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The Protective Role of Aqueous and Methanol Extracts of *Aloe Vera* on Ethanol-Induced Kidney and Brain Injury in Mice

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ABSTRACT

Impaired kidney function is associated with structural damage that usually cause negative effect to both human and animal health. It is associated with many complications such as anaemia, cardiovascular disease, and cognitive impairment. We evaluated the effect of aqueous and methanol extracts of *Aloe vera* (AV) on ethanol-induced kidney and brain injury in mice. Thirty mice were assigned to six groups (n=5) and received distilled water (control), 20% ethanol (negative control), (50 and 100) mg/kg methanol extract of *Aloe vera* plus ethanol, and (25 and 50) mg/kg aqueous extract of *Aloe vera* plus ethanol respectively for eighteen days. The mice were euthanized thereafter, and kidney function test was evaluated from the serum while oxidative stress markers were evaluated from the brain homogenate. One half of each brain was processed for light microscopy. The result showed that pretreatment with methanol and aqueous extracts of *Aloe vera* significantly reduced ($p<05$) the serum urea level relative to the ethanol-treated mice. The methanol extract (50mg/kg) and aqueous extract (25mg/kg) of *Aloe vera* significantly elevated ($p<05$) catalase activity relative to the ethanol-treated mice. Both the aqueous and methanol extracts of *Aloe vera* significantly reduced ($p<05$) malondialdehyde activity compared to the ethanol-treated mice. The cerebellum and cerebrum of the control mice and the mice pretreated with both the methanol and aqueous extracts of *Aloe vera* at 50mg/kg showed normal neurons. Conclusively, aqueous and methanol extracts of *Aloe vera* regulated serum urea levels, significantly increased brain catalase and reduced glutathione activities in ethanol-treated mice. It also prevented lipid peroxidation and neurodegeneration.

Keywords: *Aloe vera*; Brain; Catalase; Histology; Oxidative Stress

INTRODUCTION

The kidneys are excretory organs that primarily functions to filter the blood by removing toxins and nitrogenous waste. Impaired kidney function is associated with structural damage that usually cause negative effect in both human and animal health (Valkova *et al*., 2023). Kidney disease is the common cause of mortality and morbidity in domestic and wild animals, as well as humans (Chang *et al*., 2023). It is associated with many complications such as anaemia, cardiovascular disease, and cognitive impairment (Miglinas *et al*., 2020; Kalantar-Zadeh *et al*., 2021). Chronic kidney disease (CKD) is reported as one of the leading causes of death and disability world-wide with a global prevalence of about 700 million people with an estimated 800 thousand and 1.4 million deaths in 2012 and 2019 respectively as well as about 3 million disability adjusted life years loss (Drew *et al*., 2019; Stern-Nezer, 2021). CKD is common in pet animals like cats and dogs. In cats, the prevalence is estimated to range from 1.6-20% depending on age, vaccination status, hypertension and breed. It is the most common cause of death in cats over 15 years old (Chen *et al*., 2020). In dogs, the prevalence of CKD varies from 0.05-3.74% with the risk factors ranging from old age, breed, periodontal disease and small body size (O'Neill *et al*., 2013).

Aloe vera (Aloe barbadensis) is a medicinal plant with a lanceolate and succulent spined leaf containing mucilaginous central pulp. The succulent leaves allow them to store water preventing desiccation while the spines protect against predators (Dangi *et al*., 2015; dos Santos *et al*., 2021). *Aloe vera* have been used as medicinal plant for centuries by many cultures including the Chinese, Egyptians, Greeks, Indians, Mexicans, and Romans (Parthipan *et al*., 2011). Previous studies on

rodents reported the anti-inflammatory, laxative, immunostimulatory, antibacterial, nephroprotective and anti-tumour properties of *Aloe vera* (Christaki and Florou-Paneri 2010; El-Shafie *et al*., 2015; Dalkilic *et al*., 2023). The high content of anthraquinones and phenols in the latex are believed to be responsible for the laxative, anti-inflammatory, anti-tumour, nephroprotective, and antibacterial properties while the glycoprotein and polysaccharides content of the gel play a role in the wound healing and immunostimulatory properties (Djeraba and Quere, 2000; Boudreau and Baland, 2006; Hamman, 2008; Yu *et al*., 2009). With the wide range of uses of *Aloe vera* in the prevention and treatment of many diseases in both humans and animals, the current study was aimed at evaluating the effect of methanol and aqueous extracts of *Aloe vera* on ethanol-induced kidney and brain injury in mice.

MATERIALS AND METHODS

Plant and chemicals

Aloe vera was collected from a farm in University of Maiduguri campus and authenticated at the Faculty of Pharmacy (UMM/FPH/ASH/002). All the chemicals used were of analytical grade. They include ethanol, methanol, Sodium chloride, trichloroacetic acid, sodium carbonate, hydrogen peroxide, and ketamine hypochlorite injection.

Extraction of Aloe vera

Fresh *Aloe vera* was washed and homogenized using a blender and dissolved in methanol and water both at 1:1 ratio for 48 hours. The solutions were filtered and evaporated in an oven at 45 ° C to get the methanol and aqueous extracts.

Animals

Thirty male mice, 6-8 weeks old were used for the study. The animals were kept at the Department of Biochemistry Animal House, University of Maiduguri. They were fed with hybrid feed (Chikun Feed, Nigeria) and water *ad libitum*.

Experiment design

The thirty mice were assigned to six groups of five. The groups received distilled water (normal control), 20% ethanol at 10 ml/kg (negative control), (50 and 100) mg/kg methanol extract of *Aloe vera* plus 20% ethanol, and (25 and 50) mg/kg aqueous extract of Aloe vera plus 20% ethanol orally respectively for eighteen days. All the mice were euthanized using ketamine hypochlorite injection on the 19th day and blood collected in a plain bottle while the brain was removed and one half was fixed in Bouin's fluid.

Biochemical analysis

The blood was centrifuged at 5000 rpm and serum levels of creatinine and urea were evaluated spectrophotometrically using their respective kits (Randox Laboratories Ltd, US) according to the manufacturer's instructions.

Oxidative stress markers

The other half of the brain was homogenized in normal saline, centrifuged and the supernatant was used to evaluate the activities of catalase, malondialdehyde, superoxide dismutase, and reduced glutathione as described in our previous study (Dibal *et al*., 2022a).

Histological study

The kidney, cerebellum and cerebrum of the brain were dehydrated in graded alcohol, embedded in paraffin, and sectioned at 5 µm. The sections were cleared in xylene, rehydrated in graded alcohol, stained with hematoxylin and eosin (H&E), and mounted on glass slides. The tissues were observed with a light microscope and interpreted by two researchers that are blinded to the groupings. Photomicrographs were taken with a microscope camera (M500, Version 3.7) at x200 magnification.

Statistical analysis

The data were analyzed with GraphPad Prism 9.0 (San Diego, USA). One-way ANOVA followed by Sidàk multiple comparison was conducted. Statistical significance was considered at $p< 0.05$ and results were presented as mean ± standard error (SE).

Ethical Statement

The research was approved by the Department of Human Anatomy, Research and Ethics Committee, University of Maiduguri (UM/UGP/22-23/085) and conducted according to the ARRIVE Guidelines.

RESULTS

Kidney function

Ethanol was shown to significantly elevate ($p<0.05$) serum creatinine and urea levels compared to the control. Pre-treatment with methanol and aqueous extracts of *Aloe vera* could not significantly reduce the creatinine level relative to the ethanol-treated mice (Figure 1). However, pretreatment with methanol extract of *Aloe vera* at (50mg/kg & 100mg/kg) and aqueous extract of *Aloe vera* at (25mg/kg & 50mg/kg) were shown to significantly reduce ($p<0.05$) the serum urea level relative to the ethanol-treated mice (Figure 1).

Oxidative stress markers

The brain catalase activity was significantly reduced ($p<0.05$) in ethanol-treated mice compared to the control. However, pretreatment with methanol extract of *Aloe vera* at 50mg/kg and aqueous extract of *Aloe vera* at 25mg/kg were shown to significantly elevate ($p<0.05$) the catalase activity relative to the ethanol-treated mice (Figure 2). No significant change ($p>0.05$) was observed in the brain catalase activity of mice-pretreated with *Aloe vera* methanol (50mg/kg) and aqueous (25mg/kg) extracts compared to the control. The reduced glutathione activity was significantly decreased ($p<0.05$) in the ethanol-treated mice as well as the mice pretreated with methanol extract (100mg/kg) and aqueous extract (25mg/kg) *Aloe vera* relative to the control. However, no significant change ($p>0.05$) was observed in the mice pretreated with both the methanol and aqueous extracts of *Aloe vera* at 50mg/kg compared to the control (Figure 2). Superoxide dismutase activity was significantly reduced ($p<0.05$) in ethanol-treated mice as well as the mice pretreated with both the methanol and aqueous extracts of *Aloe vera* relative to the control. The malondialdehyde activity was significantly higher ($p<0.05$) in ethanol-treated mice and

the mice pretreated with aqueous extract of *Aloe vera* at 50mg/kg relative to the control. Nevertheless, pretreatment with methanol extract of *Aloe vera* at 50mg/kg and 100mg/kg as well as 25mg/kg of aqueous extract of *Aloe vera* significantly reduced ($p<0.05$) the malondialdehyde activity compared to the ethanol-treated mice (Figure 2).

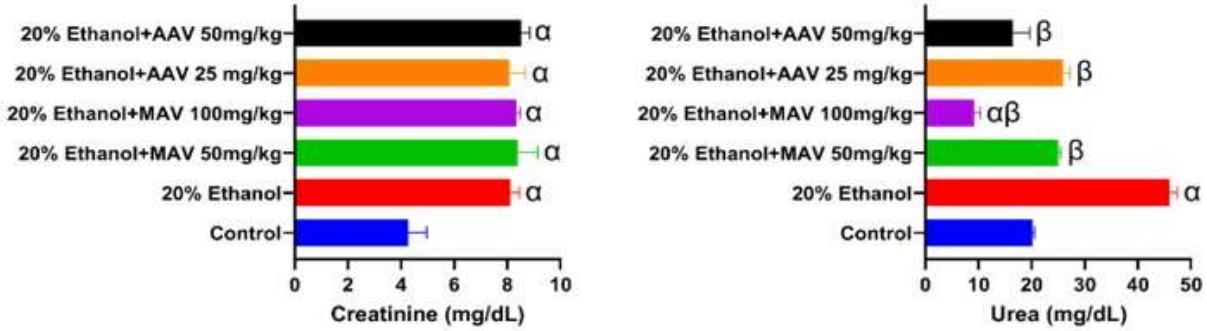

Figure 1: Serum urea and creatinine levels of ethanol-treated mice pretreated with methanol and aqueous extracts of *Aloe vera*. Values are expressed as Mean±SE, α and β indicates significant increase or decrease with the control and ethanol groups respectively at $p<0.05$. AAV= Aqueous extract of *Aloe vera*, MAV= methanol extracts of *Aloe vera*, SE= standard error

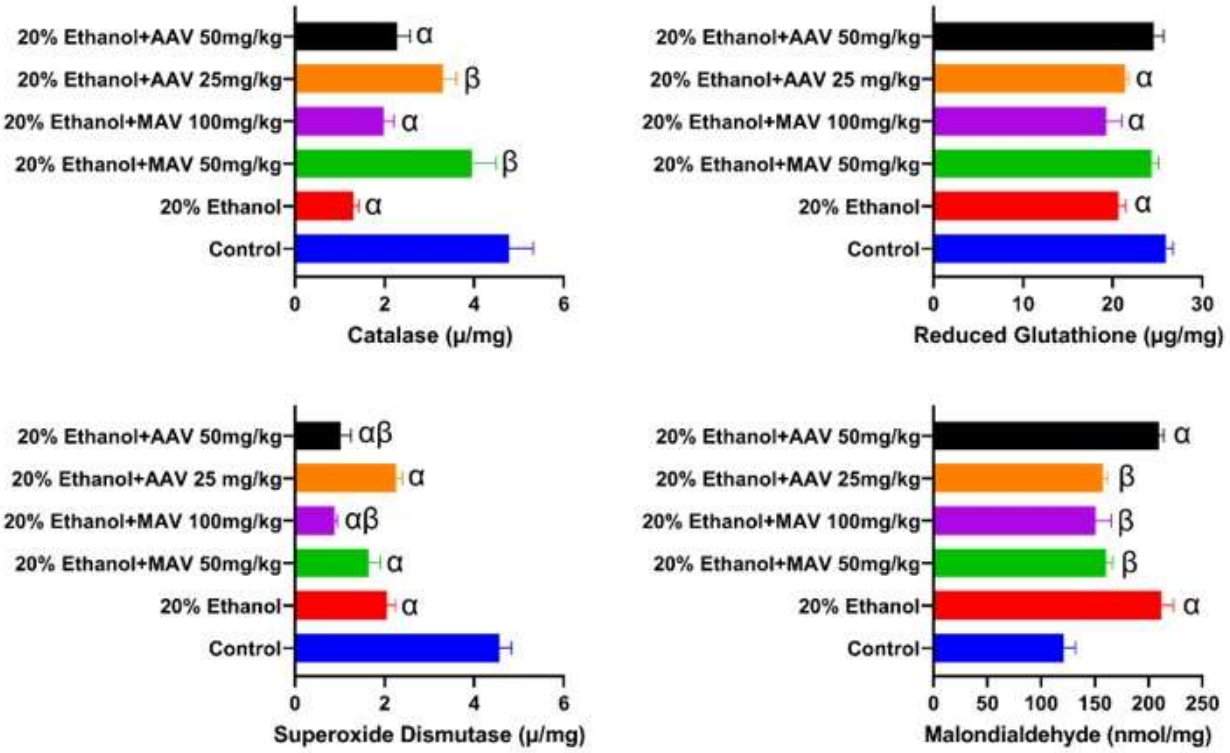

Figure 2. The oxidative stress markers of ethanol-treated mice pretreated with methanol and aqueous extracts of *Aloe vera*. Values are expressed as Mean±SE, α and β indicates significant increase or decrease with the control and ethanol groups respectively at $p<0.05$ AAV= Aqueous extract of *Aloe vera*, MAV= methanol extracts of *Aloe vera*, SE= standard error

Histology

The cerebellum of the control mice showed normal molecular and granular layers as well as the Purkinje neurons (Figure 3a). Ethanol treatment result in the degeneration of Purkinje neurons while pretreatment with 100mg/kg methanol extract of *Aloe vera* did prevent Purkinje neurons degeneration (Figure 3b & 3d). Pretreatment with 50mg/kg methanol extract and 25mg/kg aqueous extract of *Aloe vera* cause mild distortion of Purkinje neurons (Fig. 3c & 3e). The mice pretreated with 50mg/kg aqueous extract of Aloe vera had intact Purkinje neurons in the cerebellum (Figure 3f). The cerebrum of the control mice, the mice pretreated with both the methanol and aqueous extracts of *Aloe vera* at 50mg/kg showed normal neurons with mild distortion (Figure 4a, 4c, & 4f). The cerebrum of ethanol-treated mice showed sever degeneration of neurons (Figure 4b) while those of mice pretreated with 100mg/kg (methanol extract) and 25mg/kg (aqueous extract) of *Aloe vera* showed moderate degeneration of neurons (Figure 4a & 4e).

DISCUSSION

In the current study, both methanol and aqueous extracts of *Aloe vera* were found to significantly reduce serum urea level in ethanol-treated mice. Previous studies

reported that elevated serum urea level is associated with chronic kidney disease (Vanholder *et al*., 2018; Brookes and Power, 2022). Aloe vera was also reported to be beneficial in the prevention of diabetes-induced kidney damage (dos Santos *et al*., 2021) and hydrogen peroxide-induced kidney injury (Abdal *et al*., 2020). The ability of both the methanol and aqueous extracts of *Aloe vera* to alleviate ethanol-induced elevated serum urea may be attributed to the phenolic compounds present as reported in a previous study (Manye *et al*., 2023).

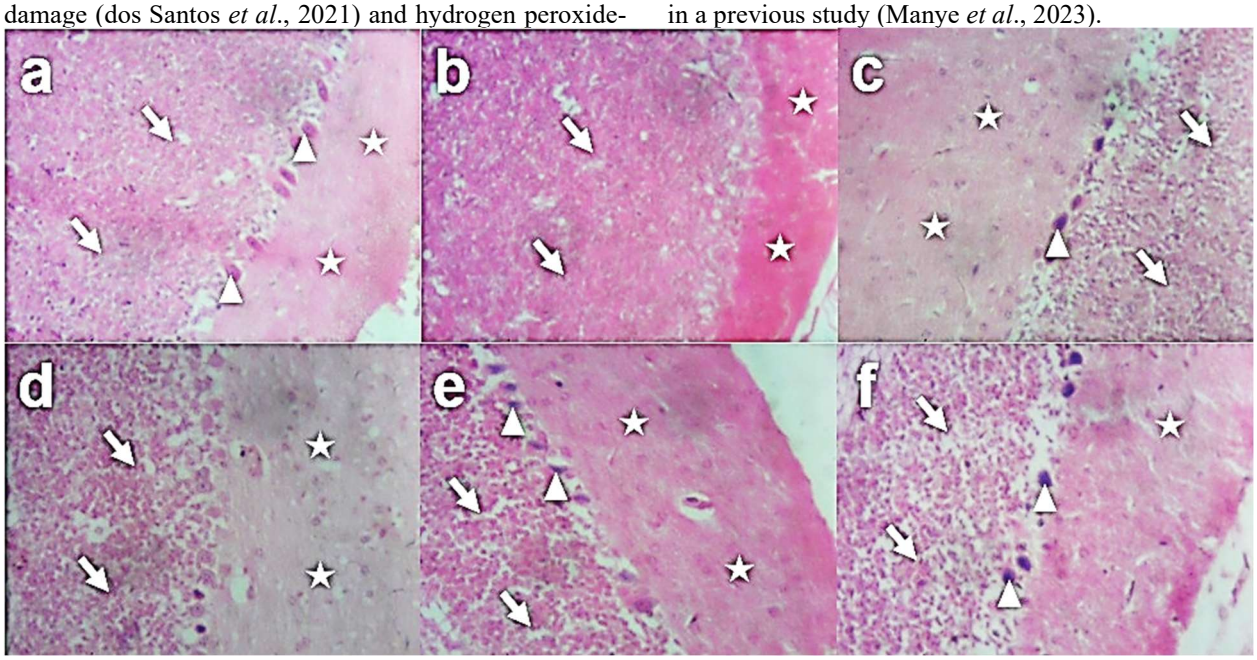

Figure 3: The cerebellum of control mice (a), ethanol-treated mice (b), mice pretreated with methanol extract of *Aloe vera* at 50mg/kg & 100mg/kg (c & d), and mice pretreated with aqueous extract of *Aloe vera* at 25mg/kg and 50 mg/kg (e & f). The granular and molecular layers are labelled with arrows and stars respectively while the Purkinje fibers are indicated with arrowheads. H&E, x200 magnification

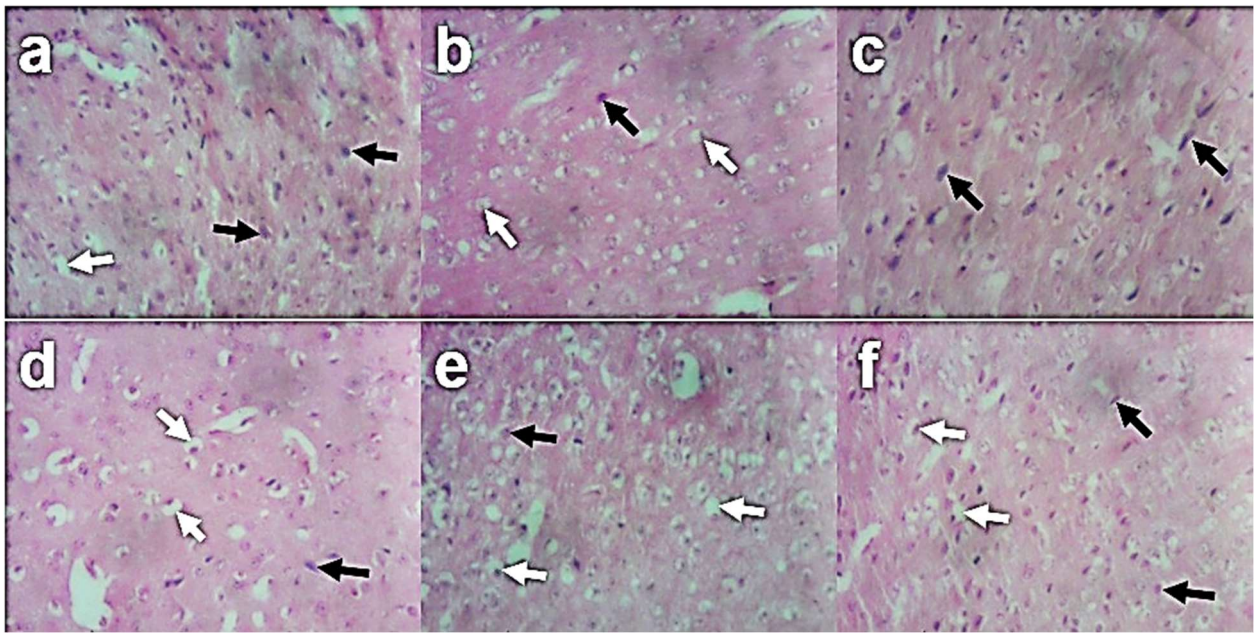

Figure 4: The cerebrum of control mice (a), ethanol-treated mice (b), mice pretreated with methanol extract of *Aloe vera* at 50mg/kg & 100mg/kg (c & d), and mice pretreated with aqueous extract of *Aloe vera* at 25mg/kg and 50 mg/kg (e & f). Normal and degenerating neurons are indicated with black and white arrows respectively. H&E, x200 magnification

Previous studies have reported a link between kidney disease and neurological disorders (Ster-Nezer, 2021; Xie *et al*., 2022). Hence, the significant decrease in brain catalase and reduced glutathione activities and increased lipid peroxidation that was observed in ethanol-treated mice in the present study suggest that kidney injury is associated with brain damage. Pretreatment with methanol and aqueous extracts of *Aloe vera* were shown to significantly elevate the catalase and reduced glutathione activities. This is an indication that *Aloe vera* could prevent oxidative stress and the progress of neurological disorders. Previous reports also highlighted the role of *Aloe vera* on enhancing the antioxidant activity and preventing lipid peroxidation (Abubakar *et al*., 2022; Dibal *et al*., 2022b). Therefore, the possible mechanism through which *Aloe vera* prevent oxidative stress is by

regulating serum urea and reducing the number of circulating free radicals.

The current studies reported that both methanol and aqueous extracts of *Aloe vera* prevented neuronal degeneration in the cerebellum and cerebrum of ethanol-treated mice. Neurological disorders commonly occur because of neurodegeneration and are considered as the second leading cause of death and disability world-wide (Zahra *et al*., 2020; Mathur *et al*., 2023). The ability of *Aloe vera* to prevent and/or alleviate neurological disorders is also reported in many previous studies (Tabatabaei *et al*., 2017; Ceravolo *et al*., 2021; Wang *et al*., 2022). We postulated that methanol and aqueous extracts of *Aloe vera* could prevent neurodegeneration in three stages as follows: (i). by regulating serum urea level to prevent kidney injury. The normal kidney function will reduce the number of circulating free radicals. (ii). by enhancing the antioxidant capacity of cells and tissues to prevent oxidative stress, and (iii). by preventing neurodegeneration. Therefore, the neuroprotective effect of *Aloe vera* may be a complex mechanism that involves different cascade of events to prevent the onset and progress of neurological disorders.

The study evaluated the kidney function, brain oxidative stress markers, and neurodegeneration in ethanol-treated mice. The 18 days administration of ethanol to the mice mimics two years continuous alcohol consumption in humans. Hence, the result of our study might not be applicable to chronic alcohol consumption in humans.

Conclusions

The methanol and aqueous extracts of *Aloe vera* regulated serum urea level in ethanol-treated mice. It also increased brain catalase and reduced glutathione activities and prevented lipid peroxidation. The consequential effect alleviate neurodegeneration that usually occur because of oxidative stress.

Conflict of Interest

The authors have no conflicts of interest to declare.

Author Contribution

Conception and design: All authors. Methodology and investigation: SB, HIA, JDM, DCD, DS, BA, HJM, SG, & AML. Analysis and interpretation of data: NID, JVZ, SJM, FB, & BI. Supervision: NID, JVZ, SJM, & FB. Initial draft of manuscript: SJM, SB, & BI. Critical review of the manuscript: NID, JVZ, SJM, & FB. All authors have read and approved the final manuscript.

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