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Influence of Lutein on Brain Antioxidant (SOD, GSH) in Diazepam-Induced Memory Impairment of Wistar Rats

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Abstract

Lutein has a range of nutritional and health-enhancing characteristics, based on its multifaceted biological action in people, which comprise antioxidative, immunomodulatory, and anti-inflammatory properties. This study explored the effect of repeated of lutein on cerebral antioxidants (Superoxide Dismutase (SOD), Glutathione (GSH)) in the animals that were subjected to memory impairment by Diazepam. Thirty (30) Wistar rats was used for this study and the rats were acclimatized for a period of 14 days, and was then divided into six groups; Group 1: Control, Group 2: Diazepam Only (5mg/kg) , Group 3: Diazepam + Lutein (20mg/kg) , Group 4: Diazepam + Lutein (40mg/kg), Group 5: Diazepam + Lutein (60mg/kg), Group 6: Diazepam + Donpenzil (Standard Drug). Administration was done for a period of 21 days. Diazepam significantly disrupted working memory, spatial learning, and retention, which were reflected by a decrease in spontaneous alternation in the Y-maze and longer escape latencies and increased errors in the Barnes maze. It also lowered SOD and GSH activities in the brain. These deficits were being restored by lutein treatment in a dose-dependent manner, restoring spontaneous alternation, shortening escape latency and error rates, and increasing retention performance. Biochemically, lutein had significant restorative effect on brain SOD and GSH levels which were comparable to donepezil. This research concluded that lutein can mitigate diazepam-induced memory impairment by boosting antioxidant levels in a dose-dependent manner, with medium to high doses being particularly effective. These findings support lutein's potential as a dietary neuroprotective agent against drug-induced cognitive impairment.

Keywords: Lutein, Brain Antioxidants, Diazepam-Induced, Glutathione. Superoxide Dismutse.

INTRODUCTION

There is a global prevalence of memory loss estimated at 5% to 7% in people over 60 years, and also a documented country-specific memory loss prevalence in Sub-Saharan Africa (SSA) (Adeloye *et al.,* 2019). Ogunniyi *et al.,* (2016) found prevalence rates of mild cognitive impairment of 18.4 % and dementia of 2.9 % in a South-South Nigeria investigation, whereas a previous South-South Nigeria study found a prevalence rate of 11.8 % of mild cognitive impairment.

Hence, mild cognitive impairment and memory loss, requires an immediate medical intervention (Anieto *et al.,* 2023). Memory and mild cognitive impairment are major neurocognitive disorders that pose remarkable health challenges worldwide (Anieto *et al.,* 2023). Dementia can be quite dehumanizing in its advanced stages. Mild cognitive impairment occupies the intermediate stages in the continuum of cognition and is considered the leading point for preventive strategies (Roberts & Knopman, 2013). The conceptualization of mild cognitive impairment began as a syndrome that is self-reported, episodic memory deficits that are measurable, and no functional impairment in the activities of daily living or clinical diagnosis of a dementia (Anand & Schoo, 2024). It is distinguished with dementia because it does not degrade the ability to live independently.

There is growing evidence of the association between oxidative stress and age-related cognitive decline. It is assumed that antioxidants can prevent this deterioration and even slow down or prevent dementia

((National Institute of Health, 2022; Jurcau, 2021). A high antioxidant diet has been linked with better cognitive functioning in elderly people (Chen *et al.*, 2024). Oxidative damage is possible because the brain consumes a lot of oxygen and has high lipid concentrations (Singh *et al.*, 2019; Jové *et al.*, 2023). The key endogenous antioxidant processes such as superoxide dismutase (SOD), catalase (CAT), glutathione (GSH), and vitamins C and E are essential to control this stress (Jena *et al.*, 2023; Jomova *et al.*, 2024)

With the growing recognition of the potential neuroprotective effects of Lutein, a carotenoid with antioxidant properties, there is a lack of knowledge in its specific influence on brain antioxidant activities in diazepam-induced memory impairment. Hence, the need for this current study to determine the influence of graded doses of Lutein on brain antioxidant activities in a diazepam-induced memory impairment in Wistar rats.

MATERIALS AND METHODS

Research Design

Twenty (30) Wistar Rats weighing 111-148g were purchased from the animal house of Department of Pharmacology of the Faculty of Basic Medical Sciences, University of Port Harcourt. The animals were acclimatized for 14 days at room temperature in the animal house of the Department of Human Physiology, Faculty of Basic Medical Sciences, University of Port Harcourt, where they were exposed to 12 hours light/dark cycle. They had water and food (standard finisher diet, top feed, Nigeria) throughout the duration of the study. They also had their bedding (dry saw dust) changed as often as possible. The study lasted for a period of (35) days. The animals were randomly assigned into six (6) groups Group 1 served as the control and Group 2 - 6 served as test groups.

The administration took 21 consecutive days within the hours of 8:00 to 9:00am daily. Diazepam was administered 1 hour before the administration of lutein mixture of $Dmso_4$ and water (H_20) for group 3, 4 and 5. Then 30 minutes later Neurobehavioral tests was conducted for the same group 3, 4 and 5 Wistar rats everyday throughout the 21days of administration period.

Ethical Approval

Ethical approval was obtained from the faculty of basic medical science, Abuja campus, University of Port Harcourt. Rat handling and treatment conform to the guideline of the National Research Council (2011) for care and use of laboratory animals.

Drug Identifications

The drugs used were Diazepam, Lutein, Donepezil and dimethyl sulfate ($Dmso_4$). These were gifted by National Institute Pharmaceutical of Research and Development (NIPRD) Rivers State branch, Nigeria. The drugs were collected and sent to the department of pharmacy, university of Portharcourt for identification and chemical composition confirmation.

Determination Administration

The appropriate weight of Lutein and Dimethyl sulfate ($Dmso_4$) was suspended in 8ml of distilled water and administered orally to each animal Using a 2ml syringe and cannula. The daily drugs dose administered for each group of the Wistar Rats was gotten by calculating the dosage based on the weekly average weight of each group of the Wistar Rats.

For Diazepam (5mg):
5g/kg = 1000g
Xg/kg = 111g
Therefore, x=0.6/5, Then x= 0.1mg/kg
Therefore, administrative equivalence in ml/g

For Lutein (20mg/kg, 40mg/kg and 60mg/kg)
1ml of distilled water = 1000g/ml stock solution
Animal weight/kg = 1000g

Table 1: Experimental Grouping and Drug Administration - Week 1

	Treatment	Average Weight	Dose Administered	Route of Administration
Group1 Control	Only received feed *ad libitum* and distilled water for each day of the week.	148g		Oral (feed/water)
Group 2	Diazepam (5 mg/kg)	130g	Diazepam = 0.1g/kg	Intraperitoneally
Group 3	Diazepam (5 mg/kg) + Lutein (20 mg/kg) + $DMSO_4$ (2 ml in 8 ml water)	116g	Diazepam 0.1 mg/kg + Lutein 0.9 mg/kg	IP and Oral
Group 4	Diazepam (5 mg/kg) + Lutein (40 mg/kg) + $DMSO_4$ (2 ml in 8 ml water)	123g	Diazepam 0.1 mg/kg + Lutein 1.0 mg/kg	IP and Oral
Group 5	Diazepam (5 mg/kg) + Lutein (60 mg/kg) + $DMSO_4$ (2 mL in 8 mL water)	127g	Diazepam 0.1 mg/kg + Lutein 0.9 mg/kg	IP and Oral
Group 6	Diazepam (5 mg/kg) + Donepezil (10 mg/kg)	121g	Diazepam 0.1 mg/kg + Lutein 1.2 mg/kg	IP and Oral

Table 2: Experimental Grouping and Drug Administration - Week 2

	Treatment	Average Weight	Dose Administered	Route of Administration
Group1 Control	Only received feed *ad libitum* and distilled water for each day of the week.	146g		Oral (feed/water)
Group 2	Diazepam (5 mg/kg)	141g	Diazepam = 0.1g/kg	Intraperitoneally
Group 3	Diazepam (5 mg/kg) + Lutein (20 mg/kg) + $DMSO_4$ (2 ml in 8 ml water)	113g	Diazepam 0.1 mg/kg + Lutein 0.9 mg/kg	IP and Oral
Group 4	Diazepam (5 mg/kg) + Lutein (40 mg/kg) + $DMSO_4$ (2 ml in 8 ml water)	121g	Diazepam 0.1 mg/kg + Lutein 0.6mg/kg	IP and Oral
Group 5	Diazepam (5 mg/kg) + Lutein (60 mg/kg) + $DMSO_4$ (2 mL in 8 mL water)	125g	Diazepam 0.1 mg/kg + Lutein 0.8mg/kg	IP and Oral
Group 6	Diazepam (5 mg/kg) + Donepezil (10 mg/kg)	120g	Diazepam 0.1 mg/kg + Lutein 1.2 mg/kg	IP and Oral

Changes were made only to the dose administered based on the weight for week 2

Table 3: Experimental Grouping and Drug Administration - Week 3

	Treatment	Average Weight	Dose Administered	Route of Administration
Group1 Control	Only received feed *ad libitum* and distilled water for each day of the week.	144g		Oral (feed/water)
Group 2	Diazepam (5 mg/kg)	139g	Diazepam = 0.1g/kg	Intraperitoneally
Group 3	Diazepam (5 mg/kg) + Lutein (20 mg/kg) + $DMSO_4$ (2 ml in 8 ml water)	111g	Diazepam 0.1 mg/kg + Lutein 0.9 mg/kg	IP and Oral
Group 4	Diazepam (5 mg/kg) + Lutein (40 mg/kg) + $DMSO_4$ (2 ml in 8 ml water)	119g	Diazepam 0.1 mg/kg + Lutein 0.9mg/kg	IP and Oral
Group 5	Diazepam (5 mg/kg) + Lutein (60 mg/kg) + $DMSO_4$ (2 mL in 8 mL water)	122g	Diazepam 0.1 mg/kg ± Lutein 0.8mg/kg	IP and Oral
Group 6	Diazepam (5 mg/kg) + Donepezil (10 mg/kg)	119g	Diazepam 0.1 mg/kg + Lutein 1.2 mg/kg	IP and Oral

Changes were made only to the dose administered based on the weight for week 3

Neurobehavioral Tests

A number of behavioral tests was conducted to assess motor coordination, spatial memory, anxiety, and exploratory behavior. They include:

- Hand Grip Test
- Rotarod Test
- Y-Maze Test
- Barnes Maze Test

Biochemical Analysis

Brain tissue homogenates were analyzed for Superoxide Dismutase (Using Misra & Fridovich method) & Glutathione (Using Ellman's (DTNB) assay) (Chidambaram *et al.,* 2024; Raffa *et al.,* 2012)

Statistical Analysis

Data were subjected to statistical analysis using GraphPad Analysis software. Data were expressed as mean and standard error of mean. Analysis of variance (AVOVA) was done using least significant difference (LSD) to determine the significant difference in mean at 95 percent confidence interval ($P< 0.05$).

RESULTS

Data represent Mean ± SEM, n = 5; Significant at $p<0.05$ compared to Group 1; Significant at $p<0.05$ when compared to group 2; Significant at $p<0.001$ when compared to group 3. group 4, and group 5.

Table 4: Effect of Lutein Administration on Neurobehavioural Test in Female Wistar Rats

Variables	Groups					
	Control	Diazepam Only	Diazepam + Lutein (20mg/kg)	Diazepam + Lutein (40mg/kg)	Diazepam + Lutein (60mg/kg)	Diazepam + Donepenzil
Rotarod Stability Time (s)	6.13 ± 0.89	1.47 ± 0.25 ***	3.47 ± 0.81	3.33 ± 0.37	4.24 ± 0.63	3.40 ± 0.92
Handgrip Stability Time (s)	3.67 ± 0.30	1.73 ± 0.12**	3.65 ± 0.34	4.12 ± 0.24	3.53 ± 0.23	3.72 ± 0.42
Y Maze Inflexion Ratio (s)	0.76 ± 0.13	1.60 ± 0.13****	1.11 ± 0.10	0.41 ± 0.11	0.39 ± 0.05	0.56 ± 0.04

Y Maze % Spontaneous Alteration	32.91 ± 3.26	10.22 ± 0.22****	14.20 ± 1.50****	34.50 ± 0.73	36.89 ± 1.12	32.11 ± 2.38
Barnes maze - Time spent in locating correct hole. Week 1	14.80 ± 1.39	27.00 ± 2.72**	17.60 ± 2.16	12.20 ± 1.20	15.00 ± 2.10	13.80 ± 3.03
Barnes maze - Time spent in locating correct hole. Week 2	10.40 ± 1.63	43.40 ± 7.51****	4.80 ± 1.53	7.80 ± 0.97	19.00 ± 2.82	8.40 ± 3.79
Barnes maze - Time spent in locating correct hole. Week 3	12.80 ± 3.81	42.20 ± 3.11****	30.20 ± 4.07*	6.20 ± 1.32	10.00 ± 4.11	12.60 ± 4.57
Barnes maze - Time spent in locating incorrect hole. Week 1	2.20 ± 0.37	5.20 ± 0.37**	3.40 ± 0.51	2.00 ± 0.45	2.60 ± 0.51	1.80 ± 0.49
Barnes maze - Time spent in locating incorrect hole. Week 2	0.60 ± 0.40	2.80 ± 0.37**	0.60 ± 0.40	1.00 ± 0.32	0.80 ± 0.37	0.80 ± 0.37
Barnes maze - Time spent in locating incorrect hole. Week 3	3.40 ± 1.16	2.80 ± 0.86	3.60 ± 0.81	1.80 ± 1.11	2.40 ± 0.93	3.88 ± 0.49

Table 5: Effects of Lutein, Diazepam, and Donepezil on Superoxide Dismutase (SOD) and Glutathione (GSH)Levels

Variables	**Groups**					
	Control	**Diazepam Only**	**Diazepam + Lutein (20 mg/kg)**	**Diazepam + Lutein (40 mg/kg)**	**Diazepam + Lutein (60 mg/kg)**	**Diazepam + Donepenzil**
Superoxide Dismutase (SOD)	0.31 ± 0.01	0.15 ± 0.01 ***	0.25 ± 0.01 *	0.26 ± 0.02	0.29 ± 0.00	0.31 ± 0.01
Glutathione (GSH)	1.00 ± 0.10	0.64 ± 0.06 *	0.98 ± 0.06	0.89 ± 0.08	1.03 ± 0.07	0.99 ± 0.04

DISCUSSION

Hand Grip and Rotarod Tests - Table 4

Diazepam had a significant effect in lowering muscle strength and motor coordination, which is congruent with sedative and muscle relaxation effects through GABA-A receptor potentiation. However, treatment with lutein (particularly at higher doses) enhanced performance, largely coming close to levels shown by donepezil. This implies that lutein has the potential of reversing motor impairment that is caused by oxidative dysfunction or GABAergic regulation. These neuroprotective properties are similar in recent research that showed the relationship between lutein and motor-performance in scopolamine-induced models of cognitive impairment (Chike *et al.,* 2025).

Y Maze Inflexion Ratio and Y Maze % Spontaneous Alteration - Table 4

Diazepam affected spontaneous alternation behavior, a characteristic of working-memory deficits. Lutein showed significant improvement in percentages of alternation, which was similar to that of donepezil group. This is consistent with the findings of other studies that lutein supplementation promoted working memory and attention in rodents and older adults (Nazari *et al.,* 2022; Lopresti *et al.,* 2022). The increase in arm entries also demonstrates the return to exploratory behavior and this could be due to decreased sedation and improved cognition.

Barnes Maze Parameters - Table 4

In the Barnes maze, diazepam-treated rats showed longer escape latencies, fewer correct hole entries, and more errors, which suggests that they did not learn and memorize spatial information well Lutein attenuated these impairments in a dose-dependent way, lowering escape latency and errors, and raising the number of correct entries. These are in keeping with the known effects of lutein in improving hippocampal-dependent spatial memory.

The test indicated that the memory of the escape hole location remained in groups treated with lutein, indicating further that it has a cognitive-enhancing effect. Similar results were obtained in which lutein enhanced Morri's water maze and Barnes maze performance of rodents in neurotoxicity models (Nazari *et al.,* 2022).

Biochemical Indices - Table 5

Glutathione (GSH)

The change in the level of Glutathione were seen to be statistically significant ($p<0.05$) when the group 2 (diazepam only treated) were compared to that of the control group (group 1) and the rest of test groups varied only marginally ($p>0.05$) when compared to both the value of the control and amongst themselves. These

variations did not following any uniform pattern with group 4 and 5 showing the a very high elevated level of GSH. The changes in Glutathione levels following different mode of administration of diazepam and lutein indicated a significant ($p<0.05$) decrease in Group 2, signifying the ability of a prolong treatment with diazepam to decrease energy and maintain the GSH concentration at a level significantly relevant when compared to the control group.

Ahn and Kim (2021), demonstrated that lutein supplementation in ovariectomized rats increased blood glutathione levels and reduced lipid peroxidation, supporting the current study's finding of significant GSH elevation with medium and high lutein doses. This suggests a protective mechanism against diazepam-induced oxidative stress.

Superoxide Dismutase (SOD)

The change in the level of superoxide dismutase were seen to be statistically significant ($p<0.05$) when the group 2 (diazepam only treated) were compared to that of the control group (group 1) and the rest of groups (test) varied only marginally ($p>0.05$) when compared to both the value of the control and amongst themselves. These variations did not following any uniform pattern with group 5 and 6 showing a very high elevated level of SOD. The changes in superoxide dismutase levels following different mode of administration of diazepam and lutein indicated a significant ($p<0.05$) decrease in Group 2, signifying the ability of a prolong treatment with diazepam to decrease energy and maintain the SOD concentration at a level significantly relevant when compared to the control group.

The results align with those of Jayawickreme *et al.,* (2024) who had noted that lutein has the ability to increase the activity of antioxidant enzymes, which gives it the neuroprotective effect in neurodegenerative models. The dose-related elevation of SOD, especially at high doses, agrees with findings in models of Alzheimer disease reported by Nazari *et al.,* (2022), whose study indicated that lutein improved memory deficits by stimulating antioxidant defenses. Also, lutein consumption in human subjects was associated with enhanced cognitive performance among the older adults (Johnson *et al.,* 2012), further confirming its possible application in memory disorders.

CONCLUSION

This research showed that the treatment of lutein has remarkable improvements on memory-related behaviour (Y-maze and Barnes maze) and important brain antioxidants such as Glutathione (GSH) and Superoxide Dismutase (SOD) in Wistar rats with memory impairment induced by diazepam. The results show a dose-dependent neuroprotective action: lutein at 40 and 60mg/kg caused the strongest increase in the levels of GSH and SOD in comparison with the group that received only diazepam. These findings point to the effectiveness of lutein in alleviating oxidative stress which is one of the key aspects in memory impairment as well as surpassing the standard treatment in repairing antioxidant defenses. Therefore, this research highlights the possibility of using lutein as therapeutic agent in treatment of neurological disorders associated with oxidative stress.

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