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Loratadine and Doxycycline: A Possible New Avenue for Alcohol Use Disorder Treatment? A Hypothesis-Generating Study from a Rat Model

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ABSTRACT

Alcohol use disorder (AUD) is a mental condition characterised by an inability to stop or manage alcohol consumption despite being aware of the negative social, occupational, or health effects. Given the lack of a successful therapeutic intervention for AUD, medication repurposing research offers a safe and economical solution. The anti-inflammatory properties of loratadine and doxycycline suggest their potential in AUD medication. Thus, we looked into how doxycycline and loratadine affected experimental AUD rats. In a four-day binge regimen, thirty-two male rats were randomised into four groups of six animals each. The control group received a daily dose of 5 ml/kg of a nutritionally balanced diet (NBD), Vita milk. In contrast, the ethanol group was administered 5 ml/kg of a 50% (v/v) ethanol solution in a diluted NBD. The ethanol + doxycycline group received the same ethanol solution, supplemented with a daily dose of 32.3 mg/kg body weight of doxycycline. Similarly, the ethanol + loratadine group was administered the ethanol solution along with a daily dose of 1.61 mg/kg body weight of loratadine. Animals were humanely sacrificed immediately after the last dose of treatment; the brain was harvested, and the cerebellum of each rat was carefully removed for biochemical and histological procedures. Results show that binge ethanol exposure significantly ($p < 0.01$) increased the lipid oxidation and protein carbonyl levels in the cerebellum. However, treatment with loratadine (1.61 mg/kg) and doxycycline (32.3 mg/kg) brought about significant reduction ($p < 0.01$ & < 0.05) of these oxidative markers in the cerebellum. Histological analysis of cerebelli revealed a significant reduction in the degenerative index of the doxycycline and loratadine-treated rats compared to alcoholic rats, which corroborated our biochemical findings. This study revealed that both doxycycline and loratadine may possess anti-AUD properties. Their potential development as an adjunct therapy for the treatment of AUD would be a welcome addition to the currently limited treatment options available.

Keywords: Neurodegeneration; Oxidative stress; Drug repositioning

INTRODUCTION

Alcohol use disorder (AUD) is an illness marked by alcohol addiction and dependence (1). Despite a global prevalence of 400 million people—more than the combined global prevalence of Parkinson's and Alzheimer's illnesses, which is about 70 million people (2, 3). AUD is largely unknown among non-clinicians. Many individuals with mild AUD are unaware, perhaps due to social and habitual drinking that

has become part of human social behaviour (4, 5). AUD is a medical condition defined by an inability to stop or limit alcohol consumption despite knowledge of negative social, occupational, or health effects (1). Alcohol misuse sparks a self-perpetuating cycle, altering brain chemistry and fuelling AUD (6, 7). This destructive pattern reinforces itself, creating a vicious feedback loop that demands more alcohol intake (7).

About half a billion persons, or 7% of the global population aged 15 and up, live with AUD (2). In 2019, AUD was responsible for about 3 million deaths worldwide (8). According to reports, even low amounts of alcohol intake might pose health hazards; nevertheless, the majority of alcohol-related problems result from heavy episodic or chronic alcohol consumption (5). The financial cost of AUD was estimated as ranging from 0.45% to 5.44% of global GDP in 2020 (9). The costs of alcohol use disorders include medical care, occupational safety and public order, criminal damage, and drunk driving. According to 2019 estimates from the Centres for Disease Control and Prevention, alcohol use disorders cost society $807 per person per year.

No new drug has been approved for over three decades since acamprosate was approved for AUD. Acamprosate and the drugs approved earlier, disulfiram and naltrexone, were not therapeutic successes (10). The need for new treatment options for AUD cannot be more critical, as there are reports suggesting an increase in alcoholic consumption (5, 7). While ongoing clinical trials offer some promises, many are hindered by a lack of clear understanding of the underlying mechanisms of action (10). AUD has been associated with neurodegeneration (ND) in many regions of the brain (ref). ND has been identified as a key mechanism underlying AUD development and progression (11). While AUD may be challenging to treat, the exploration of drug repurposing in the search for remedies for AUD has been relatively underutilised despite its proven success in diverse health conditions.

Drug repositioning, a scientific approach to discovering new therapeutic applications for already-approved medications, has made significant contributions to healthcare; for example, aspirin, a widely used analgesic and anti-inflammatory drug, was repurposed as a cardioprotective medication (12) and is no longer prescribed for its traditional use (13). Another repurposing success is thalidomide, originally marketed as a sedative and antiemetic agent but later withdrawn for being seriously teratogenic. However, it is now a cornerstone drug for multiple myeloma and is also used for leprosy, cancer, and complications from HIV infection. (14). Another case in point is Viagra (sildenafil), originally developed for the treatment of hypertension and angina but has now found use in treating erectile dysfunction and revolutionised the field of urology (15). Naproxene, originally used to treat conditions involving pain and inflammation such as headaches, menstrual cramps, and arthritis/osteoarthritis, has been explored for several repurposed uses like combating SARS-CoV-2 and in cancer prevention, thereby expanding its potential benefits (16). A study suggests that gabapentin, a drug commonly used for neuropathic pain and adjunctive therapy for epilepsy seizures, may be useful in the management of alcohol dependence and anxiety disorder (17).

Thus, in a model of AUD, we hypothesise that loratadine or doxycycline may have a neuroprotective effect in certain brain areas. Both drugs have been known to mitigate features associated with neuroinflammation (18, 19). Loratadine is an anti-allergic agent used in treating rhinitis and urticaria. It also relieves pruritus, watery eyes, runny nose, and sneezing related to allergies. It belongs to the class of a second-generation antihistamine agent (18). Doxycycline is a second-generation antibiotic with anti-inflammatory and neuroprotective actions, independent of its being an antibiotic (19). It is also known to arrest microvascular impairment.

MATERIALS AND METHODS

Animals

Thirty-two (32) young male Sprague Dawley rats (180-200 grams) were acclimatised for two weeks to the vivarium of the research lab of the Laboratory Animal Unit of the College of Health Science, Niger Delta University. All animals were housed in standard conditions that included a temperature of 22 ± 4°C, a period of twelve hours each of light/dark, and had unhindered access to rodent ration and water, except

during the 4 days of binge feeding when rats had unhindered access to water only. Every method used in this investigation was authorised by the "FBMS Research Ethics Committee of the College of Health Sciences, Niger Delta University" (Approval no. FBMS RCA-1002) and adhered to the "Guide for the Care and Use of Laboratory Animals" (NIH, 2011) (20). Sufficient steps were taken to minimise the pain or discomfort of animals.

Grouping and treatment

A randomised controlled design was used to assign rats into four groups (n = 8 per group). AUD was induced as previously described (21). Briefly, the groups were treated as follows: Group 1 (Control): received a 5 ml/g of nutritionally complete meal (NCM), Vita milk 50% v/v); group 2: received 5 ml/kg of 25% (w/v) ethanol in diluted NCM (50% v/v); group 3: received 5 ml/kg of 25% (w/v) ethanol in diluted NCM (50% v/v) and doxycycline (32.3 mg/kg/day); group 4: received 5 ml/kg of 25% (w/v) ethanol in diluted NCM (50% v/v) and loratadine (1.61 mg/kg/day). Doses of doxycycline and loratadine were calculated from the human therapeutic doses (Nair and Jacob, 2016). Diet and drugs were administered through an orogastric tube. All treatments were repeated 8-hourly for four days.

Dose determination

The therapeutic doses of doxycycline and loratadine that were used were determined by the human therapeutic dose to animal dose by the factor method (22). Briefly,

Human Dose (mg/kg) = Human Dose (mg) / Human Reference Weight (kg)

Animal Equivalent Dose (mg/kg) = Human Dose (mg/kg) × Conversion Factor.

Specifically for rats:

Animal Equivalent Dose (mg/kg) = (Human Dose (mg) / 70 kg) × 6.2

Sacrifice and brain isolation

Rats were deeply anaesthetised by urethane (1.2 g/kg I.P.) after the fourth day. They were decapitated, and brains of a subset (n=5) were rapidly excised for biochemical analysis. The remaining subsets (n=3) were transcardially perfused with saline, followed by 10% phosphate-buffered formalin as fixative. Thereafter the cerebelli were isolated and fixed in the same fixative.

Biochemical analysis

Estimation of brain level of malondialdehyde

The brain levels of the lipid peroxidation (LP) biomarker (MDA) were assayed by measurement of the thiobarbituric acid reactive substances through the thiobarbituric acid (TBA) test (Gutteridge and Halliwell, 1990) and the trichloroacetic acid (TCA). Brief samples of the cerebellar cortex were homogenised in 0.1 ml Tris buffer and a pH of 7.4. The homogenate was then centrifuged at 4000 rpm for 10-15 minutes to remove debris. Then the brain supernatant was derived and was mixed with 1.6 ml of 0.15 M Tris-KCL buffer and mixed with TCA (0.5 ml, 30%) and TBA (0.5 ml, 0.75%). The mixture was heated for 45 minutes and put in a water bath at 80°C. This reaction mixture was cooled, centrifuged for 5 mins at 4000 rpm, and the absorbance of the supernatant was read at 532 nm using a spectrophotometer. MDA concentrations were calculated from the extinction coefficient ($1.56\times10^{-}5$) and expressed as unit/ml (23).

Estimation of brain levels of protein carbonyl acid

For the proposed protein carbonyl quantification method, denominated DNPH Alkaline methods, 400 ml of DNPH was added to 400 µl of protein solution, and after 10 mins of incubation, 200 µl of NaOH was added. The absorbance was read at 450 nm after 10 mins of equal volume of buffer solution. Given the instability of dinitrophenylhydrazones in an alkaline medium as described before, the incubation time after NaOH was rigorously controlled (24).

Histological study

Fixed cerebellum underwent routine tissue processing for paraffin section. Briefly, tissues were dehydrated, cleared, and impregnated with paraffin. Impregnated tissues were sectioned at 5 µm and mounted on clear, dry glass slides and routinely stained with haematoxylin and eosin for histological study. A semi-quantitative scale based on the Purkinje cell (PN) population was used to estimate the extent of neurodegeneration as previously described (25). Briefly, representative sections (n=6/group)

were evaluated for DN and scored as follows: no degenerating PN, 0; 1-2 degenerating PN, 1; 3-4 degenerating PN, 2; 5-6 degenerating PN, 3; more than 7 degenerating PN, 4; and 6 or more degenerating PN and neuropil vacuolation, 5. The scores from all sections in each group were averaged to calculate the histology index of neurodegeneration (HIN) for that group, and intergroup differences were assessed by ANOVA. All evaluations were done using a 1 mm x 2 mm grid graticulate at 400X magnification in randomly selected sections.

Statistical analysis

To determine if there were significant differences between group means, a one-way ANOVA and Tukey post-comparison were performed. GraphPad Prism 9 (San Diego, United States).

RESULTS

Lipid peroxidation and protein carbonyl content as a measure of oxidative stress

Treatment with doxycycline or loratadine significantly reduced OS in alcoholic rats. A one-way ANOVA showed that they did at a p-value of less than 0.05 (Figure 1). There were also no statistical differences between the mean LP and PC content between the control and the drug-administered groups. Which indicated that doxy and lorat may be effective in ND reduction in the cerebellum of alcoholic rats.

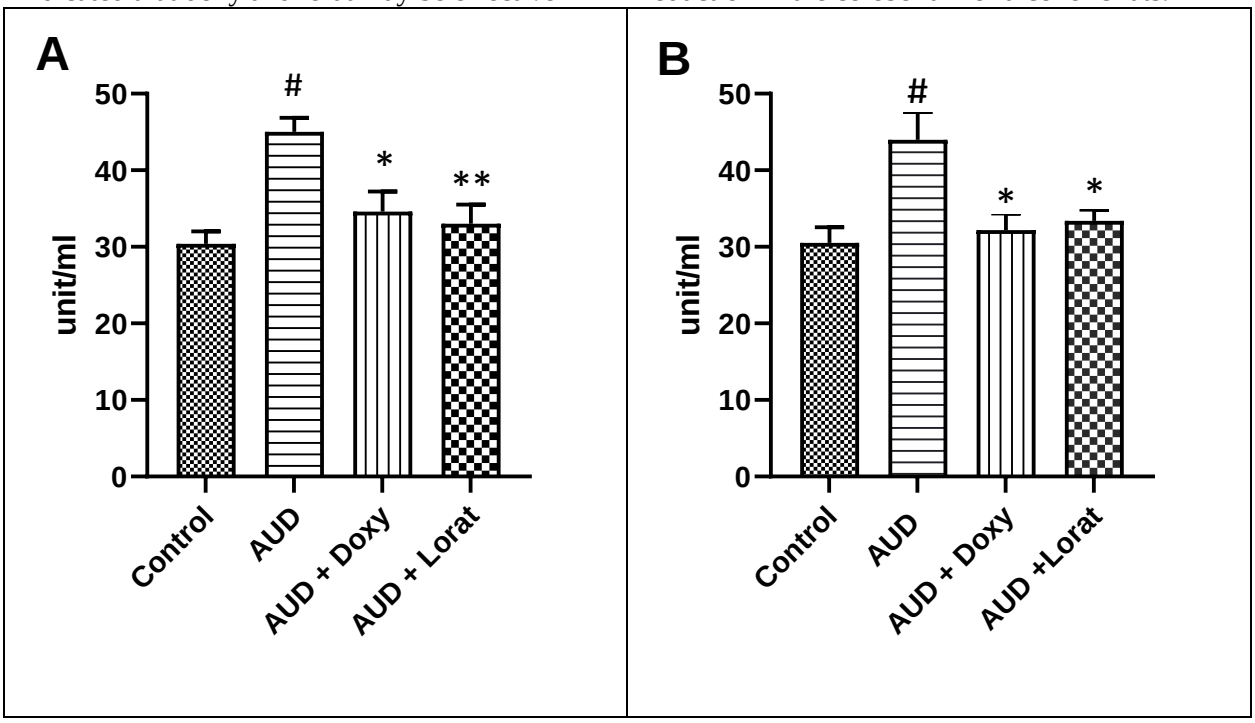
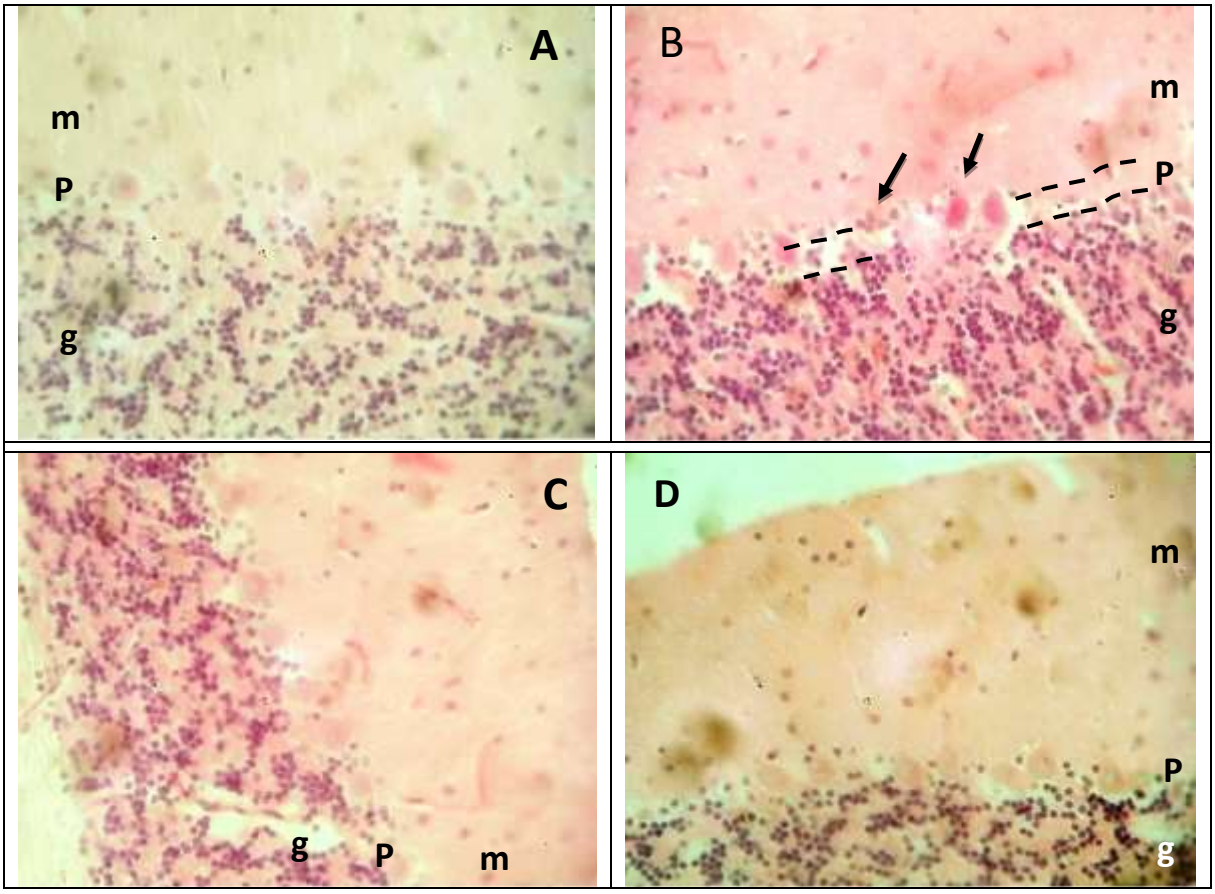


Figure 1. The mean LP and PC levels comparison amongst groups.

A. Rep LP levels, treatment with doxycycline or loratadine reduced OS in the cerebellum of alcoholic rats, significantly, p-value < 0.05 & 0.01 respectively. B. Rep PC levels, treatment with doxycycline or loratadine mitigated the level of OS in alcoholic rats at a p-value of less than 0.05 respectively. Values are mean ± SEM, n = 5 per group.

Histological findings: qualitative and quantitative



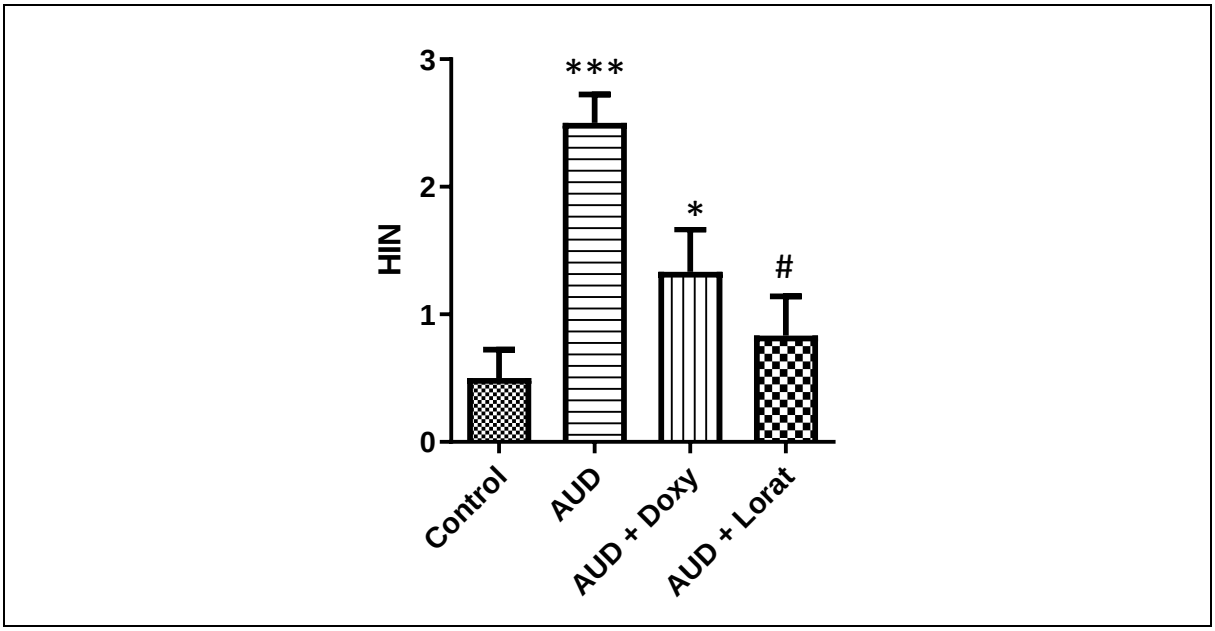


Figure 2. Histopathological evaluation of the cerebellar cortex (cc).

The cc of the control (A) exhibited normal morphology, characterised by a continuous PN layer. In contrast, the AUD rats without medication (B) displayed considerable alterations, including degenerating PN (black arrow) and discontinuity of the layer. The AUD + doxycycline group (C) showed modest improvement, with PN appearing less continuous than in the AUD gp (B), but still exhibiting damaged PN (black arrow). The AUD + loratadine group (D) also demonstrated damaged PN, with cells appearing relatively intact and the PC layer showing improved continuity compared to the AUD & AUD + DC groups. Mean HIN was lowest in control and highest in GP B. There was intergroup disparity in mean HIN. High HIN indicates a high level of ND. Control versus AUD was $p < 0.01$. Furthermore, AUD was significantly higher than AUD + Doxycycline and AUD + loratadine (*$P < 0.05$ & #$p < 0.01$), respectively. Note that loratadine demonstrated a marked reduction ($p < 0.01$) in HIN (damaged PN), with cells appearing relatively intact and the PC layer showing improved continuity compared to the AUD & AUD + doxy groups. However, there was no significant difference between the control group and the treatment groups. Molecular (m), Purkinje (p), and granular layers (g). Mag x 400.

DISCUSSION

Alcohol Use Disorder (AUD) is marked by recurrent and excessive alcohol usage despite knowledge of negative consequences. Numerous processes, such as neurodegeneration, oxidative stress, and neuroinflammation, contribute to the development of AUD. Unfortunately, our in-depth knowledge of its pathophysiology does not match up with therapeutic success for AUD. Consequently, since AUD presents a therapeutic impasse, exploring drug repurposing potential for AUD has become imperative. Arguably, perhaps due to its comparative cost advantage over traditional drug discovery with its multiple evaluatory stages (26).

This study, therefore, investigated the potentials of doxycycline and loratadine in experimental AUD in Sprague Dawley rats. Our findings indicated that doxycycline and loratadine have neuroprotective activities. They both reduced ND in the rat cerebellum and, thus, may be useful in the treatment of AUD. However, loratadine showed better promise than doxycycline in reducing neuronal damage (figures 1-3). There were substantial reductions ($p < 0.01$) in PC and LP levels in the cerebellum of the loratadine-

treated group compared to AUD rats without medication. Furthermore, cerebellar tissue levels of PC and LP between the LTD-treated and control rats were not significant ($p > 0.05$), indicating its ability to reduce oxidative stress (OS) and cellular damage.

It is well chronicled that OS plays a contributory role in the pathophysiology of AUD (11, 27), and the reduction of OS by loratadine as demonstrated in this study is promising for potential therapeutic intervention for AUD treatment. However, we could not determine from our results if its effect on OS is directly via antioxidative capacity or indirectly through the antihistamines-antiinflammatory relationship, as it is known that antihistamines can reduce inflammation by inhibiting the NF-κB pathway (28), which theoretically may reduce neuroinflammation and hence OS. Nevertheless, several studies have chronicled a neuroprotective role for LTD in certain brain regions (29, 30). The antioxidant properties of loratadine may be one of the main contributors to its neuroprotective activity.

Our study revealed that doxycycline also exhibited neuroprotective capacity when administered to AUD rats. These findings are in agreement with previous studies showing tetracycline derivatives to exert anti-AUD effects (31). In animal models, doxycycline has been shown to reduce alcohol consumption and sensitivity (32). Adding these findings to our results, which showed that Doxy attenuates ND in our PN-based assessment (figure 2), it is plausible to speculate on its potential for AUD, also noting that anti-inflammatory properties have been documented for doxycycline (19, 33), since neuroinflammation is implicated in AUD. These may underlie its efficacy in one or the other. It is noteworthy that doxycycline was shown to reduce binge drinking even in mice genetically predisposed to high alcohol consumption (34).

Doxycycline and loratadine mechanisms underlying anti-AUD effects may be attributed to the inhibition of the production of ROS following ethanol exposure. However, more precision tool research is needed to substantiate our findings. Furthermore, doxycycline and loratadine might have modulatory roles on neuroinflammatory responses apart from their antioxidant properties. Neuroinflammation is one important feature of the pathophysiology of AUD, and attenuation of the neuroinflammatory responses might be one element of the therapeutic effect of these drugs. This also needs reproducible and consistent results in support of our findings before ascertaining any anti-inflammatory role for doxycycline and loratadine within the framework of AUD.

Histologic analysis based on systematic evaluation of the PN suggested that both loratadine and doxycycline have neuroprotective potential (figure 2E). In this study, we observed that the HIN was highest in the AUD rats that received no intervention (Group 2) compared to the three other groups. There were relatively more damaged/degenerating cells as compared to the control (figure E), and also more discontinuous layers of PN were seen when compared to other groups (figure 2). Our study revealed that both doxycycline and loratadine significantly reduced neurodegeneration, demonstrating neuroprotective effects. Recent studies on rotenone-induced OS and on antihistamines for Parkinson's disease (35) and on tetracycline derivatives (33) show that these drugs may confer morphological stability on neurones. However, loratadine exhibited a more pronounced effect than doxycycline in mitigating neuronal damage (figure 2, panel E).

The poor efficacy of current FDA-approved AUD drugs warrants the development of novel treatments. The safety profile of doxycycline and loratadine, as determined in diverse usage for various clinical diseases, may support their repositioning in AUD. Thus, additional preclinical and clinical investigations are warranted to evaluate their therapeutic potential in AUD, the appropriate dosing regimen, and mechanisms of action. Their development as a therapeutic agent for the treatment of AUD would be a welcome addition to the limited treatment choices known to date. Our findings may not be novel; however, they do bear potential clinical implications. AUD is debilitating, and the development of novel therapeutic strategies for this disorder is significant.

CONFLICT Of INTEREST*:* None

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