

Taurine and/or Camel Milk Mitigates Haemolysis and Malondialdehyde Concentration in Alzheimer Rats

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Alzheimer's disease (AD) is a devastating neurodegenerative disease, affecting all age groups. Malondialdehyde (MDA) concentration and haemolysis are important oxidative stress biomarkers, implicated in the pathogenesis of AD. The study aimed to evaluate taurine, camel milk (CM) and their combined effects on MDA concentration and haemolysis in AD rats. The animal groupings were; Normal saline (0.2 mL/mg bw); AlCl₃ (100 mg/kg); CM (33 mL/kg); Taurine (50 mg/kg); AlCl₃ (100 mg/kg) + CM (33 mL/kg); AlCl₃ (100 mg/kg) + Taurine (50 mg/kg) and AlCl₃ (100 mg/kg) + CM (33 mL/kg) + Taurine (50 mg/kg). Concentration of MDA and percentage haemolysis were determined for all groups. At 0.5% NaCl, haemolysis in AD rats (64.00 ± 1.27 %) was higher ($p < 0.05$) than in AD + CM (51.50 ± 2.96 %) and AD + CM + Taurine (52.00 ± 1.53%) rats. MDA concentration was lowered ($p < 0.05$) in taurine-treated rats than controls, but it increased with haemolysis in AD rats compared to other groups. Taurine and/or CM exhibited antioxidant activity by decreasing haemolysis and MDA concentration in AD groups, and may be beneficial in mitigating AD-induced oxidative stress changes.

Key words: Aluminum chloride, camel milk, malondialdehyde, taurine, oxidative stress

Alzheimer's disease (AD) is a devastating and chronic disease in humans. It is characterized by loss of memory (Jahn, 2013; Borelli *et al.*, 2020; Putcha *et al.*, 2022), learning deficit (Bernaud *et al.*, 2022), behavioural impairments (Tangen *et al.*, 2014; Creese and Ismail, 2022) and ultimately reduced work output (Breijyeh and Karaman, 2020; Abdulkadir *et al.*, 2021). A reduction in acetylcholinesterase (ACh) activity (Herholz, 2008; Hung *et al.*, 2022), elevated amyloid- β peptide (A β) concentration (Hao *et al.*, 2019; Gallego Villarejo *et al.*, 2022) and concentrations of oxidative stress biomarkers (Cheignon *et al.*, 2018; Fang *et al.*, 2020) has been reportedly linked to AD. Elevated MDA concentration is an AD risk factor (López-Riquelme *et al.*, 2016; Rao *et al.*, 2021). Efforts to treat or prevent AD based on available prophylactic and therapeutic agents have not yielded the desirable beneficial results. Pathophysiological mechanisms underlying AD have been linked in part to redox imbalance and haematological disorders (Ma *et al.*, 2010; Rahim *et al.*, 2010; Issa *et al.*, 2018; Emoto *et al.*, 2021). Both camel milk (CM) and taurine have been shown to exhibit antioxidant activities (Jong *et al.*, 2012; Homayouni-Tabrizi *et al.*, 2017), and may be beneficial in AD intervention. There is need to shed more light on the impact of CM and taurine on the blood of aluminium chloride (AlCl₃)-induced AD in rats. The CM represses the formation of MDA and inhibits oxidative stress (OS) levels (Al-Asmari *et al.* 2014; Badawy *et al.*, 2018; Shaban *et al.*, 2022). The increased generation of reactive oxygen species (ROS), occurring in AD (Mohsenzadegan and Mirshafiey, 2012; Leyane *et al.*, 2022) may increase the haemolysis and lipid peroxidation of cytomembrane. Haemolysis, measured by percentage erythrocyte osmotic fragility (EOF), indicates the damage due to oxidative stress (Igbokwe, 2018; Vicente-Ferreira *et al.*, 2021). It is of value in the assessment of degree of stabilization or resistance to membrane lipid peroxidative damage by ROS, generated in excess during oxidative stress (Gwozdinski *et al.*, 2021). One of the important by-products of lipid peroxidation induced by oxidative stress is MDA, and its concentration in the body may indicate

the level of redox imbalance and severity of AD (Greilberger *et al.*, 2008). Therefore, variations in haemolysis and MDA concentration may be of diagnostic importance in AD cases.

The study aimed to evaluate changes in MDA concentration and haemolysis in AlCl₃-induced AD rats.

MATERIALS AND METHODS

Aluminium chloride (AlCl₃) (CAS: 7764-15-6) and taurine (CAS: 107-35-7) were bought from Sigma-Aldrich Company (Munich, Germany and St. Louis, U.S.A., respectively). Both rat AChE (CK-bio-14126) and A β 1-42 (CK-bio-14171) ELISA kits were bought from Shanghai Coon Koon Biotech Co., Ltd., China. At 09:00 h, fresh milk was obtained from normal camel reared in Chiranchi (12°40'N, 07°43'E) Nigeria. The CM until use was stored in an ice chest.

Animals

Female Wistar rats (n =35) and weighing 120 – 150 g (135 \pm g), served as subjects. They were kept in plastic cages in a well-ventilated animal pen under 12/12 h light/dark cycle. The animals had access freely to food and water. The study was performed based on the policy, ethics and regulations on care and use of research animals, approved by Ahmadu Bello University, Zaria, Nigeria (ABUCAUC/2021/004).

Experimental design and groupings (Table 1)

Alzheimer disease (AD) was induced by administering AlCl₃ that was dissolved in distilled water. The AlCl₃ was administered immediately after being dissolved via oral gavage and for eight weeks. Following 24 hours after the last administration, rats were adequately anaesthetised by ketamine/diazepam (75:25 mg/kg) injection. From each group (Table 1), blood sample was collected from each rat for biochemical analysis via cardiac puncture (Parasuraman *et al.*, 2010).

Assessment of haemolysis and malondialdehyde concentration

Evaluation of percentage haemolysis

In vitro EOF was estimated to serve as indication of haemolysis in the rats in accordance with Faulkner and

King (1970) and based on sodium chloride (NaCl) concentrations (pH 7.4), ranging from 0.0 to 0.9 g/L of distilled water. Fresh blood samples obtained via cardiac puncture were transferred into NaCl-containing test tubes. The content was gently shaken and then incubated at 25 – 26°C (room temperature) for 30 minutes. Thereafter, the tubes were centrifuged at 800 x g, 10 minutes. The optical density of the supernatant was measured spectrophotometrically by a spectrophotometer (Spectrum 20, Philip Harris Limited, Shenstone, UK) at 540 nm.

$$\text{Percentage haemolysis (\%)} : \frac{\text{Optical density of test solution}}{\text{Optical density of standard solution}} \times 100$$

Determination of malondialdehyde concentration

Hippocampus tissue was obtained from each rat as described by Ojha *et al.* (2021) for evaluation of MDA concentration. Hippocampus tissue MDA concentration was determined using MDA enzyme-linked immunosorbent assay (ELISA) kit on the basis of biotin double antibody sandwich technology in accordance with Janero (1990). The tissue sample (40 µL), 10 µL of rat MDA antibody and streptavidin-horseradish peroxidase (50 µL) were transferred to wells coated with MDA monoclonal antibody. A blank well without sample contained 10 µL of rat MDA, while 50 µL of standard and 5 µL streptavidin- horseradish peroxidase was poured into the standard well. Mixing of solution was performed by shaking the plate gently. The solution was incubated at 37°C for 60 minutes. Thereafter, the liquid was drained from the plate. A washing solution was poured into each well, which stood for 3 seconds and then washed off. The washing procedure was done for 5 cycles. Both Chromogen A and B (50 µL) were transferred into the blank, standard and sample wells, respectively. Mixing of the solution was performed by shaking the plate gently. The solution was incubated at 37°C for 10 minutes without access to light in order to prevent colour development. The removal of the plate was done after 10 minutes, and the reaction halted using stop solution (50 µL) as the colour was observed to change to yellow. The absorbance recorded from each well was obtained under 450 nm and 10 minutes

after the addition of stop solution. The concentration in each sample was measured by determining the optical density using MyAssays Software (MyAssays, 2016).

Data analyses

Values recorded were presented as mean ± standard error of the mean (Mean ± SEM). The analysis was performed using one-way analysis of variance. The percentage haemolysis and MDA concentration recorded in each group were evaluated using Tukey's *post-hoc* test to determine the significance of the differences between the means. The statistical analysis was carried out by GraphPad Prism 5.03 for windows (GraphPad Software, San Diego, California, U.S.A.). Level of significance was set at $p < 0.05$.

RESULTS

Erythrocyte Osmotic Fragility

The percentage haemolysis (or EOF) at 0.7% NaCl concentration in AD rats was similar to that obtained in AD + Taurine + CM, although AD + CM and AD + Taurine rats showed a relatively higher percentage, when compared to AD rats (Figure 1). At 0.5% NaCl, the percentage EOF in AD (64.00 ± 1.27%) rats was higher ($p < 0.05$) than the percentages obtained in AD + CM (51.50 ± 2.96%) and AD + CM + Taurine (52.00 ± 1.53%) rats. At 0.4% NaCl, percentage haemolysis was significantly higher ($p < 0.05$) in AD (83.60 ± 1.94%) rats than in AD + CM (74.25 ± 3.40%). Taurine when administered either alone or to AD + Taurine rats did not significantly lower the percentage haemolysis, compared to AD rats. There was a significant negative relationship between the percentage haemolysis and NaCl concentration ($r = -0.984$, $p < 0.001$) in AD rats (Table 2).

Malondialdehyde evaluation

The concentration of MDA was higher ($p < 0.05$) in AD (55.32 ± 6.02 nmol/mL) rats than in either AD + Taurine (20.28 ± 1.37 nmol/mL) rats or AD + Taurine + CM (40.34 ± 5.54 nmol/mL) rats (Figure 3).

Table 3 below shows the correlation coefficients between MDA concentration and percentage haemolysis at 0.5% NaCl. The AD + CM and AD + Taurine + CM groups recorded higher values, when compared to AD

group, respectively. The scattered plots showing the fluctuations in the relationships between MDA concentrations and percentage haemolysis, and their corresponding regression equations in individual AD

rats, AD + Taurine and AD + CM rats, are presented in Figure 4 A - C, respectively. The relationship was negative in AD, and AD + Taurine rats, but positive in AD + CM rats.

Table 1: The experimental animal groupings

S/No.	Groups	Treatment	Duration
1	Group I	Normal saline at 0.2 mL/kg/body weight orally	8 weeks
2	Group II	Aluminum chloride (AlCl ₃) 100 mg/kg orally (Prakash <i>et al.</i> , 2013)	6 weeks
3	Group III	Camel milk (33 mL/kg) orally (Khatoun <i>et al.</i> , 2016)	8 weeks
4	Group IV	Taurine (50 mg/kg) orally (Cetiner <i>et al.</i> , 2005)	8 weeks
5	Group V	AlCl ₃ (100 mg/kg) + Camel milk (33 mL/kg) orally	8 weeks
6	Group VI	AlCl ₃ (100 mg/kg) + Taurine (50 mg/kg) orally	8 weeks
7	Group VII	AlCl ₃ (100 mg/kg) + Taurine (50 mg/kg) + Camel milk (33 mL/kg) orally	8 weeks

N=5

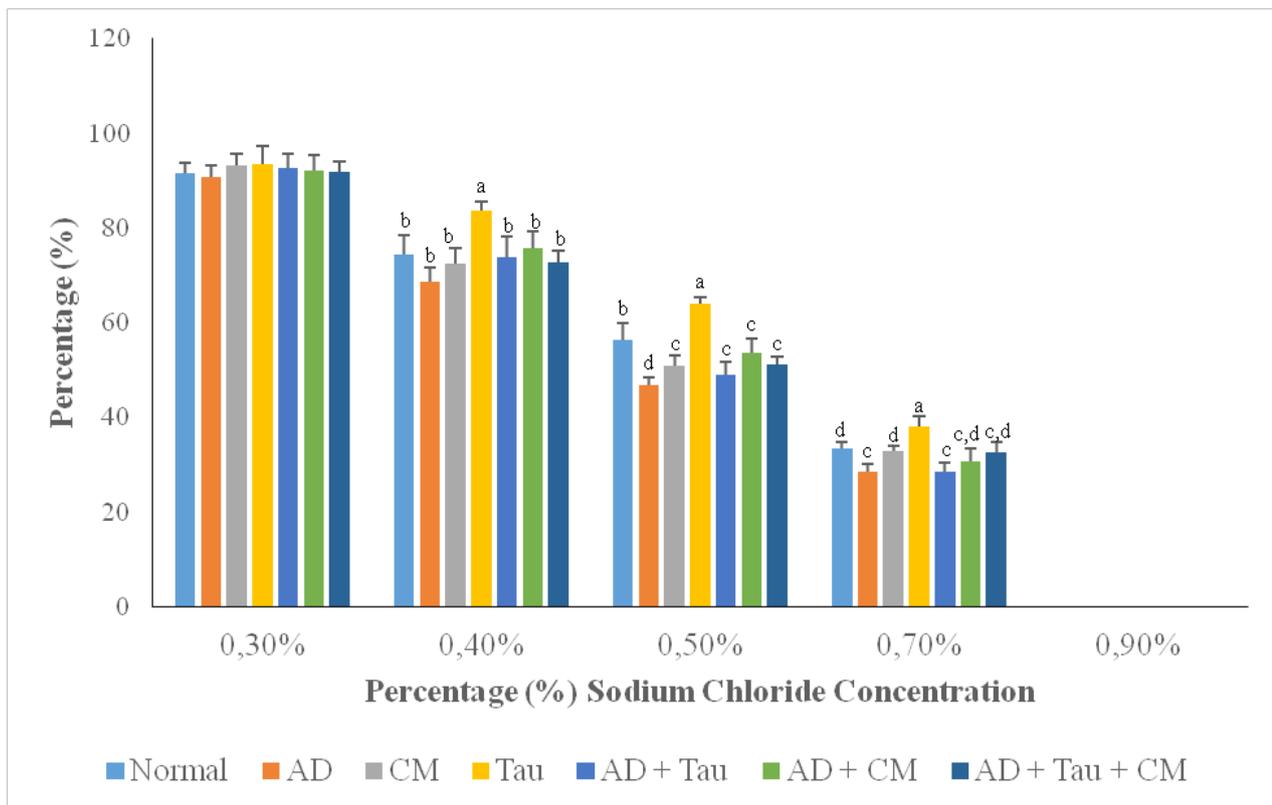


Figure 1. Effect of taurine and camel milk on erythrocyte osmotic fragility in aluminum chloride-induced Alzheimer's disease in rats

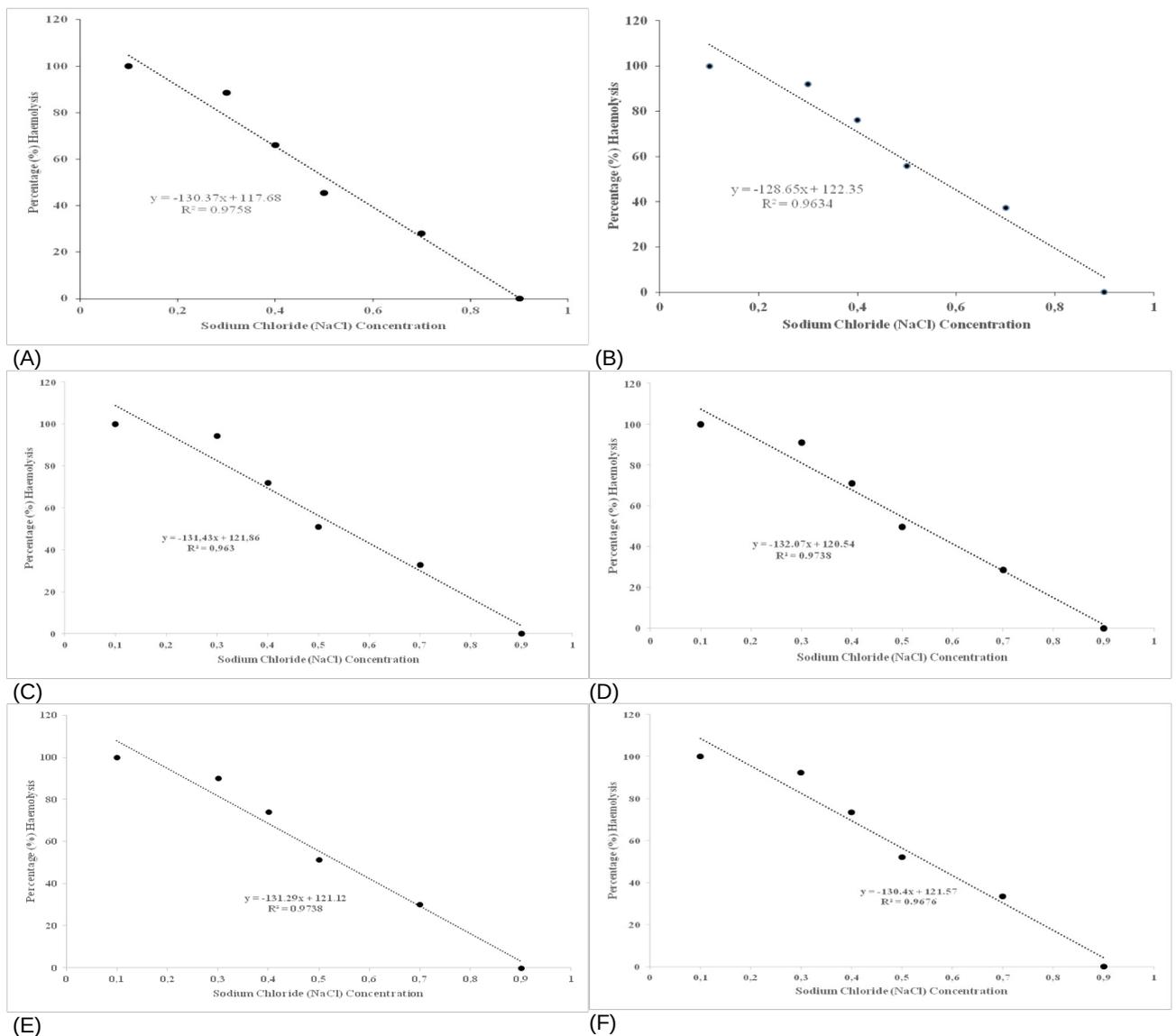
AD: Alzheimer's disease, CM: Camel milk, Tau: Taurine, n = 5

a,b,c,d= means with different letters differ significantly ($p < 0.05$)

Table 2: The relationship between sodium chloride concentration and percentage erythrocyte osmotic fragility in AlCl_3 -induced AD rats administered with taurine and camel's milk

Groups	Correlation coefficient (r)
Normal	-0.990***
AD	-0.971***
CM	-0.974***
Taurine	-0.984***
AD + Taurine	-0.984***
AD + CM	-0.987***
AD + Taurine + CM	-0.980***

AD: Alzheimer's disease, CM: Camel milk

*** = $p < 0.001$ **Figure 2:** Scattered plot showing the relationship between percentage sodium chloride concentration and percentage erythrocyte osmotic fragility in (A) Alzheimer's disease group, (B) in taurine group, (C) in camel milk group and (D) Scattered plot for percentage sodium chloride concentration against Alzheimer's disease group treated with taurine group, (E) Alzheimer's disease group treated with camel milk, (F) Alzheimer's disease group treated with taurine and camel milk.

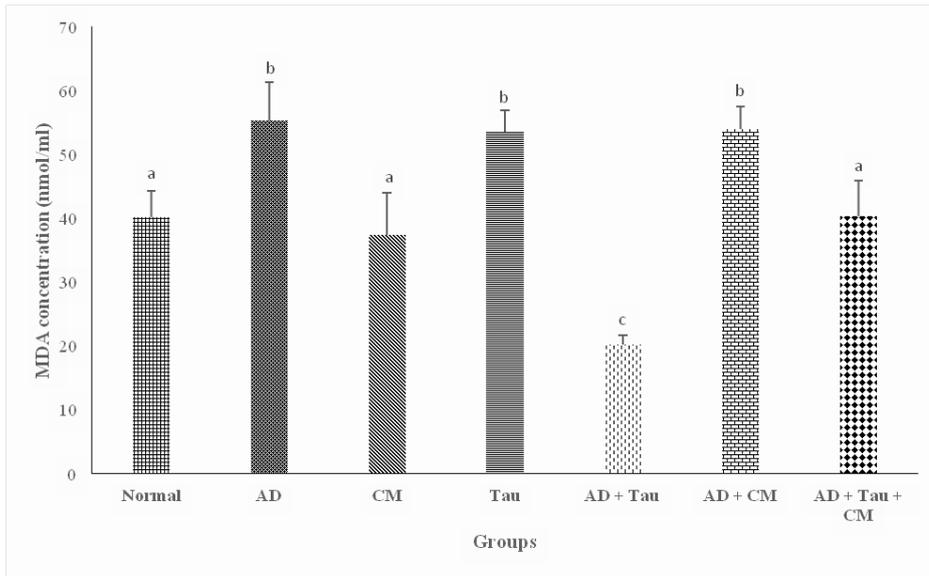
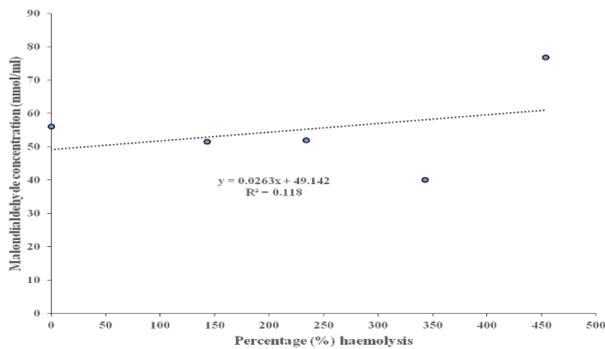


Figure 3 Effect of taurine and camel milk on malondialdehyde concentration in aluminum chloride-induced Alzheimer's disease in rats. AD: Alzheimer's disease, CM: Camel milk, Tau: Taurine, MDA: Malondialdehyde

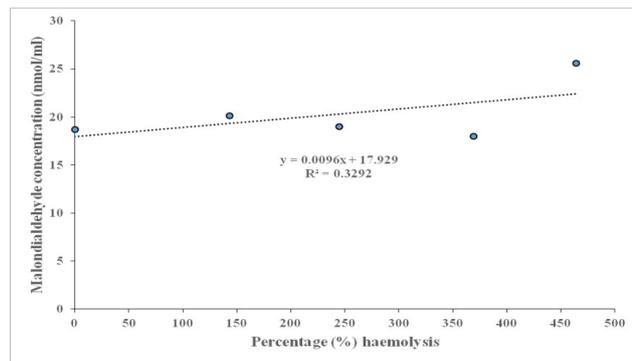
Table 3: The relationship between malondialdehyde concentration and percentage erythrocyte osmotic fragility in Alzheimer's disease rats.

Groups	Correlation
Normal	-0.993***
AD	-0.973***
CM	-0.975***
Taurine	-0.996***
AD + Taurine	-0.980***
AD + CM	-0.990***
AD + Taurine + CM	-0.979***

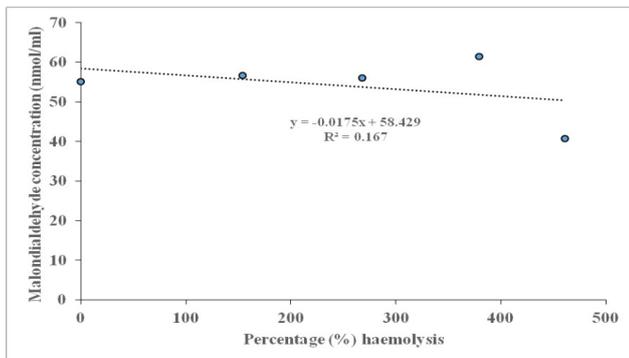
Key: AD: Alzheimer's disease, CM: camel milk, *** p < 0.001



(A)



(B)



(C)

Figure 4 Scattered plot of malondialdehyde concentration against percentage (%) haemolysis in Alzheimer's disease group (A), haemolysis in Alzheimer's disease group rats treated with taurine (B) and in Alzheimer's disease group rats treated with camel milk (C).

DISCUSSION

Effect on haemolysis

The result of haemolysis demonstrates that CM and/or taurine significantly decreased haemolysis in AD rats; indicating that the two agents exhibited antioxidant activity, apparently by increasing the cytomembrane integrity of the erythrocytes. The EOF as an index of haemolysis has been demonstrated to be also an index of lipoperoxidation in rats exposed to increased oxidative stress, induced by poisoning (Ambali *et al.*, 2010; Uchendu *et al.*, 2014; Yusuf *et al.*, 2018), heat stress (Alhassan *et al.*, 2010), and transportation stress (Yaqub *et al.*, 2014). The current study has established, for the first time, that AlCl_3 -induced oxidative stress resulted in increased haemolysis, which was alleviated by the administration of taurine and CM.

The findings show that CM exerted a more potent inhibitory effect on haemolysis than taurine. The mechanism by which CM exerted its inhibitory effect on haemolysis was not elucidated in this study. However, the results suggest that the antioxidant, taurine, also known to be a neurotransmitter exerting inhibitory effect on the nervous system, exerted its antioxidant effect via a pathway that differs from that of CM. The CM which is also an antioxidant contains both electrolytes and other compounds (Rasheed, 2017; Rahmeh *et al.*, 2019) that, apparently, enhanced the anti-haemolytic activity of CM at the erythrocyte membrane level. This requires further investigations.

Effect on malondialdehyde

The result of MDA concentration shows that taurine significantly reduced MDA concentration in AD rats compared to any other group; thus, indicating that the degree of lipid peroxidation in AD + Taurine rats was the least. The MDA is established to be the product of damage to cell membranes. Therefore, its low concentration is an evidence of low ROS generation or high scavenging activity by taurine and/or CM in the treated rats. The result was similar to that of Rao *et al.* (2021), who showed that the administration of resveratrol and its combination with donepezil lower the levels of MDA in colchicine-induced AD. Akbari *et al.* (2016) reported that the probiotic (also an antioxidant)

supplementation significantly decreased MDA level in a randomised, double-blinded and controlled trial of AD patients.

Overall, CM and/or taurine, especially in combination, decreased percentage haemolysis and MDA concentration. The CM and taurine may exhibit protective mechanism in the rats partly by stabilizing cell membrane from ROS damage, induced with AD by AlCl_3 administration.

CONCLUSION

Taurine either alone or in combination with CM alleviated AlCl_3 oxidative stress changes in AD rats, induced with AlCl_3 by decreasing haemolysis and MDA concentration. The administration of taurine and, especially, CM prophylactically mitigated AD-induced oxidative stress changes, and may be utilised in drug discovery.

DECLARATION

All applicable international, national, and/or institutional guidelines for the care and use of laboratory animals were adhered to in the study.

CONFLICTS OF INTEREST

The authors declare that they have no potential conflicts of interest.

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