OPEN ACCESS

Scholars Bulletin

Abbreviated Key Title: Sch Bull
ISSN 2412-9771 (Print) | ISSN 2412-897X (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Subject Category: Physiology

Evaluation of Antioxidant Enzyme Activity and Oxidative Stress Markers in Male Wistar Rats Following Scopolamine-Induced Depression and Lutein Treatment

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DOI: https://doi.org/10.36348/sb.2025.v11i07.002 | **Received:** 13.06.2025 | **Accepted:** 18.08.2025 | **Published:** 20.08.2025

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Abstract

The neuropsychiatric conditions; depression and anxiety develop from oxidative stress together with neuroinflammation. The research evaluates if lutein ameliorates anxiety and depression symptoms in rats exposed to scopolamine. 36 male Wistar rats (105g - 153g) were distributed randomly into six distinct groups. Group 1: Negative Control, Group 2: Scopolamine only treated group, Group 3: Scopolamine + Lutein (20mg/kg), Group 4: Scopolamine + Lutein (40mg/kg), Group 5: Scopolamine + Lutein (60mg/kg), Group 6: Scopolamine + Imipramine (standard drug - 10mg/kg). Scopolamine was administered intraperitoneally and lutein orally. Statistical analysis was conducted through one way ANOVA with Post hoc Fischer's LSD. The experiment used $P<0.05$ for multiple comparison significance detection. Superoxide Dismutase (SOD), and Glutathione (GSH) levels in Group 2 decreased substantially ($p < 0.01$ and $p < 0.0001$) when compared to control, Groups 4, 5, 6 which improved the SOD and GSH levels toward normal levels. Catalase decreased dramatically ($p < 0.0001$) in Group 2 but treatment in Groups 4 and 5 elevated significantly ($p < 0.01$). These outcomes establish that Lutein protects against scopolamine induced oxidative stress, behavioral deficits and neurotoxicity. The research established that lutein treatment produced positive results for reversing both oxidative stress conditions and neurotoxicity effects and behavioral deficits provoked by scopolamine. Scopolamine caused a decrease in antioxidant enzymes levels which Lutein treatment at middle and high doses (40 and 60 mg/kg) successfully countered by restoring biomarkers, boosting neurotrophic signals for better behavioral results.

Keywords: Lutein, Scopolamine-induced depression, Oxidative stress, Glutathione, Catalase (CAT), Superoxide dismutase (SOD).

INTRODUCTION

A mental disorder known as depression affects people worldwide frequently. Approximately 5% of adult population worldwide experience this condition according to Remes *et al.,* (2021). Depression as a mental condition affects patients with ongoing depressive symptoms who lose interest in activities that used to bring them satisfaction (Chand & Arif, 2023). Sleep disturbances together with appetite problems represent additional side effects of this condition (Moitra *et al.,* 2020). Depression has been linked to various physical health issues, It may impact everything from your heart, kidney, nervous system, and immune system health (Pietrangelo, 2022). Individuals with depression often have disrupted sleep patterns, poor appetite, and reduced physical activity, which can lead to serious health issues such a diminish one's quality of life, suicidal tendencies, (Goldman, 2019).

Depression develops through multiple factors which include both serotonin monoamine deficits and hypothalamic-pituitary-adrenal (HPA) axis disturbances (Mikulska *et al.,* 2021). Research shows that elevated HPA axis activity creates higher glucocorticoid levels while producing oxidative stress and glutamatergic excitotoxicity which leads to hippocampal nerve cell death and affects mood regulation (Mikulska *et al.,* 2021; (Cui *et al.,* 2024). Chronic stress causes substantial changes to the hippocampus structure which leads to cognitive dysfunction (Kim *et al.,* 2015).

Researchers believe that inflammation plays a role in depression process (Miller & Raison, 2015). Medical tests identify elevated levels of pro-inflammatory cytokines IL-1β, IL-6, TNF as well as chemokines CCL2 and CXCL10 and inflammatory marker C-reactive protein (CRP) within the blood of patients suffering from depression based on Kouba *et al.,* (2024) and Eyre *et al.,* (2016). Findings indicate that patients dealing with depression show high levels of 8-hydroxy-2'-deoxyguanosine as this molecule functions as an indicator for DNA damage due to oxidative processes (Forlenza & Miller, 2006). These results indicate that depression appears to be closely related to oxidative stress.

Taking the above into account, lutein has the potential to play a protective role in depression through various mechanisms. First, pro-inflammatory cytokines such as IL-6 and TNF impair the expression of BDNF, leading to the onset of depression (Felger & Lotrich, 2013). Today we know that lutein as a carotenoid can effectively remove reactive oxygen species as well as other free radicals. Therefore, considering that lutein has both antioxidant and anti-inflammatory effects, it is expected that they may exert an antidepressant effect (Zeni *et al.,* 2019)

There is a growing body of evidence that the antioxidant and anti-inflammatory properties of lutein may promote efficient cognitive function (Johnson, 2012) by increasing neuronal efficiency or stabilizing the lipid-protein bonds in neuronal membranes (Rasmus & Kozłowska, 2023). Other neuroprotective mechanisms of lutein include enhancement of communication between clefts and modulation of the functional properties of synaptic membranes (Rasmus & Kozłowska, 2023). Studies indicate that higher intake of lutein may be related to lower prevalence of depression, anxiety, and stress (Yu *et al.,* 2022; Zeni *et al.,* 2019).

Research shows that lutein stands as the leading carotenoid in the primate brain since brain tissue samples reveal higher lutein concentrations in occipital and prefrontal cortex and cerebellum regions (Jeon *et al.,*2018; Vishwanathan *et al.,*2013). All brain cortex and membranes contain lutein while serum levels of β-carotene, β-cryptoxanthin, and α-carotene act as biomarkers to measure brain lutein concentration (Johnson *et al.,* 2011). Lutein increases serum IL-10 concentrations which helps stop atherosclerosis progression while simultaneously reducing inflammation and very low and medium-density lipoprotein levels and oxidative stress (Paradentavida Prathyusha *et al.,* 2025; Ahn & Kim, 2021).

Pharmaceutical agent scopolamine causes dose-proportional CNS depression as increased doses may lead to CNS excitation through disrupted feedback loops (Eyre *et al.,* 2016). Parasympathetic treatment with scopolamine usually maintains daily doses below 1.2 mg since adverse effects become unpredictable and severe. Current scientific knowledge about lutein's antioxidant and anti-inflammatory properties in the eye is well known about but research on how lutein affects anxiety and depression like behaviors during scopolamine induced depression remains insufficient. Despite this, the effect of lutein on anxiety and depression like behaviors especially in scopolamine induced depression has not been fully researched. Studying this interaction might help to elucidate how lutein could exert the neuroprotective effects. To achieve the objective of this study, we shall compare the effects of scopolamine and lutein on antioxidant enzyme activity and levels of oxidative stress in Wistar rats, with the aim of filling the existing knowledge gap and identifying potential interventions for the management of depression-related oxidative stress.

MATERIALS AND METHODS

Experimental Animals

Experimental rats were purchased from the animal house of the Faculty of Basic medical sciences, Abuja campus, University of Port Harcourt. The animals were housed in steel cages and kept at room temperature. The rats had no history of drug consumption, that is; they had not been used for any investigation. The rats were put on standard rat pellet (feed) and pure drinking water and allowed to get acclimatized for 21 days before the start of the experiment. The study was done in accordance with the guidelines for animal use of the Faculty of Basic Medical Sciences, University of Port Harcourt.

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.

Chemicals and Reagents Used

The chemicals and reagents used for this study were purchased from GGI Intl' Nigeria Ltd. located at GGI Place, Plot 8 GGI Crescent, (Opp. Mikab Filling Station), Port Harcourt, Rivers State, Nigeria. The chemicals and reagents are as follows:

a. Scopolamine hydrobromide: Used to induce depression-like behavior.
b. Lutein: Administered as the test compound.
c. Imipramine hydrochloride (10 mg/kg)(standard antidepressant drug)
d. Glutathione assay kit: For measuring glutathione (GSH) levels.
e. Catalase assay kit: For catalase activity measurement.
f. Thiobarbituric acid (TBA): For malondialdehyde (MDA) estimation.
g. Superoxide dismutase (SOD) assay kit: For enzymatic antioxidant analysis.

Collection of Lutein and Scopolamine

The lutein capsule and scopolamine liquid were collected from the department of Pharmacology, Faculty of Pharmacology, University of Port Harcourt. The identity was authenticated by Mr Akoko Sokipirim at Pharmacology department, Faculty of Pharmacology, University of Port Harcourt Rivers State. Lutein capsules were dissolved in $DMSO_4$ and water.

Experimental Design

Thirty (30) male wistar rats were weighed and allocated into six different groups, each containing five wistar rats. To check for the impact of lutein supplementation on scopolamine-induced anxiety and depression like behavior in rats, and the physiological mechanism by which lutein may modulate scopolamine-induced anxiety and depression like behavior in rats, thirty male Wistar rats were weighed and allocated into five groups of five animals each. The groups were designated as groups 1, 2, 3, 4, 5 and 6.

The experimental groups were administered different doses of scopolamine and lutein as follows;

- Group 1 (negative control group) was given feed and 250mg/kg of distilled water only
- Group 2 (positive control group) was administered 0.06ml of scopolamine
- Group 3 (low dose group) was administered with 0.056ml of scopolamine and was treated with 0.026ml of lutein.
- Group 4 (medium dose group) and was administered with 0.055ml of scopolamine and treated with 0.07ml of lutein.
- Group 5 (high dose group) and was administered with 0.054ml of scopolamine and was treated with 0.15ml of lutein.
- Group 6 (standard drug group) and was given 0.096ml scopolamine 30 mins before being administered with 0.035ml of imipramine.

Scopolamine was induced intraperitoneally into the rats and dissolved lutein capsule was used to treat the effect of brain toxicity. Group 6 were given scopolamine 30 mins before being administered imipramine intraperitoneally; this was done to check for the prophylactic attributes of scopolamine against imipramine.

Lutein Administration: Lutein was given orally to the designated groups for a specified period daily. Doses were chosen based on previous research and human dietary intake levels.

Scopolamine-Induced Anxiety and Depression: All experimental groups (except the negative control) received scopolamine to induce anxiety and depression following established protocols.

Exposure of Animals to Test Substances

Animal Acclimatization: Upon arrival, the rats were weighed, identified, and housed in wire-mesh cages with sawdust bedding for dryness.

They were allowed to acclimate for one week under standard laboratory conditions:
Temperature: 18-26°C (64-79°F)
Light/dark cycle: 12 hours each

After acclimatization and toxicity test, the rats were weighed, and the weight was between 105g-153g. The Wistar rats were allocated into six groups. Administration of lutein was done orally using oral cannula and administration of scopolamine was done Intraperitoneally using a Iml syringe.

Collection of Blood Samples

After 14 days of administration, prior to the termination of the experiment, the rats were weighed and their weight was recorded. Blood was obtained through jugular vein after the rats were anesthetized and put into heparinized bottles and blood samples (Serum) was analyzed for biochemical parameters (Neurotransmitter, Neuropeptide, Protein and Lipid)

Statistical Analysis

Data were analyzed using the Graph Pad prism 8 software, and Results were expressed as mean ± SEM. Comparisons was done by using One-way Analysis of Variance (One-way ANOVA) followed by Newman-Keuls'post hoc multiple comparison test.

RESULTS AND DISCUSSION

The experimental groups in this study were categorized as follows:

Group 1: Negative Control
Group 2: Scopolamine only treated group
Group 3: Scopolamine + Lutein (20mg/kg)
Group 4: Scopolamine + Lutein (40mg/kg)
Group 5: Scopolamine + Lutein (60mg/kg)
Group 6: Scopolamine + Imipramine (10mg/kg).

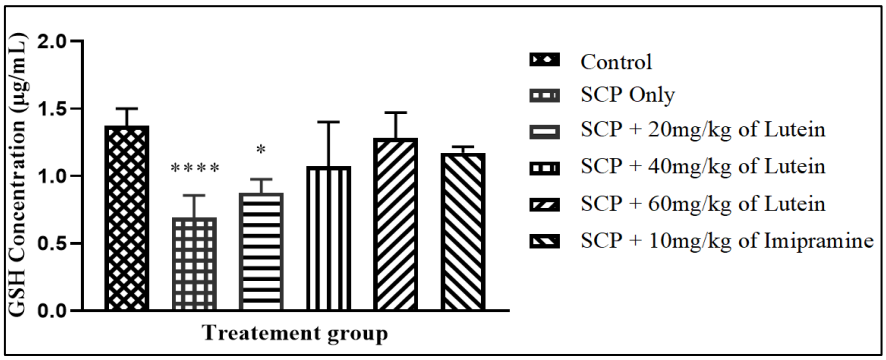

Figure 1: Graphical Representation of the Glutathione Concentration

The columns represent the mean values and error bars indicate the standard deviation (SD) of our independent experiments. CTRL = Control, SCP = Scopolamine, STD = Standard drug. * indicates statistical significance of scopolamine and treatment versus the negative controls. * significant at P<0.05 and **** significant at P<0.0001.

The figure shows a very significant rise in catalase concentration in group 2) P<0.0001) and in group 3 (P<0.001) when compared to Control group. There was no significant difference in GSH concentrations in group 4, 5 and 6 when compared to the control group. This suggests that medium dose, high dose and imipramine improved GSH concentration levels to normal.

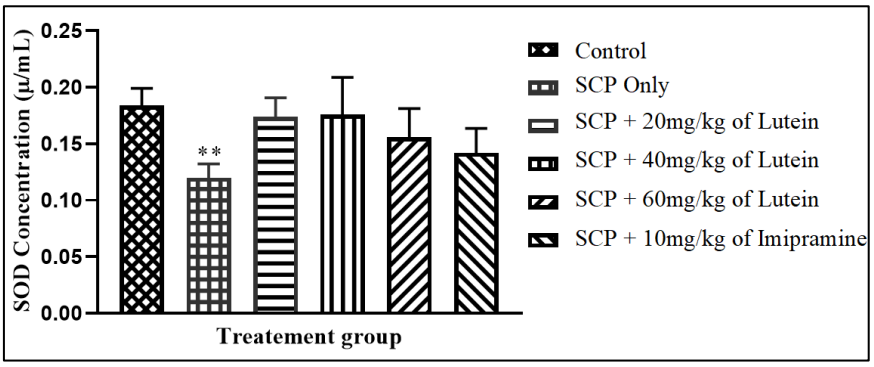

Figure 2: Graphical Representation of the Superoxide Dismutase Concentration

The columns represent the mean values and error bars indicate the standard deviation (SD) of our independent experiments. CTRL = Control, SCP = Scopolamine, STD = Standard drug. *Indicates statistical significance of scopolamine and treatment versus the negative controls. **significant at P<0.01.

There was a significant decrease in the concentration of SOD in group 2 (P < 0.01) when compared to the control group. Also, there was no significant difference in SOD concentrations of groups 3, 4, 5 and 6 when compared to the control group. This suggests that scopolamine decreases the level of SOD while lutein and imipramine improve the decreased level of SOD.

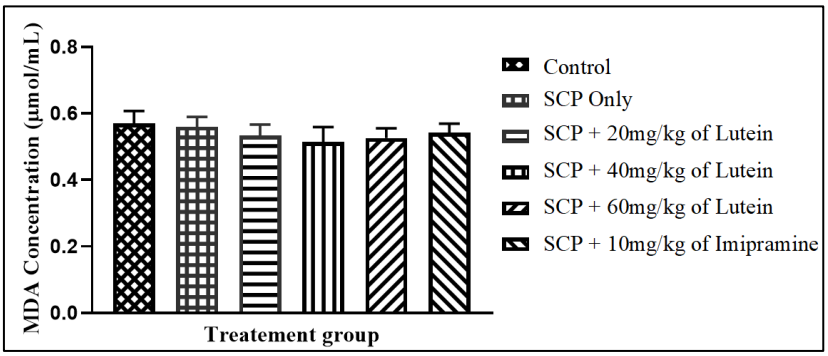

Figure 3: Graphical Representation of the Malondialdehyde Concentration

The columns represent the mean values and error bars indicate the standard deviation (SD) of our independent experiments. CTRL = Control, SCP = Scopolamine, STD = Standard drug.

It can be seen that there is no significant difference in MDA concentration across all groups. This suggests that MDA concentrations is not affected by scopolamine, lutein and imipramine.

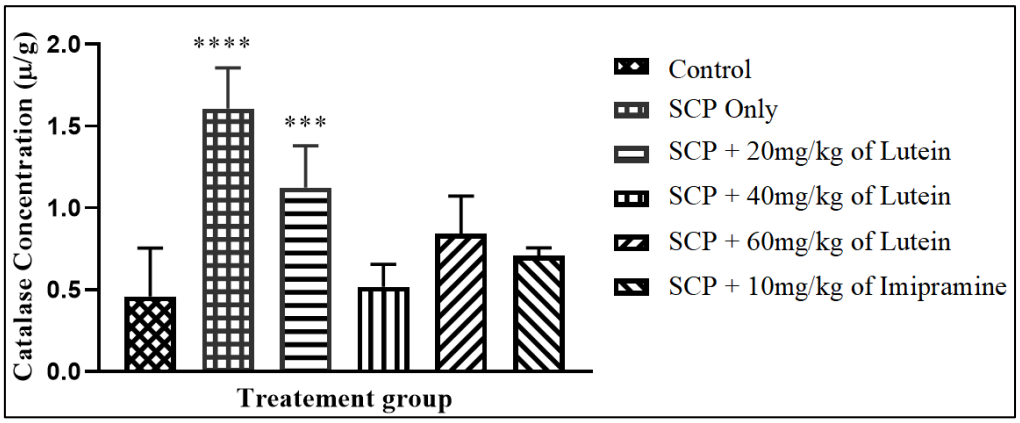

Figure 4: Graphical Representation of the Catalase Concentration

The columns represent the mean values and error bars indicate the standard deviation (SD) of our independent experiments. CTRL = Control, SCP = Scopolamine, STD = Standard drug. * indicates statistical significance of scopolamine and treatment versus the negative controls. *** significant at P<0.001 and **** significant at 0.0001.

From the figure above, it can be seen that there is no significant difference in MDA concentration across all groups. This suggests that MDA concentrations is not affected by scopolamine, lutein and imipramine.

DISCUSSION

Figure 1: Glutathione (GSH) Concentration

In scopolamine-only group (Group 2), the GSH levels were significantly decreased ($P < 0.0001$) suggesting that scopolamine has caused oxidative stress. Nevertheless, Lutein supplementation at a moderate (40 mg/kg) and high (60 mg/kg) dose significantly increased GSH concentrations to the levels of the control group. This implies that Lutein could reduce oxidative stress a result which is in line with the study conducted by Nataraj *et al.,* (2015) and Iyer *et al.,* (2024) that observed that Lutein had antioxidant effects in neurodegenerative models.

Figure 2: Superoxide Dismutase (SOD) Concentration

The level of SOD was found to be significantly lower in scopolamine group ($P < 0.01$) that indicates the scopolamine has caused oxidative stress. Groups treated with Lutein at dose of 20, 40 and 60 mg/kg exhibited recovery of SOD towards normalcy as seen in the control group underlining the antioxidant property of Lutein. These findings are also consistent with the findings of Budzynska *et al.,* (2014), who underlined that antioxidants may have a beneficial impact on scopolamine-induced oxidative damage.

Figure 3: Malondialdehyde (MDA) Concentration

There was no significant difference in MDA levels across all groups, which implied that lipid peroxidation might not be a major factor in scopolamine induced toxicity or is effectively prevented by Lutein and imipramine treatment.

Figure 4: Catalase Concentration

Catalase levels were reduced in the scopolamine only group by 42% ($P < 0.0001$), which reflects low antioxidant activity. Lutein at medium and high doses increased the enzyme's concentration to the levels of the control group. These findings support the earlier work done on the part played by Lutein in increasing the enzymatic antioxidant defense.

CONCLUSION

The findings of the present study support the neuroprotective and antidepressant-like role of Lutein for the amelioration of scopolamine-induced depression like behavior in Wistar rats. The behavioral and biochemical changes induced by scopolamine, which is well known for its effects on oxidative stress, cholinergic dysfunction and neurotrophic factors were significant. Lutein reduced these effects in a dose-dependent manner by elevating antioxidant enzyme activity (GSH, SOD, and catalase).

The forced swimming test (FST), tail suspension test (TST), and open field test (OFT) also supported the ability of Lutein in reducing depression-like behavior. In the tests, Lutein was shown to be highly potent with high doses giving results that were almost as good as imipramine, a drug used in the treatment of depression. This means that the antioxidative, anti-inflammatory and neurotrophic-enhancing effects of Lutein play a major role in its therapeutic value.

The present study demonstrates that Lutein has the potential to enhance cognitive and behavioral functions, and reduce scopolamine-induced neurotoxic

effects, which suggest that Lutein could be a safe and natural adjunct or an add-on therapy in the management of depressive disorders and neurodegenerative diseases. The impact on oxidative stress and neurotrophic signaling pathways indicates that it may have potential uses in other ailments that are characterized by impaired cognition and neuronal damage.

These outcomes are in consonance with the findings of Nataraj *et al.,* (2015), Ahn and Kim (2021) and Tonin et al., (2019) who have shown that Lutein has potential to restore mitochondrial dysfunction, oxidative stress and cholinergic deficits. Due to the fact that depression and related conditions involve multiple pathways, Lutein can be a good candidate due to its activity on several pathways.

Future studies should explore;

1. The precise molecular pathways through which lutein exerts its neuroprotective effects, particularly its interaction with neurotransmitter systems and neuroinflammatory markers.
2. The most effective dose of lutein for neuroprotection, considering both efficacy and potential toxicity.
3. Clinical trials in human populations are necessary to assess lutein's potential.

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