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Original Research Article

Rutin and Vitamin C Improved Neurobehavioral Parameters and Cerebellar Cytoarchitecture in Monosodium Glutamate and Alcohol Induced Neurotoxicity in Male Wistar Rats

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Abstract: Toxins can alter the nervous system in ways that can disrupt or damage the brain or peripheral nervous system because of repeated exposure to natural or man-made toxic substances. The present study aims to investigate the neuro-behavioral and cytoarchitecture protective functions of rutin and vitamin C in monosodium glutamate and alcohol induced neurotoxicity in male Wistar rats. After two weeks of acclimatization, the animals were randomly selected into ten (10) groups with each group having five animals each (n=5). Neurotoxicity was induced with an oral single daily administration of 30% alcohol and 1.5g/kg body weight of Monosodium glutamate for 28 days consecutively in all rat groups except group1. The animals were subsequently treated as follows: **Group 1:** Control; animals in this group had free access to water and laboratory rat chow. **Group 2:** MSG only; animals in this group received no additional treatment after induction of neurotoxicity with a single daily administration of 1.5g/kg of MSG. **Group 3:** Alcohol only; animals in this group received no additional treatment after induction of neurotoxicity with a single daily administration of 30% alcohol. **Group 4:** MSG + Alcohol; animals in this group got no treatment after the induction of neurotoxicity with a single daily administration of 1.5g/kg of MSG and 30% alcohol. **Group 5:** MSG + Alcohol + Rutin; animals in this group received 30mg/kg of rutin following induction of neurotoxicity. **Group 6:** MSG + Alcohol + Vitamin C; animals in this group received 200mg/kg of vitamin C following induction of neurotoxicity. **Group 7:** MSG + Rutin; animals in this group received 30mg/kg of rutin following induction of neurotoxicity. **Group 8:** MSG + Vitamin C; animals in this group received 200mg/kg of rutin following induction of neurotoxicity. **Group 9:** Alcohol + Rutin; animals in this group received 30mg/kg of rutin following induction of neurotoxicity. **Group 10:** Alcohol + Vitamin C; animals in this group received 200mg/kg of Vitamin C following induction of neurotoxicity. The rats were subjected to behavioral checks through different Open field box checks for 5 minutes per animal to access frequency of movement and time spent at the center and peripheral areas of the field to ascertain anxiety and depressive behaviors. The rats were subsequently anesthetized, and brain harvested and washed with NFB and sucrose solution for histological analysis. A significant decrease in active time, time spent at the center but increase in stationary time and time spent at the periphery in the open field box was observed amongst groups 2 (MSG only), 3 (Alcohol only) and 4 (MSG + Alcohol) rats administered single and combined doses of monosodium glutamate and alcohol when compared to group 1 (control) rats. This is suggestive of a possible neurotoxic effect caused by MSG and alcohol. However, groups 7-10 rats treated with Rutin and Vitamin C showed increased active time, time spent at the center but decrease stationary time and time spent at the periphery of the open field box when compared to groups 2 (MSG only), 3 (Alcohol only) and 4 (MSG + Alcohol) rats suggesting a potential reversibility effect of rutin and vitamin C. Results obtained suggest that Rutin and Vitamin C improves neuro-behavioural functions and reversed MSG and Alcohol induced neurotoxicity in male Wistar rats.

Keywords: Neuro-behavioral, cytoarchitecture, protective, neurotoxicity.

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INTRODUCTION

Reality comes in many different flavors, and for one to survive food must be taken into the body. Not just any food, a suiting meal with taste and great flavor. Since the days of old, spices from herbs have been produced to enhance the natural flavor of foods (Cardoso-Ugarte & Sosa-Morales, (2022). These spices are essentially food enhancers that are used to give food a distinct flavor and aroma (García-Casal, *et al.,* (2016). A popular flavor enhancer and seasoning known as Monosodium glutamate (MSG), is the purest form of umami, the fifth taste according to the trademark producers Ajinomotto (Tracy, (2016). It is a white odorless crystalline powder produced by the fermentation of plant-based ingredients like sugarcane, sugar beets, cassava or corn (Abd-Elkareem *et al.,* (2022). As much as spices are used in food to give it taste, a chemical substance derived from the chemical process of fermentation of the use of sugars and yeast called alcohol is commonly used in the production of drinks such as beer, wine and liquor, it is also used in the production of medicines, mouthwashes, household products, body perfumes, essential oils, etc.

The source of all the quality that defines humanity is the brain. The brain is the most complicated part of the human body as it serves as the seat of intelligence, the interpreter of senses, initiator of body movement, and a controller of behavior. The brain interprets each signal differently since it regulates various processes with different signals. Billions of neurons are necessary for the brain and spinal cord function, which is made up of the central nervous system and the peripheral nervous system. It communicates information from the brain to the limbs (Thau *et al.,* (2022). Neurons are nerve cells that transmit and receive nerve signals (Wan *et al*., (2021). Axons, which transmit messages from the cell body to neighboring cells, and dendrites, which receive messages from nerve cells, are the two types of branches that emerge from their cell bodies.

Toxins can alter the nervous system in ways that can disrupt or damage the brain or peripheral nervous system because of repeated exposure to natural or man-made toxic substances kpobari *et al*., (2019), Wodward, & Marrs, (2024): Saronee *et al.,* (2024a). Because of their high metabolic rate and importance for information transmission and processing, brain neurons are more vulnerable to damage from neurotoxins (Saronee *et al.,* (2024b). Substances such as chemotherapy drugs, radiation, drug therapies and drugs of abuse, heavy metals, food additives, pesticides, and cosmetics, industrial and cleaning solvents can be neurotoxic to humans (Saronee *et al.,* 2019). The effect of neurotoxicity depends on various factors such as the characteristics of the neurotoxin, the dose exposed to, the metabolism and excretion of the toxin, the ability of the affected mechanism to recover and how vulnerable a cellular target is (Virgolini & Aschner, (2021). Scientific research in this area is quite skeletal, hence the need of the current study to determine the neuro-behavioral and cytoarchitecture protective functions of rutin and vitamin C in monosodium glutamate and alcohol induced neurotoxicity using male Wistar rats as models.

MATERIALS AND METHODS

Purchase of Experimental Animals and Ethical Approval

Forty Male Wistar rats weighing between 120 to 150g were procured from the Department of Physiology animal house PAMO University of Medical Sciences, Nigeria and were housed and treated under standard laboratory conditions with 12 hours light and dark cycle. They were fed with standard laboratory animal chow and had unhindered access to water. The animals were acclimatized for two weeks and were subsequently grouped for the study. The present study was approved by the Research Ethics Committee of the faculty of Basic Medical sciences, Rivers State University.

Procurement of Drugs and Neurotoxicity Induction

Vitamin C was sourced from a local pharmaceutical store while MSG (Ajinomoto) was obtained from a standard market in the city of Port Harcourt; Alcohol (Chelsea dry gin) was purchased from a Port Harcourt Supermarket. Furthermore, Rutin was purchased from a chemical store located in Choba, Rivers State, Nigeria. Neurotoxicity was induced with an oral single daily administration of 30% alcohol and 1.5g/kg body weight of Monosodium glutamate for 28 days consecutively in all rat groups except group1**.**

Experimental Design

After two weeks of acclimatization, the animals were randomly selected into ten (10) groups with each group having five animals each (n=5). Neurotoxicity was induced with an oral single daily administration of 30% alcohol and 1.5g/kg body weight of Monosodium glutamate for 28 days consecutively in all rat groups except group1**.** The animals were subsequently treated as follows:

Group 1: Control; animals in this group had free access to water and laboratory rat chow.

Group 2: MSG only; animals in this group received no additional treatment after induction of neurotoxicity with a single daily administration of 1.5g/kg of MSG.

Group 3: Alcohol only; animals in this group received no additional treatment after induction of neurotoxicity with a single daily administration of 30% alcohol.

Group 4: MSG + Alcohol; animals in this group got no treatment after the induction of neurotoxicity with a single daily administration of 1.5g/kg of MSG and 30% alcohol.

Group 5: MSG + Alcohol + Rutin; animals in this group received 30mg/kg of rutin following induction of neurotoxicity.

Group 6: MSG + Alcohol + Vitamin C; animals in this group received 200mg/kg of vitamin C following induction of neurotoxicity.
Group 7: MSG + Rutin; animals in this group received 30mg/kg of rutin following induction of neurotoxicity.
Group 8: MSG + Vitamin C; animals in this group received 200mg/kg of rutin following induction of neurotoxicity.
Group 9: Alcohol + Rutin; animals in this group received 30mg/kg of rutin following induction of neurotoxicity.
Group 10: Alcohol + Vitamin C; animals in this group received 200mg/kg of Vitamin C following induction of neurotoxicity. All administrations were orally carried out once daily in the morning hours with the aid of a cannula for 28 days. The rats went through behavioral checks through different Open field box checks for 5 minutes to access frequency of movement and time spent at the center and peripheral areas of the field to ascertain anxiety and depressive behaviors. The rats were subsequently anesthetized, and brain harvested and washed with NFB and sucrose solution for histological analysis.

Histological Analysis

Harvested organs were analyzed using the methods previously described by Ghosh and Greenberg (1995) and Eckenhoff & Hossain (2016). The brain was dissected and fixated for 48 hrs., the sectioning was done with paraffin and a microtome used to cut sections. Sections were placed on microscope slides to dry and H&E was used to stain, and microscope used to examine the structure. The cell counts and structural features were viewed using image J. 3.10.

Behavioral Analysis

Open field test box was used to assess exploratory behavior and anxiety. Animals were placed at the center of the open field box and were allowed to explore for 5 minutes. Manual observation was done, and the focus was on the time spent at the center, and peripheral zones including active time and stationary time.

Statistical Analysis

Data was expressed as Mean + standard error of mean. All data was analyzed using one way analysis of variance (ANOVA) and comparison of the groups was performed with post hoc Newman-Keuls test using Graphpad prism 7.0 (Graphpad Software, San Diego, CA, USA) and a P <0.05 was considered statistically significant.

RESULTS

Figure 1 shows a significant decrease in active time spent in an open field box amongst groups 2 (MSG only), 3 (Alcohol only) and 4 (MSG + Alcohol) rats administered single and combined doses of monosodium glutamate and alcohol when compared to group 1 (control) rats. This is suggestive of a possible neurotoxic effect of MSG and alcohol. However, groups 7-10 rats treated with Rutin and Vitamin C showed increased active time when compared to groups 2 (MSG only), 3 (Alcohol only) and 4 (MSG + Alcohol) rats indicating a potential reversibility effect of rutin and vitamin C.

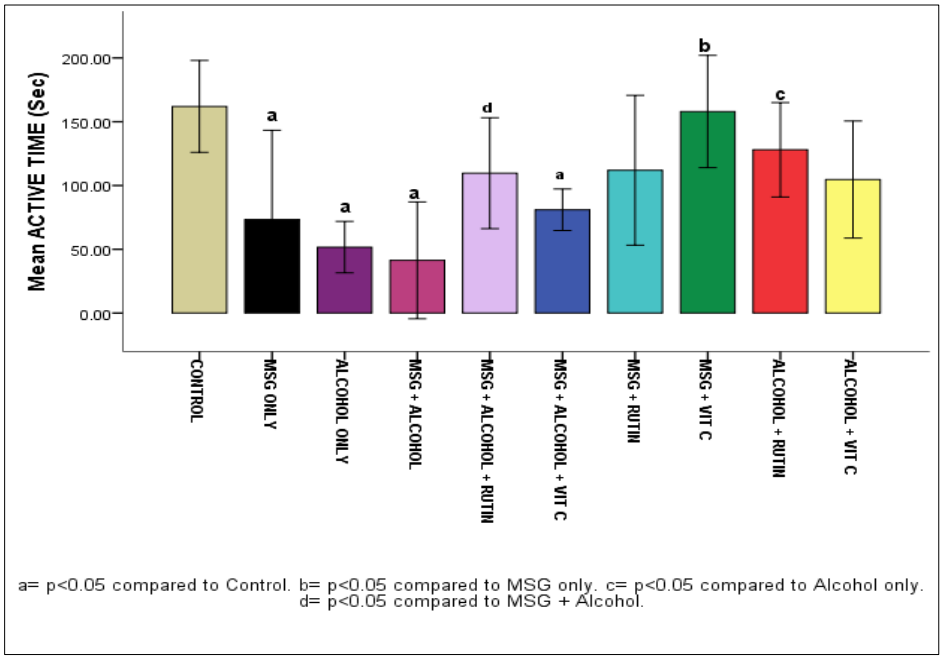


Figure 1: Shows the effect of Rutin and Vitamin C on active time in MSG and Alcohol induced neurotoxicity in male Wistar rats

Significant increases were observed in stationary time spent in an open field box amongst groups 2 (MSG only), 3 (Alcohol only) and 4 (MSG + Alcohol) rats treated with MSG and alcohol when

compared to group 1 (control) rats as seen in figure 2. Indicating a potential toxic effect of MSG and alcohol. Administration of Rutin and Vitamin C to animals in groups 5, 7, 8, 9 and 10 demonstrated measurable decline in stationary time when compared to groups 2 (MSG only), 3 (Alcohol only) and 4 (MSG + Alcohol) rats respectively. Suggesting a beneficial neurobehavioral effect of both rutin and vitamin C.

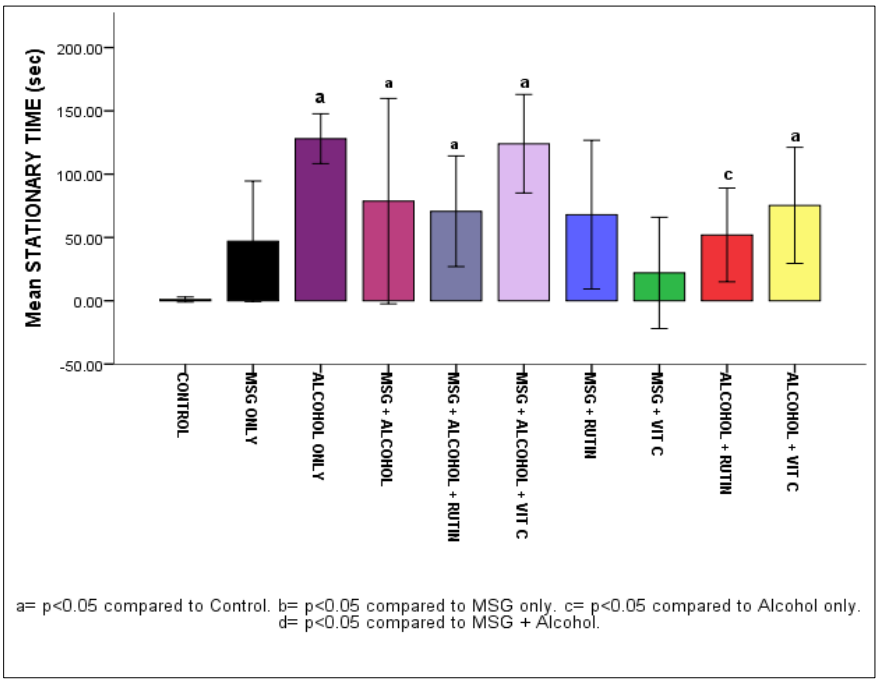


Figure 2: Shows the effects of Rutin and Vitamin C on stationary time in MSG and Alcohol induced neurotoxicity in male Wistar rats

Figure 3 shows significantly lower values in time spent at the center of an open field box amongst groups 2 (MSG only), 3 (Alcohol only) and 4 (MSG + Alcohol) rats when compared to group 1 (control) rats. Rutin and Vitamin C treatment significantly increased time spent at the center when compared to group 1 (MSG only), 2 (Alcohol only) and 3 (MSG + Alcohol) rats suggesting a likely positive neurobehavioral outcome.

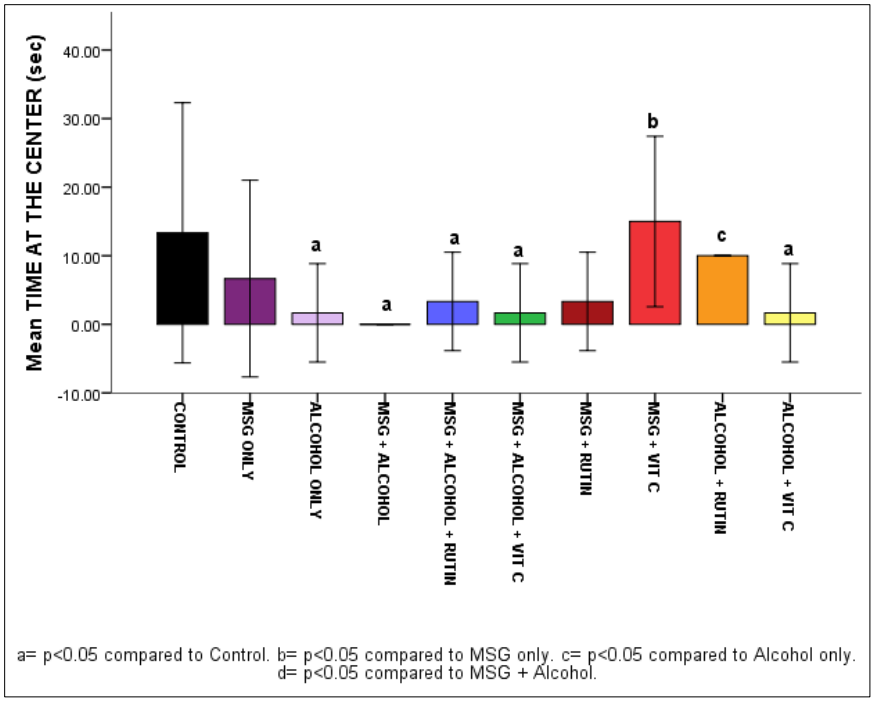


Figure 3: Shows the effect of Rutin and Vitamin C on time spent at the center in MSG and Alcohol induced neurotoxicity in male Wistar rats

A slight increase in the time spent at the periphery of an open field box was observed amongst groups 2 (MSG only), 3 (Alcohol only) and 4 (MSG + Alcohol) rats when compared to group 1 (control) rats as shown in figure 4. Slight decreases were observed in groups 7 – 10 rats treated with Rutin and Vitamin C when compared to groups 2 (MSG only), 3 (Alcohol only) and 4 (MSG + Alcohol) rats.

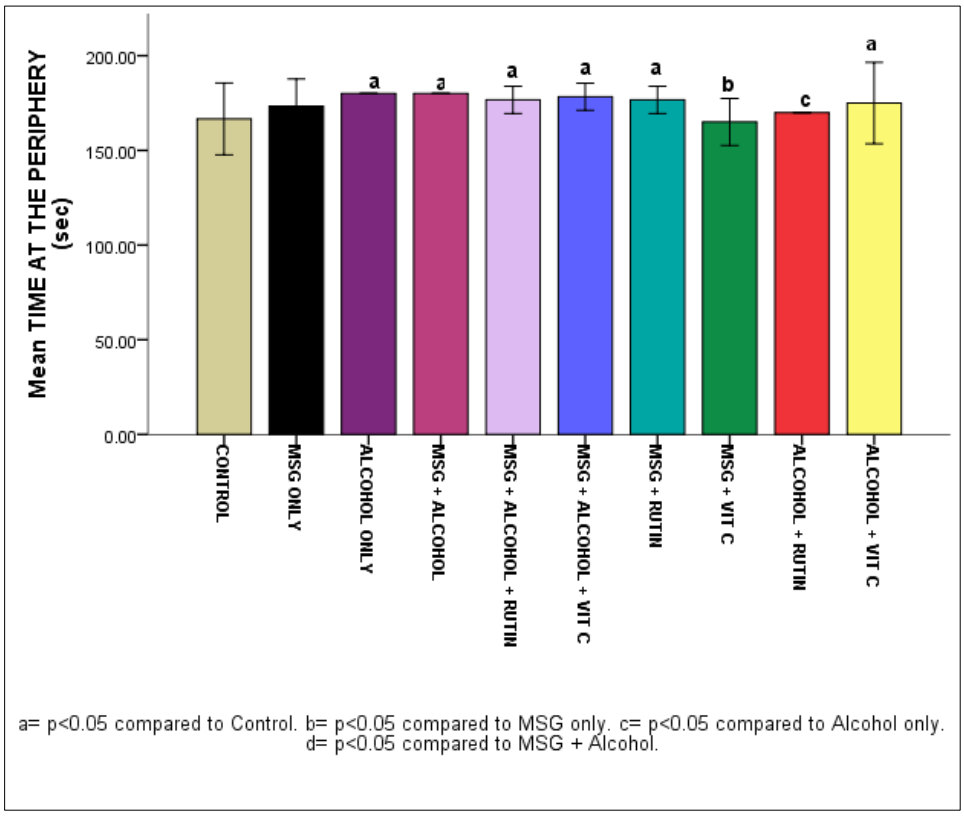
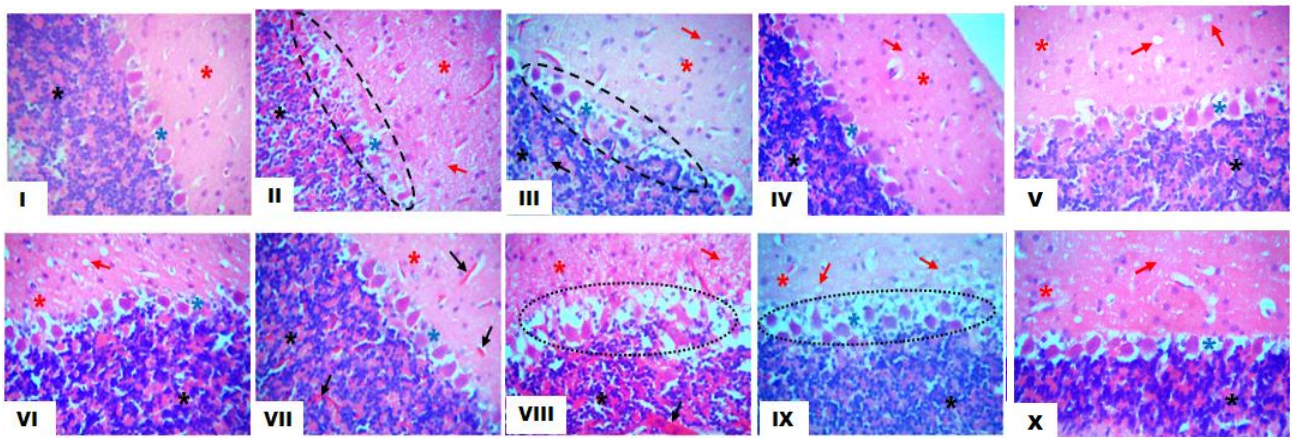


Figure 4: Shows the effect of Rutin and Vitamin C on time spent at the periphery in MSG and Alcohol induced neurotoxicity in male Wistar rats



Plates 1 -10: Show the effect of Rutin and Vitamin C on the histopathology of the cerebellum in MSG and Alcohol induced neurotoxicity in male Wistar rats

Group i: (Control) rats shows normal histology of granular layer (black asterisk), purkinje cell layer (blue asterisk), and molecular layer (red asterisk). In **Group ii, iii, vii and viii:** sparse granule cells (black asterisk) and vascular congestion (black arrow) were observed. In **Groups i, vi and x:** hyperbasophilia was observed probably due to hyperplasia of granule cells in these groups. **Groups v and ix** are apparently normal.

In the pyramidal layer (blue asterisk), note the sparse pyramidal cells (black dashed outline) in **Groups ii – iii** and disorganized pyramidal cells (black dotted outline) in **Groups viii – ix. Groups iv – vii and x** are apparently normal.

In the molecular layer (red asterisk), note vacuolation of neuropil (red arrow) in Groups ii – vi and viii – x.

However, **group vii** shows vascular congestion (black arrow) (x400 magnifications).

DISCUSSION OF FINDINGS

Effects of Rutin and Vitamin C on Neurobehavioral Functions (anxiety and depression) in MSG and Alcohol induced neurotoxicity in male Wistar rats

Results from this study showed that animals in the control group had an increased active time in the open field box. While MSG and Alcohol treated rats demonstrated visible decline in active time of experimental rats. Administration of Rutin and Vitamin C further increased active time spent in the open field box thus illustrating a possible reversal of the effects observed in MSG and Alcohol treated rats. This finding is consistent with Olumide *et al.*, (2023) and Otimenyin, (2024) in which similar interventions promoted locomotor and exploratory functions in Wistar rats. Vitamins play a crucial role in supporting immune functions. These macronutrients are essential to maintaining good health and are found in healthy diets in the form of Vitamin B6, Vitamin C, Vitamin E, Zinc, Magnesium (Pecora *et al.*, 2020), Saronee *et al.*, (2023a) and Saronee *et al.*, (2023b). MSG and Alcohol administration causes stress leading to anxiety and depression (Saronee *et al.*, (2024a): This is observed in the present study via increased stationary time, time spent at the periphery and less time spent at the center as earlier observed and reported by Brocardo *et al.*, (2012). Literature reports that rutin has protective functions against neurodegenerative conditions, cardiovascular illnesses, skin ailments, and more (Ullah *et al.*, 2020).

Effects of Rutin and Vitamin C on the histopathology of the cerebellum in MSG and Alcohol induced neurotoxicity in male Wistar rats

The histopathological examination of the cerebellar cortex (grey matter) in the granule layer shows sparse granule cells and Vascular congestion in MSG and alcohol treated rats, indicating neuronal injury. In Rutin and Vit.C treated rats, skeletal vascular congestion is observed, which may be attributed to the study duration and dosage of our interventions, though it is reduced when compared to MSG and Alcohol treated rats (Saronee *et al.*, 2024b).

In the Pyramidal layer, sparse pyramidal cells are seen in MSG, and Alcohol treated groups, suggesting the presence of neurotoxicity as well as neurodegeneration. While Vit. C and Rutin treated groups appear normal. Suggesting a possible reversal of the harmful effects caused by MSG and alcohol.

In the Molecular Layer, there is vacuolation of neutrophil in MSG and Alcohol treated rats, however, in Vit. C and Rutin treated animals there were a remarkable better effect. This is indicative of a partial reversal of neurotoxicity induced by MSG and Alcohol.

The white matter of the cerebellar medulla shows proliferation of glial cells, probably astrocytes in MSG treated group and vascular congestion in Alcohol treated groups. This indicates the presence of neurotoxicity. Rutin and Vit. C groups were all apparently normal in their structure and appearance suggesting a possible beneficial effects of rutin and vitamin C.

CONCLUSION

Obtained results suggests that Rutin and Vitamin C improves neurobehavioral functions and reversed MSG and Alcohol induced neurotoxicity in male Wistar rats.

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