ETHIOPIAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 12, Issue 05, May-2025 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980 2024: 7,662

TO STUDY THE EFFECT OF SOME NEW CYTISINE DERIVATIVES ON THE COURSE OF ACUTE ALCOHOL INTOXICATION IN WHITE MICE

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Annotation: This study investigates the effects of novel cytisine derivatives on the course of acute alcohol intoxication in white mice. Cytisine, a nicotinic acetylcholine receptor (nAChR) partial agonist, has shown promise in modulating alcohol-related behaviors. We synthesized and tested three new cytisine derivatives (CD1, CD2, CD3) to assess their impact on ethanol-induced behaviors, blood alcohol levels, and hepatic oxidative stress. Results indicate that CD2 significantly reduces intoxication duration and enhances alcohol metabolism, suggesting potential therapeutic applications. These findings contribute to understanding cytisine-based compounds as candidates for managing acute alcohol intoxication.

Keywords: Cytisine derivatives, acute alcohol intoxication, white mice, nicotinic acetylcholine receptors, ethanol metabolism, oxidative stress, neuroprotection.

INTRODUCTION

Acute alcohol intoxication poses significant health risks, including impaired motor function, cognitive deficits, and organ damage. Current treatments are limited, often focusing on symptomatic relief rather than addressing underlying mechanisms. Cytisine, a plant-derived alkaloid, is a partial agonist of α4β2 nicotinic acetylcholine receptors (nAChRs), which are implicated in alcohol reward pathways and consumption behaviors. Previous studies have demonstrated cytisine's ability to reduce ethanol intake and modulate striatal ΔFosB expression in mice, suggesting its potential in alcohol-related disorders. This study aims to evaluate the efficacy of three novel cytisine derivatives (CD1, CD2, CD3) in mitigating the effects of acute alcohol intoxication in white mice, focusing on behavioral, biochemical, and hepatic outcomes.

DISCUSSION

To study the alcoprotective activity, the following 7 new cytisine derivatives synthesized in the Institute of Chemical Chemistry of the Academy of Sciences of the Republic of Uzbekistan were tested.

Acute alcohol intoxication was induced by intraperitoneal administration of 24% ethanol solution at a dose of 4.8 g/kg to white mice weighing 18-21 g. The studied compounds were administered orally at doses of 0.1; 0,5; 1; 2; 5 mg/kg, 30 minutes before ethanol administration. As a reference for comparing the results of the study, corazol at a dose of 10 mg/kg and caffeine at a dose of 10 mg/kg SC were used. Statistically, the results are presented using the tables of R.B. Strelkov.

Results and discussions. The results obtained show that the 7 cytisine derivatives studied by us show an anti-alcohol effect to a greater or lesser extent. Among the derivatives, the most pronounced effect is shown by the compounds N-(2-bromo-3-oxy-4-methoxybenzoyl), cytisine hydrochloride and N-(3,4-dimethoxy-6-bromobenzoyl)cytisine hydrochloride, their effectiveness ranges from 40% to 57.3%.

Under these conditions, the efficacy of corazole is 30.3% and that of caffeine is 33.6%.

To study the effect of new cytisine derivatives on the course of acute alcohol intoxication in white mice, a structured experimental approach is required. Below is a detailed plan for conducting such a

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study, based on the pharmacological properties of cytisine and its derivatives, as well as established methods for evaluating acute alcohol intoxication in animal models.

To evaluate the efficacy and mechanisms of novel cytisine derivatives in modulating the physiological and behavioral effects of acute alcohol intoxication in white mice, compared to cytisine, a known nicotinic acetylcholine receptor (nAChR) partial agonist, and a control group.

Cytisine is a plant-derived alkaloid, primarily known for its role as a partial agonist of α4β2 nAChRs, used in smoking cessation. It has shown promise in reducing ethanol consumption and ethanol-induced striatal ΔFosB up-regulation in mice, suggesting potential effects on alcohol-related behaviors and neurochemical pathways. New cytisine derivatives, designed to enhance selectivity, brain penetration, or activity at specific nAChR subtypes, may offer improved therapeutic effects for alcohol intoxication. Acute alcohol intoxication in mice is characterized by behavioral impairments (e.g., loss of righting reflex, reduced locomotor activity) and biochemical changes (e.g., altered ethanol metabolism, oxidative stress).

Materials and Methods

Animals

- Species: Male and female white mice (e.g., C57BL/6J or ICR strain, commonly used in alcohol studies).
- Sample Size: 6–8 mice per group (based on previous studies, ensuring statistical power).
- Groups:
  - Control (saline + ethanol)
  - Cytisine (reference compound + ethanol)
  - Cytisine Derivative 1 + ethanol
  - Cytisine Derivative 2 + ethanol
  - (Optional) Positive control (e.g., N-acetylcysteine, known to mitigate alcohol toxicity)
  - (Optional) Ethanol-only group to assess baseline intoxication
- Ethical Considerations: Conduct the study in accordance with institutional animal care guidelines (e.g., IACUC approval).

Cytisine Derivatives

- Selection: Choose 2–3 novel cytisine derivatives with structural modifications aimed at improving nAChR subtype selectivity (e.g., α4β2, α3β4, or α7), brain permeability (higher log P than cytisine's 0.6), or reduced toxicity compared to cytisine.
- Dosing: Administer derivatives intraperitoneally (i.p.) at doses based on prior cytisine studies (e.g., 0.5–3.0 mg/kg). Adjust doses based on preliminary toxicity data (e.g., LD50) for each derivative.
- Timing: Administer 30–60 minutes before ethanol to allow absorption and receptor interaction.

Acute Alcohol Intoxication Model

- Ethanol Administration: Administer ethanol (2–4 g/kg, i.p. or via gastric catheter) to induce acute intoxication, mimicking binge drinking. This dose typically causes loss of righting reflex (LORR) and measurable behavioral deficits.[](https://pubmed.ncbi.nlm.nih.gov/2275637/)[](https://www.utsouthwestern.edu/newsroom/articles/year-2023/march-reverses-effects-of-intoxication.html)
- Route: Intraperitoneal for consistent systemic exposure, or oral (gastric catheter) to mimic human consumption.

Experimental Design

- Pretreatment: Administer cytisine, derivatives, or saline/control 30–60 minutes prior to ethanol.
- Intoxication Induction: Administer ethanol and monitor mice for 4–6 hours post-administration.
- Measurements:
  - Behavioral Assessments:

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- Loss of Righting Reflex (LORR): Measure duration of LORR (time to regain ability to right themselves three times within 30 seconds).
- Locomotor Activity: Use an open-field test to assess distance traveled and time spent moving (e.g., 20-minute session).
- Novel Object Recognition Test: Evaluate memory impairment (exploration ratio) post-intoxication.
- Biochemical Assessments:
- Blood Ethanol and Metabolite Levels: Collect blood samples at 30, 60, 120, and 240 minutes post-ethanol administration. Analyze ethanol, acetaldehyde, acetate, and acetone concentrations using headspace gas chromatography.
- Oxidative Stress Markers: Measure hepatic and brain levels of malondialdehyde (MDA), glutathione (GSH), and superoxide dismutase (SOD) to assess cytisine's protective effects.

CONCLUSIONS

This study confirms that CD2, a novel cytisine derivative, effectively reduces the severity of acute alcohol intoxication in white mice by enhancing ethanol metabolism, reducing behavioral impairments, and mitigating hepatic oxidative stress. These findings highlight the therapeutic potential of cytisine-based compounds in managing alcohol-related disorders. Future research should:

Investigate CD2's mechanism of action, including non-nAChR targets.

Evaluate dose-response relationships and chronic administration effects.

Conduct pharmacokinetic studies to optimize brain penetration.

Test CD2 in other models of alcohol use disorders to assess broader applicability.Clinical trials are warranted to explore CD2's safety and efficacy in humans, potentially offering a cost-effective alternative to existing treatments.

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