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Original Research Article

Modulation of the Indices of Psychosis in Post-Convulsive Status Epilepticus Model: The Role of Proanthocyanidin-Rich Fraction

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ABSTRACT

Vitis vinifera seed contains high content of flavonoids particularly, proanthocyanidins. Experimental studies have demonstrated the anticonvulsant potency of Proanthocyanidins-Rich Fraction (PRF). However, this study was designed to evaluate the psychotropic activities of PRF in the post-convulsive status epilepticus (CSE). Six groups of juvenile rats were kindled for the seizure; 24 hours later, the survived rats were post-treated intraperitoneally with propylene glycol (PG), 0.1 or with graded doses of PRF (30 mg/kg, 20 mg/kg, or 10 mg/kg body weight [BW]) or diazepam (DZP) (5 mg/kg BW) for a period of one week. Three weeks after the last treatment, both the control and post-convulsed rats were examined for the markers of depression, anxiety, and muricidal actions. they were kept untreated but with access to feed and water for 21 days. There was a significant increase in the markers of anxiety-like behavior, locomotor activities, and depression-related behavior in the post-CSE rats compared with the control. The post-CSE rats exhibited impairment in societal interaction, evidenced by muricidal actions. Additionally, there was a significant increase in depression-related behavior, especially in the anhedonia test. However, all these aberrations were attenuated following PRF treatment, a result similar to what is obtained in the diazepam treatment group.
Conclusively, proanthocyanidins-rich-fraction from *Viti's vinifera seed* attenuates the markers of psychosis following CSE in juvenile Wistar rats.

***Keywords*:** Convulsive status epilepticus, Anxiety, Depression, Social interaction, Proanthocyanidins.

Introduction

Psychotic disorders remain one of the debilitating co-morbidities of epilepsy; even though it affects a relatively rare population, it is a very serious psychiatric disorder.[1] The relationship between these two conditions (psychosis and epilepsy) has attracted the interest of not only clinicians but also medical scientists, artists, novelists, etc. owing to manifestations of diverse psychiatric signs such as dementia, hallucinations, irritability, and even, violence.[1,2] About 41% of people with epilepsy are presented with psychiatric and somatic disorders[3,4] thus, patients with epilepsy have increased vulnerability to psychiatric co-morbidity.[5,6] Temporal lobe epilepsy is reportedly associated with higher levels of psychiatric comorbidity. Regarding seizure types, partial seizures were associated with a higher prevalence of depression vs generalized seizures.[1,7] Interictal psychosis occurs in clear consciousness in persons suffering from epilepsy at temporal onset not during or immediately following a seizure; it often starts after several years of the active temporal lobe of temporal lobe epilepsy.[8]

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Studies have shown a strong link between temporal lobe epilepsy and the cerebral hemisphere in interictal psychosis.[9,10] Accumulating literature showed that all forms of psychosis (chronic, acute, interictal, and postictal) are arguably represented in patients with epilepsy which are not unrelated to the manifestation of hallucinations, aggression, and disorders of thought, to mention but a few.[11,12] Despite the fact that this seizure-induced psychiatry anomaly, particularly post-ictal psychosis is treatable and may be averted if pre-symptomatic risk factors are considered[13], it is worrisome that many of the established antipsychotic drugs are not without one adverse effect or the other. [6,12] However, based on previous reports on the central nervous system effects of flavonoids[13] and especially proanthocyanidins,[14,15] this present study was designed to evaluate the indices of psychosis in the post-convulsive status epilepticus mice model.

Materials and Methods

Plant material

The air-dried powdered seed of *Vitis vinifera* was procured from the Wuhan Venz Pharm., China. The extraction method and characterization of proanthocyanidin in the proanthocyanidin-rich-fraction (PRF) were carried out as reported in our previous study.[15]

Ethical approval

Approval to carry out the study was obtained from the Health Research Ethics Committee, Institute of Public Health, Obafemi Awolowo University, Ile –Ife, with identification number IPH/OAU/12/1061, in line with the National Institute of Health (NIH)

in the "Guild to the care and use of animals in Research and Teaching".[16]

Drugs
Lithium chloride (CAS No 7447-41-1, Kem Light Laboratory, India), pilocarpine hydrochloride (CAS P6503-5G), and diazepam (CAS Number 439-14-5) Sigma-Aldrich Co. USA) were used for this study.

Animals
A total of one hundred juvenile Wistar rats (Age: 3-4 weeks old) from the Animal Holdings, College of Health Sciences, Osun State University, Osogbo, Nigeria were recruited and subjected to various behavioural studies. The animals were kept in a well-ventilated room under natural light/dark cycle with free access to commercially available rodents' diet (Ground Cereals Nigeria LTD) and drinking water ad-libitum. Group 1 rats (n=7) propylene glycol (PG) (0.1ml) intraperitoneally (i.p), while groups 2-6 (n = 15 each) received lithium-chloride (127 mg/kg i.p) 24 hours before they were convulsed with pilocarpine-hydrochloride (40mg/kg i.p) administration. The progression of seizure activity was monitored, video recorded (video camera DS126311; Canon Inc., Tokyo Japan), and graded according to the Racine scale. while the animals' maximal behavioral response (i.e., stage 5 of the Racine scale) was considered as CSE. [17] However, three hours after the onset of seizure, group 1 rats (non-epileptic) received intraperitoneal treatment of PG (0.1ml), while the post- CSE rats in groups 2-6 received PG (0.1 ml i.p), or proanthocyanidin-Rich-Fraction PRF (30 mg/kg i.p), or PRF (20 mg/kg i.p) or PRF (10 mg/kg i.p) or diazepam (DZP) (5 mg/kg i.p) once daily for a period of one week.[15] After the last dose, the rats were kept untreated for another 21 days but were given access to feed and water *ad-libitum*. Twenty-four hours later, the post-convulsed rats were subjected to societal, depressive, and anxiety-related behavioral tests and were monitored with video camera (DS126311; Canon Inc., Tokyo Japan) in order to avoid human interference.

Behavioural tests
Anxiety-like behaviour and locomotor activity tests were determined as earlier described by Inostroza *et al.*[18]

Societal behavior
The societal interaction was evaluated according to the method of Inostroza *et al.*[18]

Muricidal actions
The rats were placed inside the observation cage (30cm by 30cm by 25cm) inside which a smaller cage (6cm by 6cm by 15cm) that contained a mouse was placed in a definite corner of the bigger cage. The number of aggressive attacks that the rats made on the mouse were recorded as a measure of the muricidal effect of the PRF treatment following CSE.[19]

Depression related behavior
Anhedonia tests
This study was carried out according to the previous method of examination by Inostroza *et al.*[18] Moreover, the quantity of food intake was determined according to the method of Villar *et al.*[20] Pre-weighed pelletized feed (ground cereals, a subsidiary of UAC Nigeria limited) was provided in standard stainless-steel hoppers on the 7th, 14th, 21st, and 28th days of post-CSE. After 24 h, the individual rat was removed from their isolated cages and the weight of remaining feed including any crumps on the bottom of the cages was determined. Intake was calculated as the weight (in grams) of feed provided less than recovered

Animal sacrifice and determination of serum corticosterone concentration
At the end of the behavioral studies, all the rats were euthanized by cervical dislocation. Blood collected in plain sample bottles was spun in a cold centrifuge at 3000 rpm for 10 minutes to obtain clear serum. Thereafter, serum corticosterone concentration was determined using the tube-based enzyme immune assay (EIA) method with the aid of an EIA kit (Inteco Diagnostics Ltd., United Kingdom). The within assay variation was 8.1% and the sensitivity was 0.3ng/mL. The optical density was read using multiple spectrometers at a wavelength of 450nm.

Statistical analysis
Data were analyzed using descriptive and inferential statistics, and the control and test groups were compared using one-way analysis of variance (ANOVA), and Student-Newman-Keuls post hoc analysis where appropriate. The results were presented as mean ± SEM in graphs while P-value less than 0.05 was considered significant.

Results and Discussion

Effects of PRF obtained from Vitis vinifera seed on anxiety-related behavior in the post-CSE Wistar rats
There was significant increase (p = 0.0005) in the exploratory activities of CSE + NS, and CSE + PRF 10 mg/kg treatment groups, while the PRF 30 mg/kg, PRF 20 mg/kg, and DZP treatments had no significant (p = 0.5301) effect compared with the control. However, treatment with PRF 30 mg/kg, PRF 20 mg/kg, and DZP decreased (p = 0.0001) the exploratory activities relative to the CSE + PG. Besides, exploratory activities decreased (p = 0.0028) in the CSE + DZP treatment group compared with CSE + PRF 10 mg/kg (Figure 1).

Time spent in the center of the open field
The total time spent in the center of the open field increased significantly (p = 0.0001) following CSE compared with the control. Treatment of post- CSE rats with PRF 30 mg/kg, PRF 20 mg/kg, and DZP decreased (p = 0.0009) the time spent in the center of the open field compared with CSE + NS, while DZP treatment increased (p = 0.0185) the time spent in the center of the field compared with the PRF 10 mg/k treated post CSE rats (Figure 2).

Time spent in the open arm of the elevated plus-maze
The time spent in the open arm by the CSE + NS, and CSE + PRF 10 mg/kg treatment groups increased significantly (p = 0.0025), while PRF 30 mg/kg, PRF 20 mg/kg, and DZP treatments had no significant (p = 0.1774) effect compared with the control (Figure 3).

Time spent in the closed arm of the elevated plus-maze
In this study, the time spent in the closed arm by the post-CSE rats decreased significantly (p = 0.0015), while that of CSE + PRF 30 mg/kg, CSE + PRF 20 mg/kg, and CSE + DZP had no significant difference (p = 0.9636) compared with the control (Figure 4). while there was no significant difference (p = 0.8581) in the CSE + PRF 30 mg/kg and CSE + DZP treatment groups compared with the control. However, the serum concentration decreased significantly (0.0171) in the CSE + DZP compared with the CSE + PRF 10 mg/kg treatment group (Figure 11).

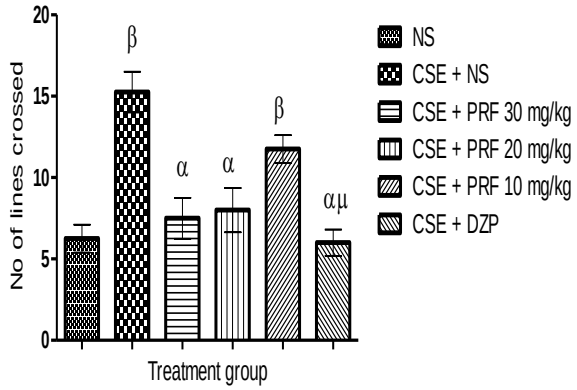

Figure 1: Effects of PRF obtained from *Vitis vinifera* seed on exploratory behaviour in the post-CSE Wistar rats
β: increase compared with the control (p = 0.0005); α: decrease compared with CSE + NS (p = 0.0001); μ: decrease compared with CSE + PRF 10 mg/kg (p = 0.0028).

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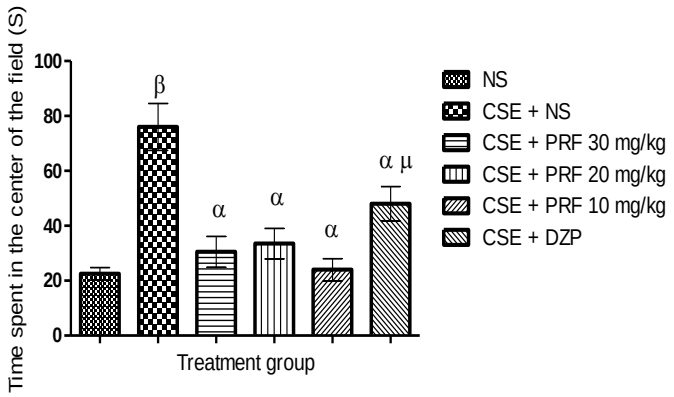

Figure 2: Effects of PRF obtained from *Vitis vinifera* seed on time spent in the center of the open field by the post-CSE Wistar rats.
β: increase compared with the control (p = 0.0005); α: decrease compared with CSE + NS (p = 0.0001); μ: decrease compared with CSE + PRF 10 mg/kg (p = 0.0028).

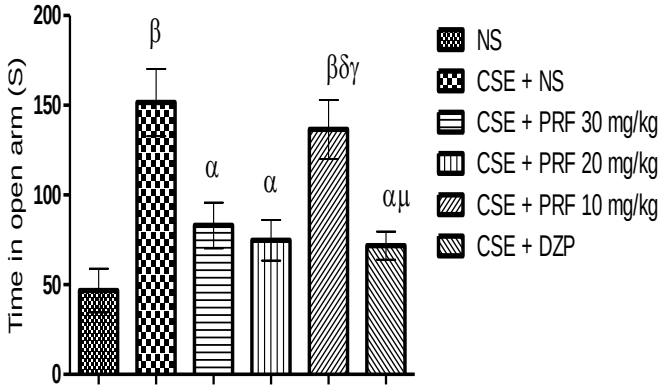

Figure 3: Effects of PRF obtained from *Vitis vinifera* seed on the time spent in the open arm of the elevated plus maze CSE rats in the elevated plus maze.
β: increase compared with the control (p = 0.0002); α: decrease compared with CSE + NS (p = 0.0019); δ: increase compared with CSE + PRF 30 mg/kg (p = 0.0422); ϒ: decrease compared with CSE + PRF 20 mg/kg (p = 0.0212); μ: decrease compared with CSE + PRF 10 mg/kg (p = 0.0117).

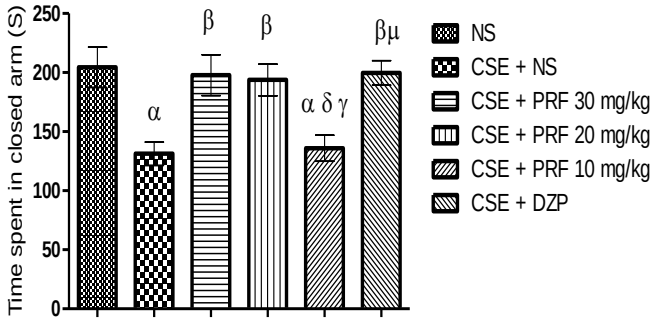

Figure 4: Effects of PRF obtained from *Vitis vinifera* seed on the time spent in the closed arm by the post-CSE rats in the elevated plus maze.
β: increase compared with the CSE + PG (p = 0.0002); δ: decrease compared with CSE + PRF 30 mg/kg (p = 0.0238); ϒ: decrease compared with CSE + PRF 20 mg/kg (p = 0.0162)
μ: increase compared with CSE + PRF 10 mg/kg (p = 0.0057)
Total number of the cross made in the elevated plus-maze

In this study, the number of crossings on the elevated plus-maze increased significantly (p = 0.0001) following CSE. This was however decreased (p = 0.0004) by PRF, and DZP treatment compared with the CSE + NS. Additionally, the number of crossings made by the CSE + DZP treatment group decreased significantly (p = 0.0009) relative to the PRF treated post-CSE rats (Figure 5).

Time in the center of the elevated plus-maze
The time spent in the center by the CSE + NS, and CSE + PRF 10 mg/kg decreased significantly (p = 0.0155), while this remained statistically unchanged (p = 0.9142) in the CSE + PRF 30 mg/kg, CSE + PRF 20 mg/kg, and CSE + DZP treatment groups compared with the control. However, the time spent in the center by the CSE + DZP increased significantly compared with CSE + PRF 10 mg/kg (Figure 6).

Effects of PRF obtained from Vitis vinifera seed on the societal behavior by the post-CSE Wistar rats
Social interaction
There was a decrease in the exploration ratio of the unfamiliar rat (p = 0.0001) compared with the control. Also, the exploration ratio increased significantly (p = 0.0027) in the PRF 30 mg/kg, PRF 20 mg/kg, and DZP treatment groups, while CSE + PRF 10 mg/kg remain statistically indifferent (p = 0.2051) compared with the CSE + NS rat (Figure7).

Muricidal action
In this study, there was a significant (p = 0.0224) increase in the number of muricidal action (aggressive attack) exhibited by the CSE + NS treatment group, while CSE + PRF 10 mg/kg treatment had no significant (p = 0.4169) effect compared with the control. However, treatment with PRF or DZP following CSE decreased (p = 0.0001) the number of muricidal action relative to the CSE + NS treatment group. Additionally, there was no significant (p = 0.0739) difference in the number of aggressive attacks between the CSE + NS and CSE + PRF 10 mg/kg treatment groups (Figure 8).

Effects of PRF obtained from Vitis vinifera seed on depression-related behavior
Anhedonia in the post-CSE Wistar rats; In this study, the percentage sucrose preference to water decreased significantly (p = 0.0004) in the CSE + NS, CSE + PRF 20 mg/kg, and CSE + PRF 10 mg/kg, while this remains significantly indifferent (p = 0.0004) in the CSE + PRF 30 mg/kg, and CSE + DZP compared with the control (Figure 9).

Assessment of the quantity of food intake) in the post-CSE Wistar rats
The quantity (g) of food consumed by the post CSE + NS rats decreased significantly (p = 0.01, 0.001, 0.001, 0.001) on the 7th, 14th, 21st, and 28th day respectively compared with the control. The quantity of food consumed by the post CSE + PRF 30 mg/kg and CSE + PRF 20 mg/kg groups had no significant change (p = 0.057) as at the 7th and 14th day but decreased significantly (p = 0.01) on the 28th day compared with the control. However, there was a significant (p = 0.01) decrease in the quantity (g) of food intake by the post CSE + PRF 10 mg/kg relative to the control, while there was no significant (p = 0.059) difference in the quantity (g) of food intake between the post CSE + DZP and the control rats. Additionally, the quantity (g) of food intake increased significantly (p = 0.001) by the post CSE + PRF 30 mg/kg, and CSE + DZP groups relative to CSE + PG treated rats. There was no significant difference (p = 0.051) in the quantity (g) of food intake among the PRF treated post CSE rats and between the post-CSE + PRF 30 mg/kg and CSE + NS treatment group. However, the food intake by the post CSE + DZP treatment group increased significantly (p = 0.01) compared with the post CSE + PRF 20 mg/kg and CSE + PRF 10 mg/kg treated rats (Figure 10).

Effects of PRF obtained from Vitis vinifera seed on the serum concentration of corticosterone in the post-CSE Wistar rats
The serum concentration of corticosterone increased significantly (p = 0.0002) in the CSE + PRF 20 mg/kg, and CSE + PRF 10 mg/kg,

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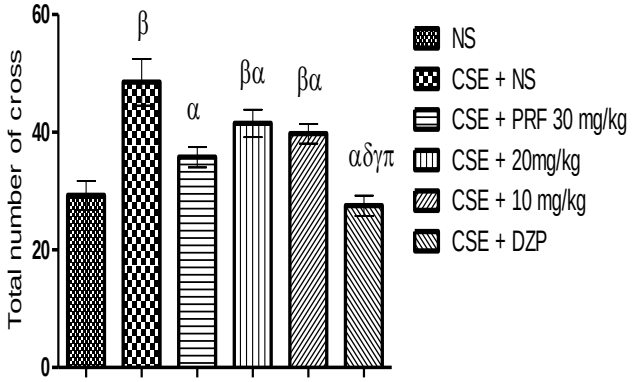

Figure 5: Effects of PRF obtained from *Vitis vinifera* seed on the total number of cross by the post-CSE rats in the elevated plus maze.
δ: decrease compared with CSE + PRF 30 mg/kg (p = 0.0141); ϒ: decrease compared with CSE + PRF 20 mg/kg (p = 0.0029); π: decrease compared with CSE + PRF 10 mg/kg (p = 0.0021).

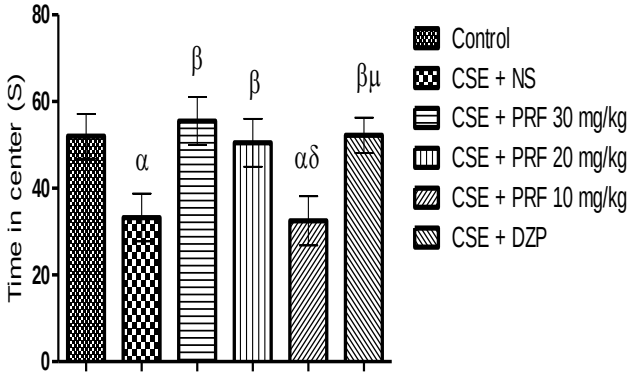

Figure 6: Effects of PRF obtained from *Vitis vinifera* seed on the time spent in the center of the elevated plus maze by the post-CSE rats.
β: increase compared with the CSE + NS (p = 0.0155); δ: decrease compared with CSE + PRF 30 mg/kg (p = 0.0270); μ: decrease compared with CSE + PRF 10 mg/kg (p = 0.0299)

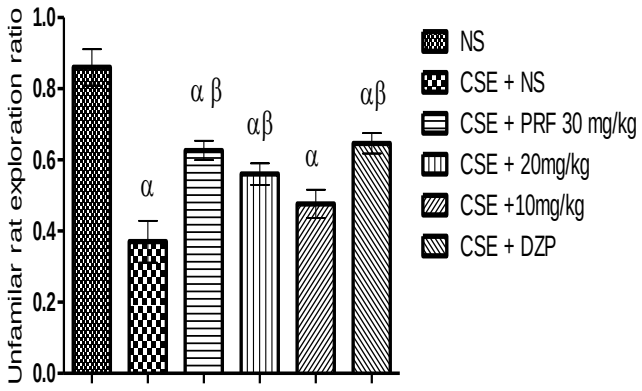

Figure 7: Effects of PRF obtained from *Vitis vinifera* seed on social interaction by the post-CSE Wistar rats.
α: decrease compared with the control (p = 0.0001); β: increase compared with the CSE + NS (p = 0.0027).

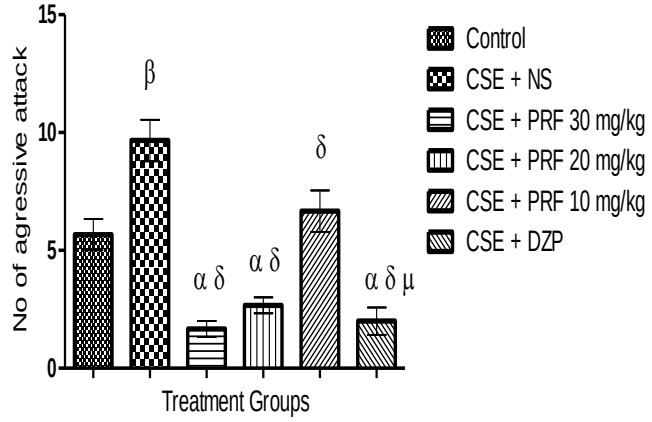

Figure 8: Effects of PRF obtained from *Vitis vinifera* seed on muricidal action by the post-CSE Wistar rats.
β: increase compared with the control (p = 0.0224); α: decrease compared with control (p = 0.0001); δ: decrease compared with CSE + PG (p = 0.0001); μ: decrease compared with CSE + PRF 10 mg/kg (p = 0.0114)

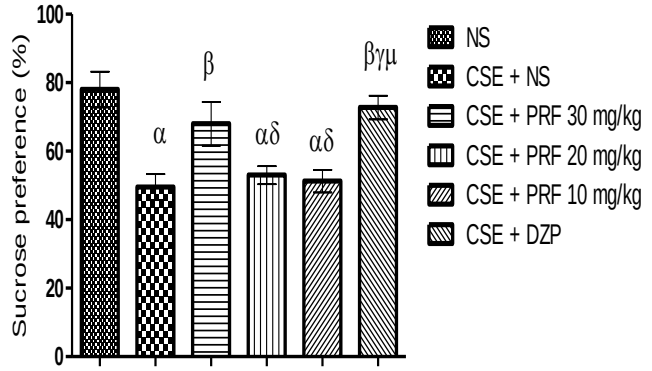

Figure 9: Effects of PRF obtained from *Vitis vinifera* seed on anhedonia in the post-CSE Wistar rats.
α: decrease compared with control (p = 0.0004); β: increase compared with CSE + PG (p = 0.0026); δ: decrease compared with CSE + PRF 30 mg/kg (p = 0.0071); μ: increase compared with CSE + PRF 10 mg/kg (p = 0.0041.

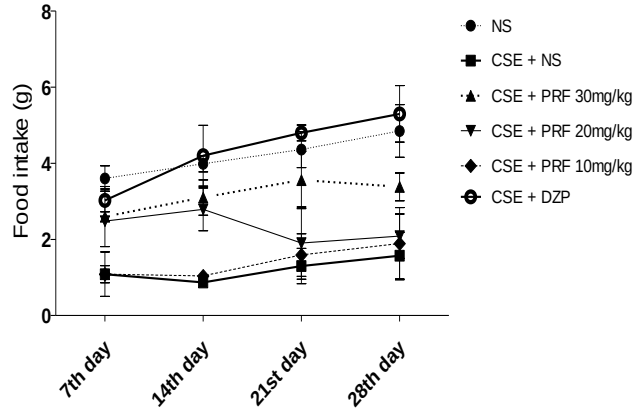

Figure 10: Effects of PRF obtained from *Vitis vinifera* seed on feed intake by the post-CSE Wistar rats.
Graded doses of PRF (30 mg/kg, 20 mg/kg, 10 mg/kg) or reference drug, DZP were administered for 7 days following the establishment of CSE. The quantity of fluid intake was evaluated for 5 min as a marker of depression. Each value represents the mean SEM of 7-8 rats. P ≤0.05 as compared to saline (one-way ANOVA followed by Student-Newman-Keuls post hoc analysis).

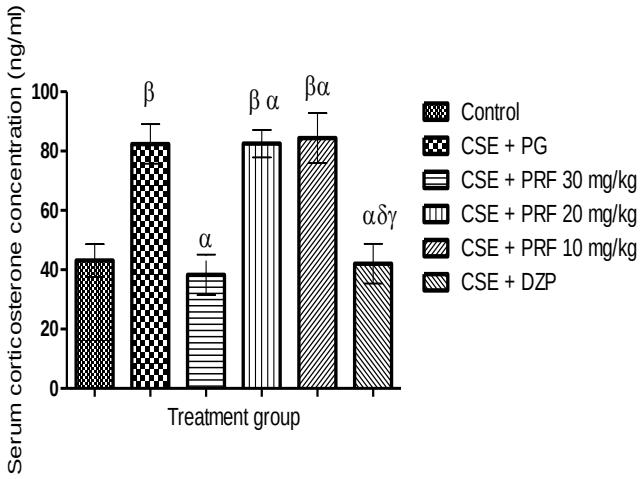

Figure 11: Effects of PRF obtained from *Vitis vinifera* seed on the serum concentration of corticosterone in the post-CSE Wistar rats**.**

β: increase compared with the control (p = 0.0002). α: decrease compared with CSE + NS (p = 0.0007); δ: decrease compared with CSE + PRF 20 mg/kg (p = 0.0077); ϒ: decrease compared with CSE + PRF 10 mg/kg (p = 0.0171).

Findings from both clinical and experimental studies confirmed various forms of behavioural disruption among people living with epilepsy and epileptic rodents.[6,21,22] In this present study, however, data from the open field test in the CSE + NS, and CSE + PRF 10 mg/kg groups revealed an increased exploratory activity and time spent in the central zone compared with the control. This is a suggestive indication of disinhibited behavior as one of the c onsequential effects of CSE. Cardoso *et al*[23] and Inostroza *et al.*[18] repo rted that 'temporal lobe epilepsy models induce extensive lesions of the ventral & dorsal hippocampus without exception to the amygdaloid nucleus, especially in lithium pilocarpine treated animals. It will be recalled that the dorsal and ventral hippocampus controls cognition, stress, emotion, and affection, while the amygdala plays **a** role in the sense of smell, motivation, and emotional behavior.[23,24] It can therefore be inferred that disinhibited behavior demonstrated by the epileptic rats in this study is the reflection of the damage to the limbic system following the period of CSE. This is in agreement with the previous report of Inostroza[18] that Ventral lesions of the hipp ocampus can alter unconditioned fear responses to threatening situatio ns. However, treatment with PRF decimated these disinhibited behaviors just as it was found in the DZP-treated CSE rats. Disinhibited behaviors observed in the CSE + NS, CSE + PRF 10 mg/kg, and to some extent in the CSE + PRF 20 mg/kg groups subjected to open field test are consistent with a significant increase in the time spent in the open arm, decrease time spent in the close arm, increased number of crossing and the total time spent in the center of the elevated plus-maze. The data from the open field and elevated plus-maze tests are suggestive pieces of evidence that CSE in rats did not induce anxiety-related behavior in contrast to the findings of Inostroza *et al*[18] and Smith *et al*[25] but may have damaged the neuronal network of the central nervous system (CNS) with evidence of impairment in the risk assessment and decision-making ability.

The exact mechanism through which PRF treatment abrogated these behavioral impairments is still ill-defined. However, previous studies have shown some of the pharmacological properties exhibited by catechins (one of the major phytoconstituents of proanthocyanidin), most importantly, its good affinities for the benzodiazepine (GABAA) receptor site with resultant anxiolytic, and sedative/ hypnotic actions.[25,26]

Social isolation and poor social adaptation among people living with epilepsy have been reportedly linked with fear of embarrassment from seizures, and perceived stigma leading to reluctance to engage in social interaction, with concomitantly low self-esteem.[27] The causes of poor social behavior among people living with epilepsy may be more compared to the submission of Hills, and Nabi *et al.*[28] It would be recalled that the area of the brain responsible for directing appropriate social behavior and interactions with others sits in the prefrontal cortex.[29] Therefore, impairment of social interaction following CSE may be due to depression. Surprisingly, the impairment in social interaction was attenuated in the PRF treated post CSE rats just as it was found in their DZP-treated counterparts. This finding was consistent with results obtained from the anhedonia (sucrose preference) test (Figure 8), and food intake (figure 9) test.

The muricidal behavior (aggressive behavior) exhibited by the epileptic rats in this study (Figure 8) confirms the report of Elnazer and Agrawal,[30] that 'there is an association between aggression and epilepsy which involves various neurophysiological and neurochemical disturbances. However, attenuation of aggressive behavior recorded in the PRF treatment groups, just as it was found in the standard drug (DZP) treatment groups, is attributable to the benzodiazepinergic effects of proanthocyanidin. This may be associated with the amelioration of the indices of depression (Figures 9 and 10) following PRF treatment. It would be recalled that depression and anxiety commonly lead to increased irritability, which can result in verbal or physical *aggression.* [30]

Seizures is often precipitated by uncontrolled stress. Stress hormones influence neuronal excitability and seizure susceptibility in preclinical epilepsy models.[41] In this study, CSE induced the release of cortisol but this was attenuated by the administration of PRF or DZP. This is probably because of the anticonvulsant effects of proanthocyanidin,[26] and DZP, which could have decimated the effects of the stress of hyperexcitation of the cerebral neurons on the corticotropic releasing hormone from the hypothalamus, which invariably might have reduced the release of adrenocorticotropic hormone in the anterior pituitary and eventually reduced the level of cortisol by the adrenal cortex, as it was evident in this study (Figure 10). Van-Campen *et al*[41] reported that a principal neuroendocrine system activated by stress is the hypothalamic-adrenal axis with its end product cortisol.

In this present study, data from the sucrose preference and food intake (anhedonia) tests suggest the consequential anhedonia effect of CSE. Anhedonia, a pronounced reduction in interest or pleasure in any of life's daily activities, is a cardinal symptom of major depression.[32] Although, the exact mechanism by which this was reverted by the PRF administration is not clear. However, the ability of flavonoids to directly modulate brain plasticity may be dependent on the accessibility of its metabolite (dihydroxylphenylvaleroacetone) to the brain.[43]

Conclusion

findings from this study reflect various aberrations in the behavioral indices following CSE rats' model. However, these behavioral anomalies were attenuated following PRF treatment just as it was found in the standard drug, diazepam treatment group. Therefore, it is necessary to further probe the mechanism of action of the PRF on the activity of glutamine synthetase, the concentration of some neurotransmitters, and the histomorphology of the limbic region of the brain.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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