobility time compared with untreated CUMS mice, indicating antidepressant-like activity. In the OFT, nicotinamide reduced urination and defecation frequencies at all doses, while the 200 mg/kg dose significantly increased rearing behavior, suggesting partial attenuation of anxiety-related emotionality. However, nicotinamide did not significantly alter center crossing frequency or any EPM parameter. These findings demonstrate that nicotinamide exerts significant antidepressant-like effects and modest anxiolytic-like effects in CUMS-exposed mice. The antidepressant-like actions of nicotinamide may be mediated through NAD^+-dependent metabolic, neuroplastic, anti-inflammatory, and oxidative stress-related pathways. Further mechanistic studies are required to elucidate the molecular basis of these behavioral effects.

Keywords: Nicotinamide, chronic unpredictable mild stress, depression, anxiety, NAD^+

INTRODUCTION

Depression and anxiety are highly disabling neuropsychiatric conditions that frequently overlap at the behavioral, neurochemical, inflammatory, and metabolic levels. Although conventional antidepressant therapies largely target monoaminergic neurotransmission, their delayed onset of action, variable efficacy, and incomplete response rates indicate that monoaminergic mechanisms alone do not fully explain the pathophysiology of depression and anxiety[1-3]. Increasing evidence implicates oxidative stress, neuroinflammation, mitochondrial dysfunction, impaired neuroplasticity, and altered cellular energy metabolism in the pathophysiology of depression and anxiety[4,5].

Chronic unpredictable mild stress (CUMS) is widely used to model stress-induced behavioral dysfunction relevant to depression and anxiety[6,7]. Exposure to unpredictable stressors can produce behavioral changes such as increased behavioral despair, altered locomotor and exploratory activity, and anxiety-like responses[7,8]. These outcomes can be evaluated using complementary behavioral paradigms, including the forced swim test, open field test, and elevated plus maze[9]. The forced swim test is commonly used to assess antidepressant-like activity through changes in immobility time, while the open field and elevated plus maze provide indices of exploratory behavior, emotionality, and anxiety-like responses[9,10].

Nicotinamide, an amide form of vitamin B3, is a precursor of nicotinamide adenine dinucleotide (NAD+), a central cofactor in redox metabolism,

mitochondrial bioenergetics, DNA repair, calcium signaling, and NAD+-dependent enzyme activity[11]. NAD+ metabolism is biologically relevant to affective disorders because stress-related neurobehavioral dysfunction is often accompanied by altered energy metabolism, oxidative imbalance, inflammatory activation, and impaired neuronal resilience. Through its contribution to NAD+ biosynthesis, nicotinamide may influence cellular pathways that extend beyond classical monoaminergic mechanisms.

Previous studies support a link between NAD+ metabolism and depression-like behavior. A previous study reported that reduced nicotinamide phosphoribosyltransferase-mediated NAD+ biosynthesis was associated with depression-like behavior, cognitive impairment, reduced social interaction, altered monoamine neurotransmitter levels, and corticosterone activation. In keeping up with the above finding, nicotinamide riboside treatment improved depressive-like and anxiolytic-like behaviors in CUMS-exposed rats and increased brain-derived neurotrophic factor expression and Cyclic AMP Response Element-Binding Protein (CREB) signaling in the prefrontal cortex and hippocampus[12]. These findings suggest that restoration of NAD+ metabolism may have behavioral and neuroplastic benefits in stress-related disorders.

NAD+-dependent sirtuins may also be relevant to the behavioral effects of nicotinamide. Sirtuins regulate inflammatory responses, mitochondrial function, oxidative stress, and neuronal survival, all of which are implicated in depression and anxiety. SIRT1 and SIRT2 have been proposed as potential targets for anti-inflammatory treatment strategies in depression and neuroinflammatory disorders[13,5]. Therefore, nicotinamide may influence affective behavior partly through modulation of NAD+-dependent signaling pathways involved in inflammation and cellular stress adaptation.

The kynurenine pathway provides another mechanistic link between nicotinamide metabolism, inflammation, and mood-related disorders. Most tryptophan metabolism occurs through the kynurenine pathway, which contributes to NAD+ production and generates neuroactive metabolites capable of modulating glutamatergic neurotransmission, oxidative balance, neuroplasticity, and immune activity[14,15]. Dysregulation of this pathway has been implicated in depression, neurodegenerative diseases, and cognitive dysfunction[15,16]. This supports the possibility that nicotinamide-related pathways may affect stress-induced behavioral outcomes through metabolic and inflammatory mechanisms.

Despite increasing interest in NAD+ biology, the antidepressant- and anxiolytic-like effects of nicotinamide in chronic stress models remain insufficiently documented. It is also unclear whether nicotinamide produces consistent effects across different behavioral assays or whether its effects are domain-specific. The present study therefore investigated the effects of nicotinamide on depressive-like behavior in the forced swim test and anxiety-like behavior in the open field and elevated plus maze tests in CUMS-exposed mice.

MATERIALS AND METHODS

Experimental animals

Thirty (30) Adult Swiss albino mice of both sexes, aged 6-8 weeks and weighing 18-28 g, were used for the study. Animals were housed at the Department of Human Physiology Animal House, Ahmadu Bello University, Zaria, under standard laboratory conditions with a normal photoperiod. Food and water were provided *ad libitum* except during specific chronic unpredictable mild stress procedures. The animals were allowed to acclimatize for 14 days before the commencement of the experiment.

All experimental procedures were conducted in accordance with Ahmadu Bello University, Zaria guidelines for the use and care of laboratory animals, was approved by the Ethics Committee on Animal Use and Care (ABUCAUC) with approval number: ABUCAUC/2024/054.

Drugs and experimental groups

Nicotinamide (BHD Laboratories, England) was administered orally at doses of 100, 200, and 400 mg/kg with a stock solution prepared daily with distilled water as vehicle. Fluoxetine (V.S. International Pvt. Ltd., Dabhel, Damen, India, Batch No.:2408050A) was used as the reference antidepressant at 20 mg/kg[12]. Distilled water, 10 mL/kg, served as the vehicle control. The experimental design and animal grouping are depicted in Figure 1.

Chronic unpredictable mild stress procedure

Depressive-like and anxiety-like neurobehavioral dysfunction was induced using a chronic unpredictable mild stress protocol[17]. Mice in the stress-exposed groups were subjected to variable mild stressors presented in an unpredictable sequence for 14 days (Table 1); the order and timing of the stressors were varied to minimize habituation.

The non-stressed control group was handled daily but was not exposed to the stress protocol.

Forced swim test

Depressive-like behavior was assessed using the forced swim test[18]. Mice were individually placed in a transparent cylinder containing water at 32°C for 6 minutes. Immobility time was recorded in seconds in the last four minutes. Immobility was defined as the absence of active escape-directed movements, with only minimal movements necessary to keep the head above water. The forced swim test was conducted at two time points. FST1 was used to assess depressive-like behavior following CUMS exposure, while FST2

was used to evaluate the effect of treatment on immobility behavior.

Open field test

Anxiety-like behavior and spontaneous locomotor activity were assessed using the open field test[19]. Each mouse was placed in the center of an open field arena and allowed to explore for 5 minutes. The following parameters were recorded: line crossing frequency, center crossing frequency, rearing frequency, urination frequency, and defecation frequency. Reduced urination and defecation frequencies were interpreted as reduced emotionality/autonomic anxiety-related responses, while rearing was considered an index of exploratory behavior.

Elevated plus maze

Anxiety-like behavior was further assessed using the elevated plus maze[20]. The apparatus consisted of two open arms and two closed arms arranged in a plus configuration and elevated above the floor. Each mouse was placed at the center of the maze facing an open arm and allowed to explore for 5 minutes. Open arm entries, time spent in open arms, percentage open arm entries, percentage time spent in open arms, and index of open arm avoidance were recorded.

Statistical analysis

Data were expressed as mean ± standard error of the mean. Statistical analysis was performed using SPSS version 27 for Windows, and Graphs were plotted using Microsoft Excel 2019. Group differences were analyzed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc. A value of $p < 0.05$ was considered statistically significant.

RESULTS

Effects of nicotinamide on depressive-like behavior in the forced swim test

A significant treatment effect was observed in the first forced swim test (FST1) on immobility time $F(5,24) = 327,\ p = 0.001$. Post hoc analysis showed that mice in the CUMS group exhibited significantly longer immobility time compared with the distilled water (DW) group (205.6±6.2 vs. 119.0±3.7 s, respectively). No significant differences were observed between the CUMS group and the fluoxetine- or nicotinamide-treated groups during FST1 (Figure 2).

Similarly, FST2 revealed a significant group effect on immobility time $F(5,24) = 12.436, p = 0.001$. Post hoc analysis showed that the CUMS group demonstrated significantly increased immobility compared with the DW group (220.6±0.86 vs. 166.6±20.7 s, respectively). Treatment with nicotinamide at 200 mg/kg and 400 mg/kg significantly reduced immobility time compared with the CUMS group (101.0±13.2 and 139.4±10.1 s, respectively) (Figure 2).

Effects of nicotinamide on anxiety-like behavior in the open field test

A significant group effect was observed for line crossing frequency $F(5,24) = 3.710, p = 0.013$. Post hoc analysis showed that mice exposed to CUMS exhibited significantly higher locomotor activity compared with the fluoxetine-treated and nicotinamide (100 mg/kg)-treated groups.

Significant group differences were also observed for rearing $F(5,24) = 2.969, p = 0.032$, urination $F(5,24) = 4.100, p = 0.008$, and defecation frequencies $F(5,24) = 9.123, p = 0.001$. Nicotinamide at 200 mg/kg significantly increased rearing frequency compared with the CUMS group, whereas all nicotinamide-treated groups showed reduced urination frequency. Nicotinamide treatment at all doses significantly reduced defecation frequency compared with both the DW and CUMS groups. No significant group difference was observed in center crossing frequency $F(5,24) = 2.040, p = 0.109$ (Table 2).

Effects of nicotinamide on anxiety-like behavior in the elevated plus maze

No significant group differences were observed in open arm entry $F(5,24) = 2.183, p = 0.090$, time spent in open arms $F(5,24) = 2.207, p = 0.087$, percentage open arm entry $F(5,24) = 1.434, p = 0.248$, percentage time spent in open arms $F(5,24) = 1.920, p = 0.128$, or index of open arm avoidance $F(5,24) = 1.350, p = 0.278$ (Table 3).

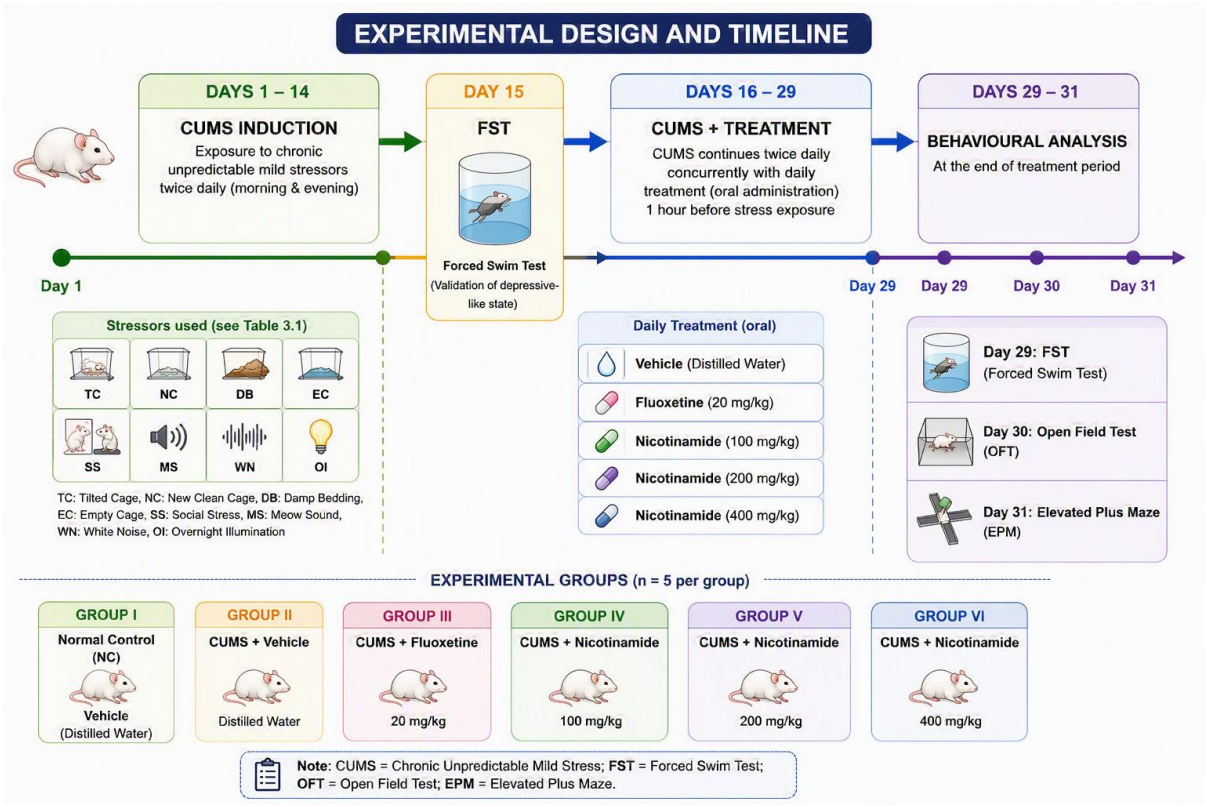

Figure 1: Experimental design, animal grouping, and research flow.

Table 1: Chronic mild stress schedule

Session	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14
Morning	TC	NC	DB	EC	TC	SS	NC	DB	EC	SS	DB	NC	EC	NC
Evening	MS	WN	SS	OI	MS	OI	WN	MS	TC	WN	OI	SS	MS	OI

Note. TC = Tilted Cage; WN = White Noise; EC = Empty Cage; OI = Overnight Illumination; NC = New Clean Cage; SS = Social Stress; MS = Meow Sound; DB = Damp Bedding.

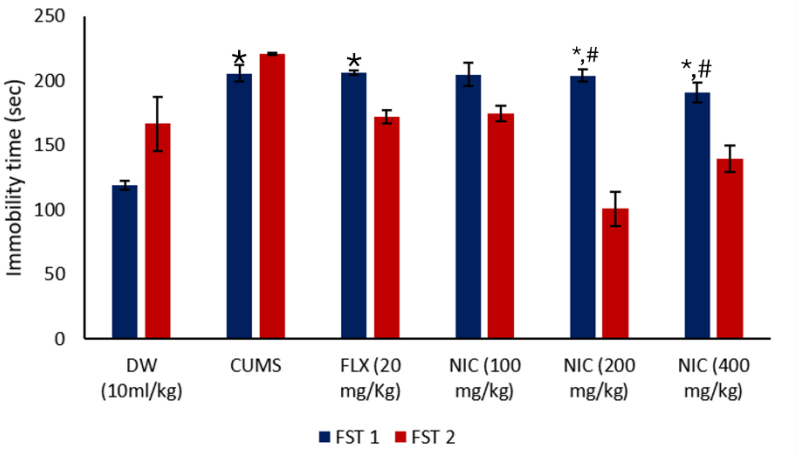

Figure 2: Assessment of immobility time using forced swim test. DW: distilled water 10 ml/Kg, CMS: Chronic unpredictable mild stress, Flx: Fluoxetine, NIC: Nicotinamide. *The mean difference is statistically significant when compared with the DW 10 ml/Kg group. #The mean difference is statistically significant when compared with CUMS.

Table 2: Assessment of anxiety-like behavior using open field test in CUMS-induced depressed mice

	LC	CC	REARING	URN	DEF
DW (10ml/kg)	84.2±15.0	2.6±.9	29.6±4.2	.2±.2	2.8±.6
CUMS	104.0±11.7	.8±.4	15.4±3.7	1.2±.5	3.6±.9
FLX (20 mg/Kg)	46.6±9.9*	.0±.0	17±5.1	.2±.2	1.4±.7
NIC (100 mg/kg)	47.4±11.5*	.8±.4	27.4±5.1	.0±.0*	.0±.0*,#
NIC (200 mg/kg)	72.4±10.6	1.0±.8	34±4.3*	.0±.0*	.0±.0*,#
NIC (400 mg/kg)	79.4±9.6	1.4±.7	24±1.9	.0±.0*	.0±.0*,#

*The mean difference is statistically significant when compared with CUMS. #The mean difference is statistically significant when compared with DW. DW: distilled water 10 mL/Kg, CUMS: chronic unpredictable mild stress, NIC: nicotinamide, LC: line crossing, CC: center crossing, URN: frequency of urination, DEF: frequency of defecation

Table 3: Assessment of anxiety-like behavior using Elevated plus maze in CUMS-induced depressed mice

Groups	**OA**	**TOA**	**POA**	**PTOA**	**IOAA**
DW (10ml/kg)	5.0±1.4	39.6±12.4	33.7±4.5	13.5±4.1	79.4±3.9
CUMS	1.2±0.6	5.8±3.0	14.6±6.5	3.0±1.4	92.4±3.2
FLX (20 mg/Kg)	2.2±0.7	19.2±5.0	21.2±5.4	6.4±1.7	86.2±3.5
NIC (100 mg/kg)	3.0±0.9	24.8±10.1	19.3±6.3	8.3±3.4	86.2±4.7
NIC (200 mg/kg)	3.4±0.5	25.4±4.9	21.8±3.5	8.5±1.6	84.9±2.3
NIC (400 mg/kg)	2.2±0.9	16.2±5.6	16.1±7.1	5.4±1.9	89.3±4.4

DW: distilled water 10 mL/Kg, CUMS: chronic unpredictable mild stress. NIC: Nicotinamide, Flx: fluoxetine

DISCUSSION

The present study investigated the antidepressant- and anxiolytic-like effects of nicotinamide in mice exposed to chronic unpredictable mild stress. The main findings were that CUMS increased immobility time in the forced swim test (FST1), confirming the induction of depressive-like behavior. Treatment with nicotinamide at 200 and 400 mg/kg significantly reduced immobility during FST2. In the open field test, nicotinamide produced partial anxiolytic-like effects, including reduced urination and defecation frequencies and increased rearing at 200 mg/kg. However, no significant differences were observed in elevated plus maze parameters. These findings suggest that nicotinamide produced a better antidepressant-like effect than anxiolytic-like effect in this model.

The reduction in immobility time during FST2 indicates that nicotinamide exerted an antidepressant-like effect after treatment. This effect was most pronounced at 200 mg/kg, followed by 400 mg/kg, suggesting that the behavioral response was not simply dose-linear. Nicotinamide may act through metabolic, mitochondrial, inflammatory, and neuroplastic pathways rather than through acute monoaminergic stimulation alone, particularly via modulation of NAD^+-dependent cellular processes, enhancement of mitochondrial bioenergetics, and regulation of neuroinflammatory signaling and neurotrophic pathways[5,11,12].

The present findings are consistent with evidence that NAD+ biosynthesis is involved in depression-like behavior. Wang and colleagues showed that disruption of NAMPT-mediated NAD+ biosynthesis produced depression-like behavior, cognitive dysfunction, and reduced social interaction, while nicotinamide riboside improved depressive-like and anxiolytic-like behaviors in CUMS-exposed rats. Importantly, nicotinamide riboside also increased BDNF expression and CREB signaling in the prefrontal cortex and hippocampus[12]. These findings

support the interpretation that the antidepressant-like effect of nicotinamide may involve restoration of cellular energy metabolism and neuroplastic signaling.

Nicotinamide may also exert behavioral effects through NAD+-dependent sirtuin pathways. NAD+ is required for the activity of sirtuins, which regulate inflammation, oxidative stress, mitochondrial function, and neuronal survival[11]. SIRT1 and SIRT2 have been implicated in depression-related neuroinflammatory processes, and their modulation has been proposed as a potential anti-inflammatory strategy for affective disorders[5,13]. Since chronic stress is associated with neuroinflammatory and oxidative changes, nicotinamide may reduce depressive-like behavior partly by improving NAD+-dependent stress adaptation.

The open field findings suggest a partial anxiolytic-like effect. Nicotinamide reduced urination and defecation frequencies at all doses and increased rearing at 200 mg/kg. Urination and defecation in the open field are commonly interpreted as indices of autonomic and emotional reactivity associated with anxiety-like states, whereas rearing behavior reflects exploratory activity and environmental engagement[10,21]. Therefore, these findings suggest that nicotinamide may reduce stress-related emotionality and enhance exploration. However, center crossing frequency was not significantly altered, and elevated plus maze parameters were also unchanged. This indicates that the anxiolytic-like effect of nicotinamide was not robust across all behavioral indices.

The discrepancy between the open field and elevated plus maze results is important. The open field test captures locomotor activity, exploration, and emotionality, whereas the elevated plus maze more directly assesses approach-avoidance conflict in exposed open arms. The absence of significant changes in open arm entry, time spent in open arms, percentage open arm entry, percentage time spent in open arms, and index of open arm avoidance suggests that nicotinamide did not produce a strong anxiolytic-like effect. Therefore, the present findings should be interpreted as evidence of partial attenuation of anxiety-related emotionality rather than broad anxiolysis.

The kynurenine pathway may provide an additional insight for interpreting the behavioral effects of nicotinamide. This pathway links tryptophan metabolism, immune activation, neuroactive metabolites, and NAD+ production[14,15]. Kynurenine metabolites can modulate glutamatergic signaling, oxidative stress, and neuroplasticity, and dysregulation of this pathway has been implicated in depression and other neuropsychiatric conditions[15,16]. Because nicotinamide is linked to NAD+ metabolism, its behavioral effects may reflect interactions among cellular energy metabolism, inflammatory signaling, and neuroactive tryptophan metabolites.

Oxidative stress may also be involved. Depression and anxiety have been linked to increased oxidative burden and altered redox signaling, while NADPH oxidases are recognized as important sources of reactive oxygen species relevant to depression and cardiovascular–psychiatric comorbidity[1]. By supporting NAD+-dependent metabolic and stress-response pathways, nicotinamide may help counteract stress-induced oxidative and inflammatory processes. However, this remains speculative in the present study because oxidative stress markers, inflammatory cytokines, NAD+ concentration, and sirtuin activity were not measured.

The dose-response pattern should be interpreted cautiously. Nicotinamide at 200 mg/kg produced the strongest antidepressant-like effect in FST2 and increased rearing in the open field test, whereas 400 mg/kg also reduced immobility but did not show superior behavioral effects across all endpoints. This suggests that nicotinamide may have an optimal effective range rather than a simple dose-dependent profile. Reviews of nicotinamide and NAD-related interventions emphasize that dose, disease context, metabolic state, and safety considerations are important when interpreting potential therapeutic effects of nicotinamide[22,23].

This study has some limitations. First, the behavioral findings were not supported by direct biochemical measurements of NAD+, NAMPT, BDNF, CREB, corticosterone, oxidative stress markers, inflammatory cytokines, or kynurenine metabolites. Second, the anxiolytic-like effect was inconsistent across tests, being more evident in open field emotionality indices than in elevated plus maze parameters. Third, whole-brain or region-specific mechanisms could not be inferred from behavioral data alone. Fourth, the study did not establish whether the behavioral effects were mediated by changes in monoaminergic transmission, neuroplasticity, mitochondrial function, or inflammatory pathways. Future studies should include hippocampal and prefrontal cortex assays for NAD+ metabolism, BDNF/CREB signaling, oxidative stress, inflammatory markers, and kynurenine pathway metabolites.

CONCLUSION

Our findings support nicotinamide as a potential modulator of stress-induced depressive-like behavior, possibly through NAD+-dependent metabolic, neuroplastic, anti-inflammatory, and oxidative stress-related mechanisms. Further mechanistic studies are required to confirm these pathways.

Conflict of interest: The authors have no conflict of interests to declare

Authors' contributions: UMA: Conceptualization, methodology, formal analysis, interpretation of data,

writing – original draft preparation, and manuscript revision; YY: Conceptualization, methodology, formal analysis, interpretation of data and manuscript revision; OBG: Investigation, data acquisition, experimental procedures, data collection, and interpretation of results; All authors have read and approved the final manuscript.

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