PROTECTIVE EFFECT OF *CAESALPINIA FERREA* GALACTOMANNAN IN A MICE MODEL OF SEIZURES

ORIGINAL ARTICLE

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ABSTRACT

Epilepsy is a public health problem of social and economic impact, characterized by the brain predisposition to generate persistent seizures accompanied by an increased oxidative stress. Plant polysaccharides emerge as an alternative therapy due to its immunomodulator and neuroprotective effects, along with low toxicity. The aim of this study was to evaluate the neuroprotective and antioxidative effects of the galactomannan isolated from the endosperm of *C. ferrea* (Cf-GM) in the mice model of pentylenetetrazole-induced seizures. Male Swiss mice (25-35 g) were treated by intraperitoneal (I.p.) route with Cf-GM (1-27 mg/kg) or 0.9% NaCl. Thirty min later, the animals were submitted to behavioral tests (open field, elevated plus maze, hole board, tail suspension and acute seizures). The anticonvulsant effect was evaluated in the model of acute seizures induced by pentylenetetrazole- PTZ (70 mg/kg; (I.p.) and the oxidative stress quantified in brain areas (prefrontal cortex, hippocampus and corpus striatum). Cf-GM inhibited the exploratory behavior, reducing the number of crossing (29-54%) and rearing (61-78%) in the Open Field test. Cf-GM also inhibited the permanence time and the entrance number in the open arms of the elevated plus maze, and the number of head dips (46-73%) in the hole board but increased (49%) the immobility time in the tail suspension test. In the model of seizures, Cf-GM increased the death latency and the animal's survival, inhibiting the oxidative stress via reduction of malondialdehyde (MDA) and increase of reduced glutathione (GSH).

The galactomannan of *C. ferrea* exhibits protective effects, modulating biomarkers of oxidative stress in the mice model of pentylenetetrazole-induced seizures.

Keywords: Brain, Oxidative stress, Convulsion, Plant polysaccharide, Behavior.

1. INTRODUCTION

Epilepsy is a public health problem of social and economic impact that affects about 50 million people worldwide, being the second most common neurological disorder after stroke (Fiest *et al*., 2017; Milligan, 2021) It is characterized by the brain predisposition to generate persistent seizures, accompanied by an increased oxidative stress (Fiest *et al*., 2017). The pharmacological therapy of epilepsy causes several adverse effects, such as vertigo, amnesia and leukopenia, being 30% of patients refractory to treatment (Sankaraneni & Lachhwani, 2015; Shorvon *et al*., 2018).

The animal model of pentylenetetrazole-induced seizures is widely used in preclinical screening of new anticonvulsant drugs, since pentylenetetrazole (PTZ) administered by intraperitoneal or intravenous route increases neuronal excitability via competitive blockade of GABAA receptors. In the PTZ-induced seizures there is also an increased oxidative stress in the cerebral cortex, mainly in hippocampus accompanied by increased levels of malondialdehyde (MDA) and reduced activity of antioxidant enzymes, such as superoxide dismutase (SOD) and catalase (Akula, Dhir & Kulkarni, 2009). Thus, the blockade of PTZ-induced seizures in rodents could be indicative of a depressor effect in the central nervous system by anticonvulsant drugs.

Plant polysaccharides are polymeric carbohydrates that emerge as alternative therapy due to its immunomodulator properties, low toxicity and antioxidant (Zheng *et al*., 2020). In the Central Nervous System (CNS) they elicit pharmacological effects such as neuroprotective (Chen, Chen & Qin, 2011), anti-inflammatory, antioxidant (Chen *et al*., 2014), anticonvulsant (Nonato *et al*., 2018; Nonato *et al*., 2024) and antidepressant (Wang *et al*., 2010). *Caesalpinia ferrea* or *Libidibia ferrea* (Leguminosae family) is a native species of Brazil, popularly known as jucá (Queiroz, 2009). Studies have demonstrated that the crude aqueous extract of *C. ferrea* leaves presents antioxidant effect mediated by the reduction of MDA in the mice model of arthritis induced by zymosan (Falcão *et al*., 2019). Besides, *C. ferrea* polysaccharides isolated from pods

and barks present anti-inflammatory effect in the acute inflammation models of paw edema and peritonitis (Pereira *et al*., 2012), and healing effect in the model of excision skin wounds in normo- and hyperglycaemic rats (Pereira *et al*., 2016; Assreuy *et al*., 2023). In respect to galactomannans they are hydrophilic polysaccharides mostly present in the endosperm of leguminous, containing in its structure mannose, galactose, rhamnose and glucose (Bento *et al*., 2013). The galactomannan isolated from *C. ferrea* (Cf-GM) seeds possesses 2.4:1 ratio mannose/galactose, revealed by ^{1}H NMR or 2.7:1 by ^{13}C NMR, composed by 33.58% of mannose and 12.39% of galactose, and low content of arabinose (0.06%) and glucose (0.94%) (Cunha *et al*., 2016). The same study demonstrated that the *C. ferrea* galactomann presents *in vivo* antidiabetic effect, being devoid of significant toxicity (Cunha *et al*., 2016). The objective of this study was to evaluate the neuroprotective effects through behavioral tests and oxidative stress of *C. ferrea* galactomannan in the mice model of seizures induced by pentylenetetrazole.

2. MATERIALS AND METHODS

2.1COLLECTION OF C. FERREA PODS AND GALACTOMANNAN EXTRACTION

C. ferrea pods were collected at Pici Campus of Federal University of Ceará (FUC) and a voucher specimen (44695) was deposited at the Herbarium Prisco Bezerra/FUC. Seeds were removed from pods and immersed in distilled water during 30 min at 85 °C for endosperm removal, that was placed in a solution of water:alcohol (1:4, v/v) at 60 °C for 20 min in order to exclude phenolic pigments. The depigmented endosperm (10 g) was lyophilized, solubilized (900 ml distilled water), maintained at 75 °C for 4 h, filtered and precipitated with a solution of 97% ethanol (1:3, v/v) for 4 h, followed by three precipitation cycles with a solution of 99% ethanol (1:1, v/v), filtration and centrifugation (Cunha *et al*., 2016). The gelatinous pellet containing the galactomannan of *C. ferrea* was named Cf-GM.

2.2 ANIMALS

Male Swiss mice (25 - 35 g, two months old) were provided by the Central Animal House from Federal University of Ceará-Brazil, maintained in controlled environment (22 ± 2 °C, 12/12 h light-dark cycle), with free access to food and water, and allowed to adapt to the laboratory for at least 1 h before experiments.

The experimental protocols were performed during the light phase of the cycle, in accordance with the Guide for the Care and Use of Laboratory Animals by the National Academy of Sciences, The National Academies Press, Washington, D.C. and Brazilian College of Animal Experimentation (COBEA), approved by the Ethics Committee for Animal Use (UECE N° 3484042/2017) and NC3R´s ARRIVE guidelines.

2.3 EXPERIMENTAL GROUPS AND TREATMENT

The animals (N=88) were divided into 7 experimental groups (n=7-10), receiving the following treatment by intraperitoneal (I.p.) route: Group 1 (Cf-GM 1 mg/kg); Group 2 (Cf-GM 9 mg/kg); Group 3 (Cf-GM 27 mg/kg); Group 4 (0.9% NaCl - sterile saline); Group 5 (Diazepam 1 mg/kg); Group 6 (Diazepam 2 mg/kg); Group 7 (Imipramine 10 mg/kg).

2.4 BEHAVIORAL TESTS

Thirty minutes after treatment the animals were evaluated by the tests (open field, elevated plus maze, hole board, tail suspension, acute seizure). Diazepam or imipramine provided from St. Louis, MO, USA were used as standard drugs. Diazepam at 1 mg/kg was administered for the anxiolytic and anticonvulsant effects in the elevated plus maze, hole board, and at 2 mg/kg for the sedative effect in the open field test.

2.4.1 OPEN FIELD TEST

The exploratory activity (n° crossings, rearing and grooming) was observed over 4 min after 1 min adaptation by the mice placement in the open field apparatus, an acrylic box (30 x 30 x 15 cm) divided into 9 squares (Archer, 1973).

2.4.2 ELEVATED PLUS MAZE AND HOLE BOARD TESTS

For evaluation of the anxiety behavior in the elevated plus maze, mice were placed in the center of the plus maze apparatus, which consists of two opposing open and closed arms (30 x 5 x 25 cm), with the head turned towards one of the closed arms. The frequency of entry and the time spent in each arms were observed during 5 min (Lister, 1987). The evaluation of the anxiety behavior in the hole board test, mice were placed in the hole board apparatus (20 x 20 cm), containing 16 equidistant holes, for recording the number of entrances in the holes during 5 min (Lister, 1987).

2.4.3 TAIL SUSPENSION TEST

The depressive behavior (immobility time) of mice, suspended 50 cm from the ground by a fixed tape 1 cm from the tail tip, was observed during 5 min (Steru *et al*., 1985).

2.5 SEIZURES INDUCTION

Thirty minutes after treatment, the acute seizures were induced by the administration of pentylenetetrazole (PTZ; 70 mg/kg, I.p.). For this, the animals were placed in individual cages during 20 min for evaluation of the onset time of first clonic or tonic-clonic seizure (seizure latency) and first clonic or tonic-clonic seizure to death (death latency), and also the percentage of survival (Czuczwar & Frey, 1986). After being tested the animals were euthanized by beheading, and the brain was dissected for evaluation of oxidative stress markers in pre-frontal cortex (PFC), hippocampus (HC) and striatum (ST).

2.5.1 BRAIN OXIDATIVE STRESS: LIPID PEROXIDATION (MDA) AND REDUCED GLUTATHIONE (GSH)

The homogenates of brain tissues (PFC, HC, ST) were prepared in phosphate buffer sodium (pH 7.4) according to the weight of the tissues. They were stored in 80° C frezzer for further quantification of MDA by the method of TBARS at A535 nm (Yagi, 1976) and reduced glutathione (GSH) by DTNB method at A412 nm (Sedlak & Lindsay, 1968).

2.6 STATISTICAL ANALYSIS

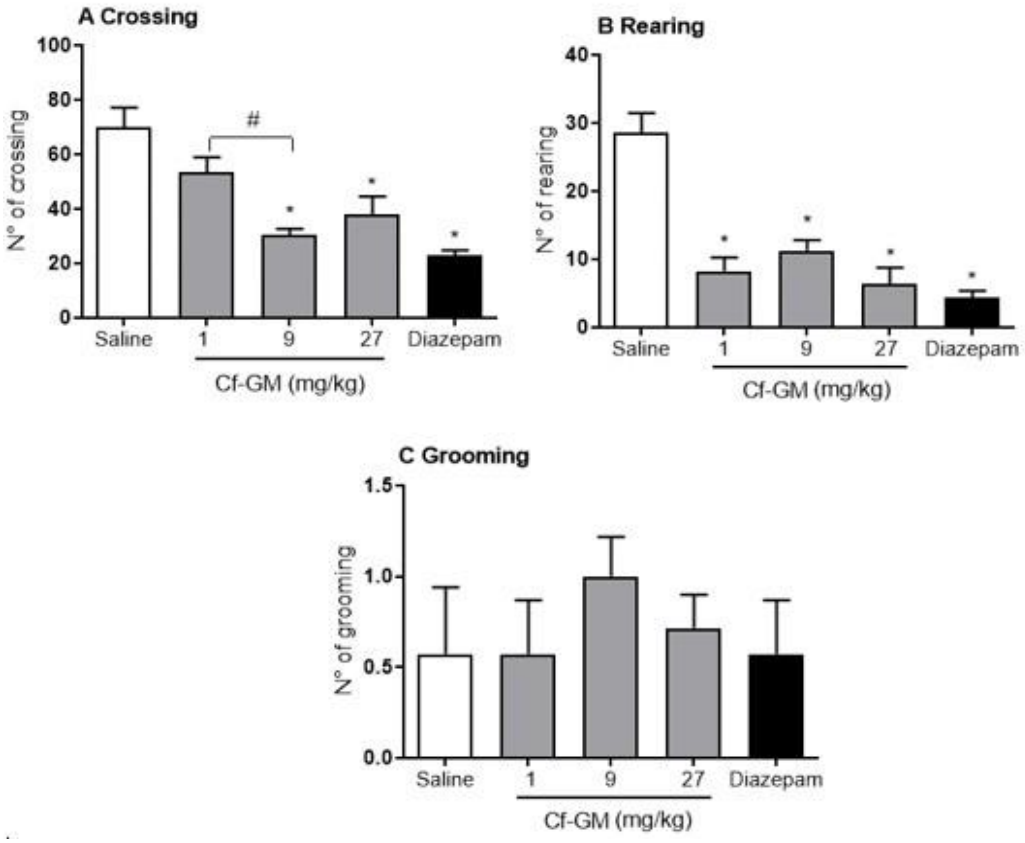
Results were expressed as mean ± standard error of the mean (S.E.M.) and analyzed by One-way ANOVA, followed by Tukey´s and Dunnet´s (elevated plus maze test) post hoc tests. The significance level was set at $p < 0.05$.

3. RESULTS

3.1 Cf-GM REDUCES THE NUMBER OF CROSSING AND REARING IN THE OPEN FIELD TEST

Cf-GM reduced the number of crossings by at 59% in the dose of 9 mg/kg (group 2) (30.57 ± 2.15; $p < 0.0001$) and 54% at 27 mg/kg (group 3) (34.17 ± 6.33; $p = 0.0003$), compared to saline (group 4) (70.00 ± 7.12), with f value ($f [4.29] = 14.70$). In addition, there was a reduction by 63% in the number of crossings between animals treated with Cf-GM at 1 (group 1) (53.29 ± 5.66) and 9 mg/kg **(Figure 1A)**. Cf-GM reduced by 71% the number of rearing at 1 mg/kg (8.28 ± 1.96; $p< 0.0001$), 61% at 9 mg/kg (11.29 ± 1.52; $p = 0.0012$) and by 78% at 27 mg/kg (6.42 ± 2.34; $p< 0.0001$), compared to saline (28.57 ± 2.89) ($f [4.42] = 18.96$) **(Figure 1B)**. However, the number of grooming was unaltered at any dose **(Figure 1C)**. The sedative drug diazepam (2 mg/kg) (group 6) reduced both the number of crossing (22.86 ± 1.95) and rearing (4.33 ± 0.77), compared to saline, but did not alter the number grooming.

Figure 1- Cf-GM reduces the number of crossing and rearing in the open field test



The open field test. (A) crossing, (B) rearing, (C) grooming. Mice received I.p. Cf-GM (1, 9, 27 mg/kg), diazepam (2 mg/kg) or Saline 30 min before evaluation. Mean ± SEM (n=8). One -way ANOVA followed by Tukey´s post-hoc test. *p<0.05 *vs.* Saline. #p< 0.05: 1 mg/kg *vs.* 9 mg/kg. Cf-GM: *C. ferrea* galactomannan. Source: Researcher's result 2024

3.2. Cf-GM INHIBITS BEHAVIORAL PARAMETERS IN THE ELEVATED PLUS MAZE AND HOLE BOARD TESTS

3.2.1. ELEVATED PLUS MAZE TEST

In the open arms, Cf-GM reduced the permanence time at all doses: 1 (39.43 ± 6.12 s; p = 0.0316) corresponding to 56% ,9 (36.33 ± 5.67 s; p = 0.0284) with a reduction of 60 % and 27 mg/kg (27.83 ± 9.91 s; p = 0.0095) reducing the time in 69% *versus* saline (90.25 ± 16.98 s), with F value (F [4.29] = 5.685). CF-GM also reduced the

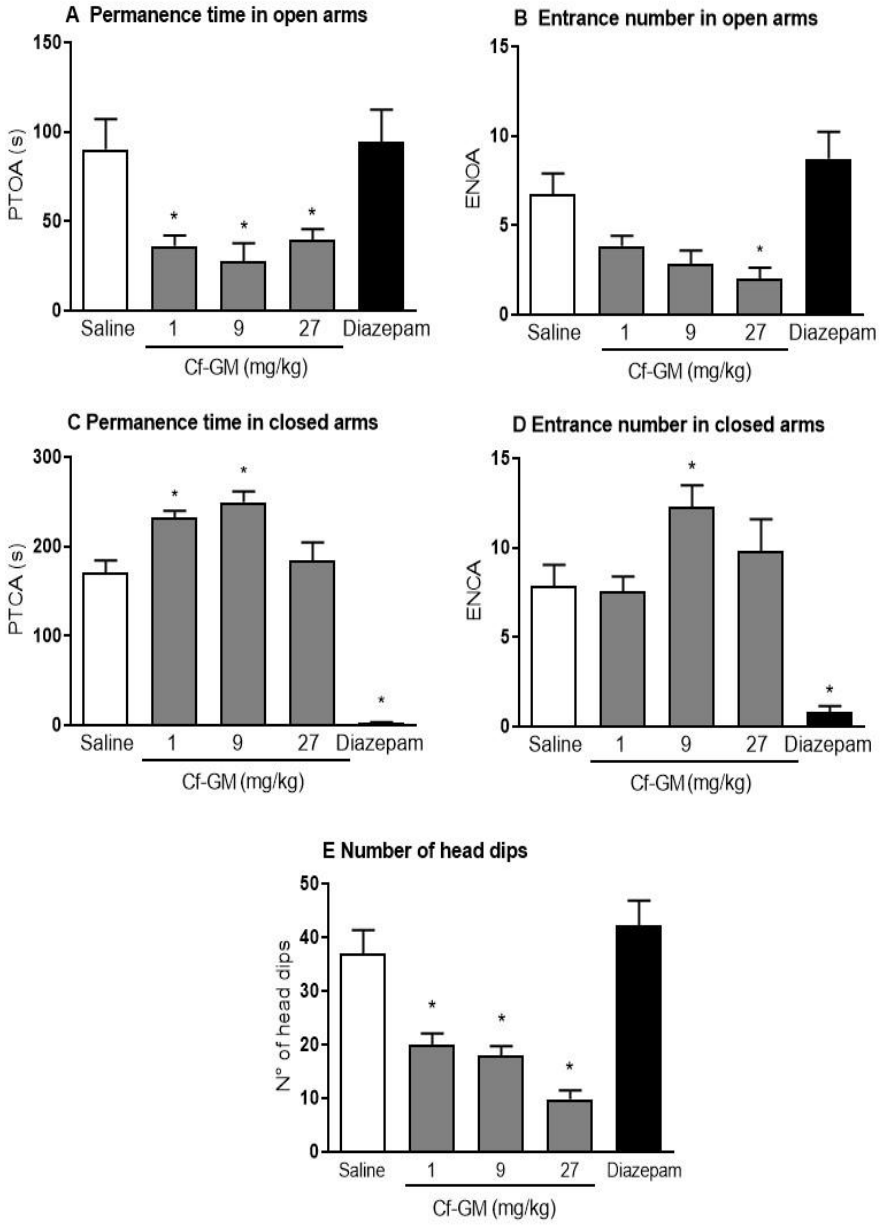
entrance number at the dose of 27 mg/kg (2 ± 0.63; p = 0.0217) by 72% *versus* saline (7.16 ± 0.98) with F value (F [4.30] = 7.421) **(Figure 2A/B**).

However, in the closed arms, Cf-GM increased both the permanence time by 36% (1 mg/kg: 231.9 ± 7.82 s; p= 0.0033) and 46% (9 mg/kg: 249.3 ± 12.02 s; p = 0.0003) *versus* saline (170.9 ± 13.27 s) with F value (F [4.29] = 64.57), and the entrance number by 56% only at 9 mg/kg (12.29 ±1.20; p = 0.0288), compared to saline (7.87 ± 1.17) (F [4.29] = 12.67) (**Figure 2C/D**). The anxiolytic drug diazepam at 1 mg/kg (group 5) reduced the permanence time (2.85 ± 0.63 s; p = 0.0006) and the entrance number (0.83 ± 0.30; p < 0.0001) in the closed arms but did not alter these behaviors in the open arms.

3.2.2. HOLE BOARD TEST

Cf-GM at all doses reduced the number of head dips: 1 mg/kg (20.00 ± 2.04; p = 0.0094) reduced by 46%, 9 mg/kg (18.00 ± 1.69; p = 0.0032) reduced by 51% and 27 mg/kg (9.85 ± 1.61; p < 0.0001) with 73 % compared to saline (37.00 ± 4.34), with F value (F [4.27] = 21.41) (**Figure 2E**). The anxiolytic drug diazepam at 1 mg/kg did not alter this behavior.

Figure 2- Inhibitory effect of Cf-GM in the elevated plus maze and hole board tests



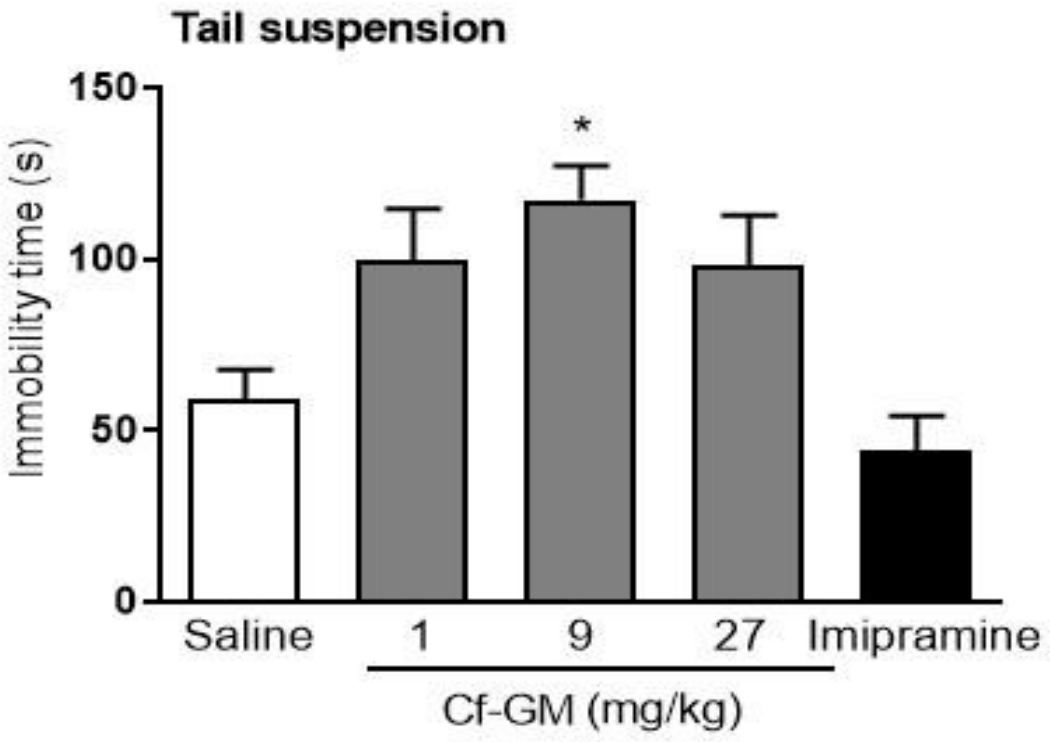
The elevated plus maze and hole board tests. (A-D) Elevated plus maze: (A) Permanence time in the open arms (PTOA); (B) Entrance n° in the open arms (ENOA); (C) Permanence time in the closed arms (PTCA); (D) Entrance n° in the open arms (ENCA). (E) Hole board test: n° of head dips Mice received I.p Cf-GM (1, 9, 27 mg/kg), diazepam (1 mg/kg) or Saline 30 min before evaluation. Mean ± SEM (n= 8). One -way ANOVA followed by Dunnett´s and Tukey´s post-hoc tests. *p<0.05 *vs.* Saline. Cf-GM: *C. ferrea* galactomannan. Source: Researcher's result 2024.

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4.3. Cf-GM INCREASES IMMOBILITY TIME IN THE TAIL SUSPENSION TEST

Cf-GM increases immobility time in the tail suspension test Cf-GM (9 mg/kg) increased by 49% (F [4.26 = 5.868]) the immobility time (117.2 ± 10.06 s vs. saline: 59.71 ± 8.50 s) with p = 0.0163, while the tricyclic antidepressant imipramine at 10 mg/kg (group 7) did not alter this behavior (Figure 3).

Figure - 3 Cf-GM increases immobility time in the tail suspension test



The tail suspension test. Mice received I.p. Cf-GM (1, 9, 27 mg/kg), imipramine (10 mg/kg) or Saline 30 min before evaluation. Mean ± SEM (n=8). One-way ANOVA followed by Dunnett´s post-hoc test. *p<0.05 *vs.* Saline. Cf-GM: *C. ferrea* galactomannan. Source: Researcher's result 2024.

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3.4. Cf-GM INCREASES DEATH LATENCY IN THE MODEL OF SEIZURES INDUCED BY PENTYLENETETRAZOLE.

Cf-GM caused no effect on seizure latency but increased the death latency at 27 mg/kg (F [4.43] = 7.884; p= 0.0126), and animals survival at 9 and 27 mg/kg compared to saline. The anticonvulsant drug diazepam at 1 mg/kg showed protective effect on the seizure and death latencies (Table 1).

Table 1-Cf-GM increases death latency in the model of seizures induced by pentylenetetrazole

Treatment (mg/kg)	Seizures latency (s)	Convulsed animals (%)	Death latency (s)	Survival (%)
Saline	53.5 ± 3.79	100	229.3 ± 45.39	00
Cf-GM (1)	74.7 ± 4.79	100	374.6 ± 116.9	00
Cf-GM (9)	84.2 ± 6.03	100	494.9 ± 98.74	10
Cf-GM (27)	82.4 ± 14.3	100	786.3 ± 129.1*	50
Diazepam (1)	121.1 ± 12.7 *	100	1046 ± 101.4*	60

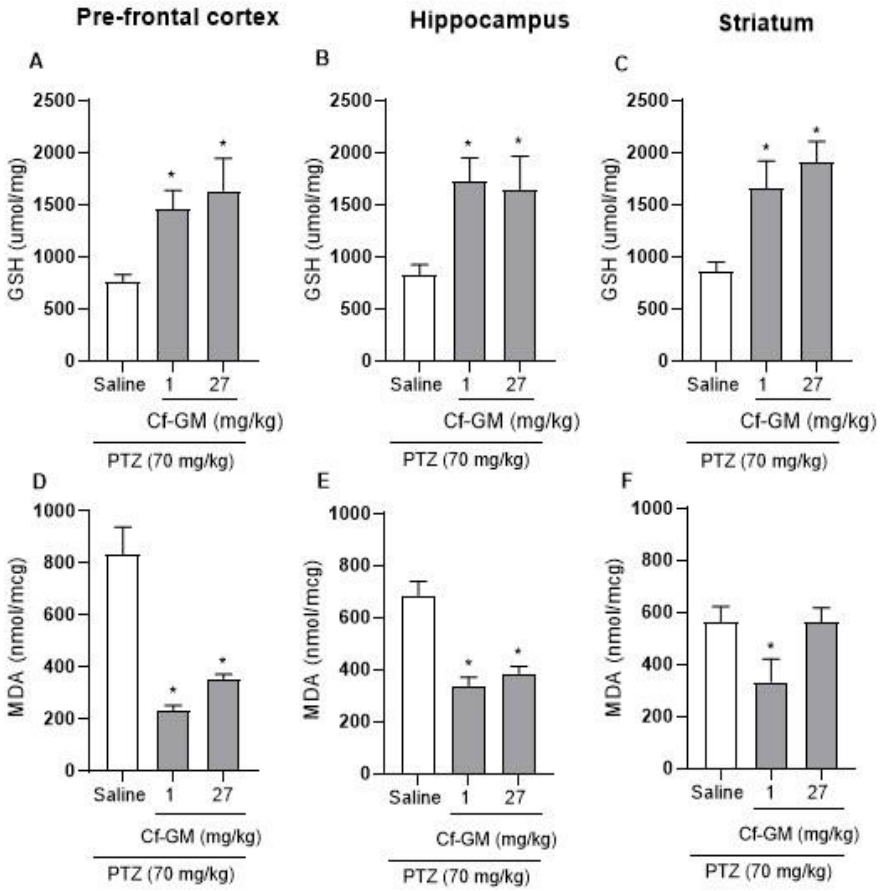
Note: *p<0.05 *vs.* Saline (n=10). [1] Cf-GM: *C. ferrea* galactomannan. One-way ANOVA followed by Tukey´s post-hoc test. Source: Researcher's result 2024.

3.5 Cf-GM REDUCES MDA AND INCREASES GSH IN MICE BRAIN AREAS IN THE MODEL OF SEIZURES INDUCED BY PENTYLENETETRAZOLE

MDA was reduced by Cf-GM in PFC at this doses: 1 mg/kg (72% - 230.8 ± 22.42; p < 0.0001), 27 mg/kg (58% - 351.5 ± 20.22; p< 0.0001) *vs*. PTZ: 832.9 ± 104.3 nmol/mg, with F value (F [2.20]= 35.07), HC: 1 mg/kg (51% - 336.1 ± 34.82; p< 0.0001), 27 mg/kg (44% - 385.7 ± 27.57; p = 0.0002) *vs.* PTZ: 685.4 ± 54.48 nmol/mg (F [2.21]= 21.42), and ST : 1 mg/kg (41% - 332.9 ± 29.27 *vs*. PTZ: 562.8 ± 59.84 nmol/mg) with p = 0.009 and F value (F [2.24]= 7.034) (Figure 4A/C). On the other hand, GSH was increased at the same doses by Cf-GM in PFC: 1 mg/kg (48% - 1456 ± 182.3; p=

0.0256), 27 mg/kg (53% - 1636 ± 313.2; p= 0.0067) *vs.* PTZ: 756.7 ± 73 71 µmol/ml (F [2.23]= 7.019), HC: 1 mg/kg (52% - 1733 ± 220.1; p= 0.0191), 27 mg/kg (50% - 1641 ± 327.5; p= 0.0364) *vs.* PTZ: 826.2 ± 99.98 µmol/ml (F [2.20]= 5.632), and ST: 1 mg/kg (48% - 1658 ± 264.00; p = 0.0134), 27 mg/kg (55% - 1909 ± 202.3; p=0.0019) *versus* PTZ: 863.0 ± 91.01 µmol/ml (F [2.22]= 9.033) (Figure 4D/F).

Figure 4- Cf-GM reduces the brain content of MDA and increases that of GSH in pentylenetetrazole-induced seizures



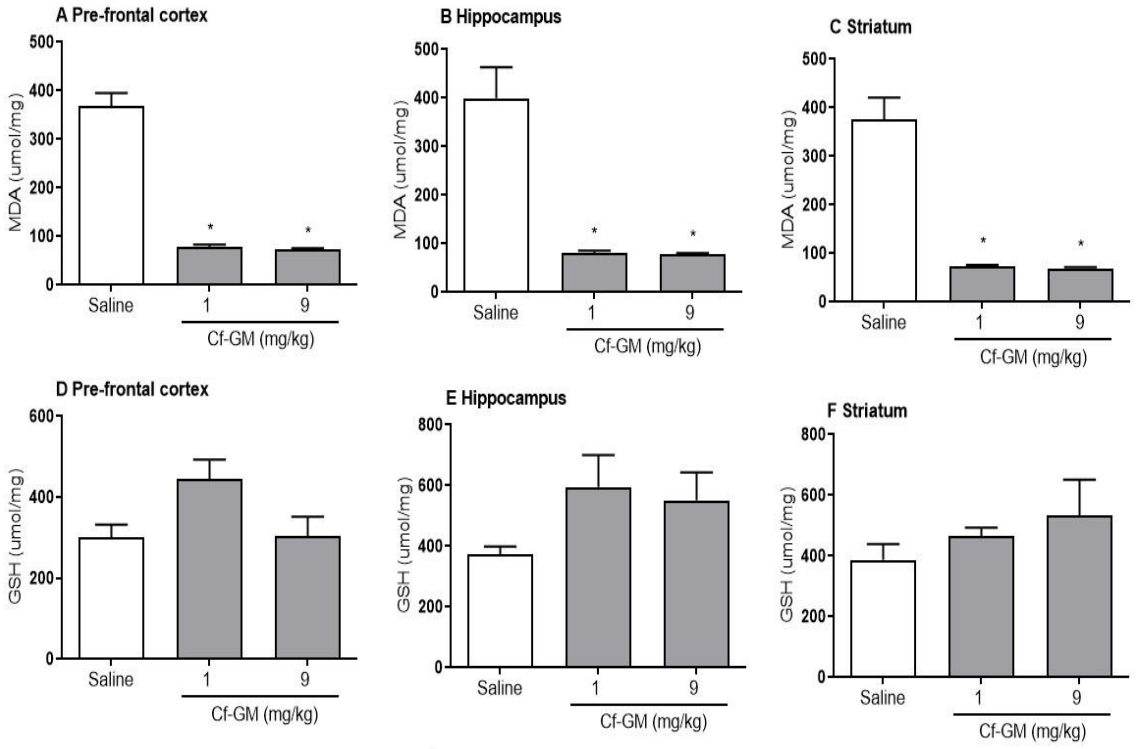
Oxidative stress. (A-C) MDA; (D-F) GSH in Pre-frontal cortex, Hippocampus and Striatum. Mice received I.p. Cf-GM (1, 27 mg/kg) 30 min before pentylenetetrazole (PTZ) (70 mg/kg). Mean ± SEM (n=8). One-way ANOVA followed by Dunnett´s post-hoc test. *p<0.05 *vs* PTZ. Cf-GM: *C. ferrea* galactomannan; PTZ: pentylenetetrazole. PFC: Pre-frontal cortex. HC: Hippocampus. ST: Striatum. Source: Researcher's result 2024.

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3.6. CF-GM PER SE REDUCES MDA BUT DOES NOT ALTER GSH IN MICE BRAIN AREAS

Cf-GM reduced MDA in PFC: 1 mg/kg (79% - 78.39 ± 4.96), 9 mg/kg (81% -74.41 ± 1.57) *vs.* saline: 368.80 ± 26.47 nmol/mg (F [2.19]= 126.8), HC: 1 mg/kg (80%- 81.46 ± 4.49), 9 mg/kg (80% - 77.53 ± 3.55) *vs.* saline: 399.2 ± 64.12 nmol/mg (F [2.18]= 24.71) , and ST: 1 mg/kg (80% - 73.55 ± 2.89), 9 mg/kg (81% - 69.74 ± 2.06) *vs.* saline: 375.7 ± 45.20 nmol/mg (F [2.20]= 41.98) , all with p value < 0.0001 (Figure 5A/C). However, GSH was not altered at any brain area (Figure 5D/F).

Figure 5- Cf-GM per se reduces the brain content of MDA



Oxidative stress. (A-C) MDA;(D-F) GSH in Pre-frontal cortex, Hippocampus and Striatum. Mice received I.p. Cf-GM (1, 9 mg/kg) or Saline 30 min before evaluation. Mean ± SEM (n=8). One-way ANOVA followed by Dunnett´s post-hoc test. *p<0.05 vs. Saline. Cf-GM: C. ferrea galactomannan.

Source: Researcher's result 2024.

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4. DISCUSSION

This study demonstrated central inhibitory behavior of Cf-GM in the open field, elevated plus maze, hole board and tail suspension tests, and in the model of pentylenetetrazole-induced seizures, modulating biomarkers of oxidative stress. The central inhibitory effect was seen in the open field test by the reduction in the number of crossings and rearing. These data are in accordance with those demonstrated in the tail suspension test, useful to the screening of antidepressant drugs (Can *et al*., 2019), in which Cf-GM (9 mg/kg) increased the animal's immobility time, suggesting depressive behavior. However, Cf-GM did not alter the grooming in the open field. This data seems to be contradictory, although it is accepted in the literature that this behavior is altered only in presence of a stressor stimuli, at least in rats (Van Erp *et al*., 1994). In this study, it was also demonstrated that Cf-GM presents stimulant-like effect either in the elevated plus maze (reduction of permanence time and number of open rms entries) as in the hole board (reduction in the number of head dips), specific tests to evaluate anxiety behavior. In fact, the inhibitory behavior in exploratory activity indicates indirect effect on anxiety (Prut & Belzung, 2003), reinforcing the anxiogenic effect of CF-GM. These data are in accordance to other behavioral studies using plant polysaccharides (Nonato *et al*., 2018; Manoj & Sasmal, 2014; Yang *et al*., 2013). In the model of PTZ-induced seizures, Cf-GM (27 mg/kg) was protective, increasing the latencies of death and animal's survival. In line with these, the aqueous extracts of *Albizia glaberrima* (Adebisi, Akindele & Adeyemi, 2015) and *Ebenus stellate* (Khodaparast, Sayyah & Sardari, 2011) presented anticonvulsant effect in this model. However, Cf-GM caused no significant effect on seizure latency. It is well known that free radical production is associated with damage to cellular structures in pathological conditions of the central nervous system, such as Parkinson's disease, stroke, dementia and epilepsy (Adibhatla & Hatcher, 2008). In this context, the literature has reported protective effects of plant polysaccharide extracts in several experimental models: a) reperfusion ischemia - *Euphoria longa* fruits (Can *et al*., 2019), *Ginkgo biloba* leaves (Yang *et al*., 2013), *Angelica sinensis* roots (Ai *et al*., 2013); b) strychnine- and PTZ-induced seizures - G*enipa americana* leaves (Nonato *et al*., 2018); c) cognitive impairment induced by D-galactose - *Millettia pulchra* (Lin *et al*.,

2014). Accordingly, in the model of PTZ-induced seizures Cf-GM reduced MDA content and increased GSH in all brain areas (CPF, HP, CE). Besides, Cf-GM *per se* showed protective effect via reduction of the oxidative marker MDA in all brain areas, without alteration of the antioxidant marker GSH. The antioxidant effect had been already demonstrated for chemically sulfated galactomannan of plant origin (Marques *et al*., 2015).

5. CONCLUSION

Cf-GM exhibits protective effects, explained by the inhibitor effect exhibits in behavioral tests, modulating biomarkers of oxidative stress in the mice model of pentylenetetrazole-induced seizures.

Thus, to fulfill the enormous pharmacotherapy lacunae in this field, the main contribution of this study was to suggest the potential application of Cf-GM for-patients during seizure crisis. We emphasize that this research, although relevant, has some limitations, since animal models exhibit varied responses based on genetic and environmental factors that may impact the reproducibility of the results. Moreover, further clinical studies are necessary to confirm the findings in animal models.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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