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Lipid-Modulatory Role of Orange (*Citrus sinensis*) Peel Extract in Paraquat-Exposed Mice

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Abstract

Several studies have looked into the effectiveness of orange peel extracts (OPE) in reducing oxidative stress and neurodegenerative diseases linked to paraquat (PQ) exposure. This study evaluated the lipid-modulatory potential of OPE in PQ-exposed animal model using thirty male Swiss mice (20 - 25g), which were divided into six treatment groups (n=5). Group 1 served as the control and received only the vehicle, Groups 2 and 3 were treated with OPE (100 mg/kg and 200 mg/kg, respectively), Group 4 received PQ (10 mg/kg), while Groups 5 and 6 received OPE (100 mg/kg and 200 mg/kg, respectively) for the first half of the experiment, followed by treatment with PQ (10 mg/kg) for the second half of the study. Administration of various treatments lasted 21 days, thereafter, biochemical assays were carried out to assess the effects of PQ and OPE on some lipid profile biomarkers. The findings demonstrated that OPE, particularly at 200 mg/kg, significantly alleviated lipid dysregulation caused by PQ (10 mg/kg) ($p<0.05$). The results showed that OPE restored PQ-induced elevation of total cholesterol (TC), triglyceride (TG), and Low-density Lipoprotein cholesterol (LDL-C), OPE also restored PQ-induced depletion of High-density Lipoprotein cholesterol (HDL-C). Conclusively, orange peel extract mitigates lipid dysregulation in the brain and serum of PQ-treated mice. Additionally, further research is warranted to elucidate the optimal dosages and potential side effects of the extracts in clinical trials.

Keywords: Paraquat, Lipid dysregulation, Orange peel

Introduction

Multiple studies have provided supporting evidence that exposure to neurotoxic pollutants like paraquat in the environment is a contributing factor to the increasing incidence of brain disease in rural agricultural areas (Tolosa *et al*., 2021). Paraquat (1,1-dimethyl-4,4-bipyridinium dichloride) (PQ) is a popularly used(non-selective herbicide in many regions (Breckenridge *et al*., 2013). Adipose tissue is the body's most lipid-rich organ, followed by the brain. In the brain, lipids are crucial for the creation of membranes, signalling pathways, and energy storage (Kao *et al*., 2020). The pathophysiology of neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD), is intimately linked to dysregulation of lipid metabolism in the brain. Exposure to environmental contaminants disrupts the synthesis or breakdown of lipids in the brain of mice and rats according to numerous in vivo or in vitro studies (Akinloye *et al*., 2013; Kao *et al*., 2020; Zhang *et al*., 2020).

Simple lipids called triglycerides (TG) are involved in the transportation and storage of energy. Serum TG comes from two sources: liver production and intestinal absorption. These lipids play a significant role in triglyceride-rich proteins, which include chylomicrons, very-low-density lipoprotein (VLDL), and the particles left

over (free fatty acids) when they are broken down (Peng *et al*., 2017). Reducing TG may enable the reversal of cognitive impairment in mice (Farr *et al*., 2008). Data obtained from animal research indicate that TG contributes to progressive cognitive decline via the decreased maintenance of the N-methyl-d-aspartate component of hippocampus long-term potentiation (Farr *et al*., 2008). The possibility of cognitive decline in old people is correlated with serum TG levels measured in midlife, according to data from multiple longitudinal studies (Kalmijn *et al*., 2000).

About 20% of total cholesterol in humans is found in the brain, which has the greatest concentration of any organ. The majority of the cholesterol in the brain is in the form of unesterified cholesterol, and the concentration of this kind of cholesterol is higher in the brain than in any other tissue (~23 mg/g) (Mahley, 2016; Jin *et al*., 2019). Multiple sclerosis (MS) and other neurological illnesses have also been linked to HDL (High-density Lipoprotein) plasma levels. According to reports, patients with acute phase MS have lower HDL-C (High-density Lipoprotein Cholesterol) levels than those in the remission phase, and they have a higher chance of developing acute inflammatory lesions, which can be seen by MRI (Magnetic Resonance Imaging) (Salemi *et al*., 2010). The potential of HDL to influence the innate immune system may be the reason for the correlation between HDL and MS. (Salemi *et al*., 2010; Weinstock-Guttman *et al*., 2011). Additionally, HDL prevents endothelial cells from expressing adhesion molecules in response to cytokines. There have been further reports of HDL-C abnormalities in people with mental illnesses (Vitali *et al*., 2014).

Tong *et al*., 2022 found that PQ exposure resulted in significant lipid metabolism disorders in the midbrain of mice. Glycerophospholipids, sphingolipids, and glycerides were the most prevalent lipids, according to classification analysis, as well as glycolipids, fatty acyl acids, and steroids. Following 8 weeks of PQ treatment, the analysis also demonstrated a substantial change in the levels of long-chain fatty acids based on the fraction of fatty acid chain lengths in each subclass of lipids. These findings unequivocally showed that PQ exposure changes the lipid profile in the mouse midbrain and causes problems related to lipid metabolism. Since mice's midbrain lipid levels changed dramatically following PQ treatment, an additional study was done to determine the modified lipid contents and compositions. It was discovered that six distinct lipid categories contained 27 significantly changed subclasses (Tong *et al*., 2022). Increased levels of triglycerides and cholesterol have been associated with cardiovascular diseases, and prior research has primarily documented these to be linked with the acute toxic effects of paraquat (Sadava *et al*., 2011). Triglycerides build up in tissues because they cannot be transferred when these lipoproteins are not generated. In a study by Sadava *et al*., 2011, an increase in oxygen radical production may have caused an observed increase in cholesterol level following PQ treatment in rats (Sadava *et al*., 2011). In 2013, a study by Akinloye *et al*., (2013) investigated the dose-dependent effects of PQ on triglycerides, cholesterol, C-reactive protein, and organ histology involved in biotransformation. The study found that a rise in PQ concentration is closely followed by a rise in triglycerides and cholesterol. The severity and prognosis of acute poisoning can be accurately predicted by these biomarkers. PQ may put an animal at risk for coronary heart disease, as evidenced by the marked rise in triglyceride and cholesterol levels. The absence of Very Low Density Lipoprotein (VLDL) synthesis could be the cause of the elevated triglyceride levels (Akinloye *et al*., 2013).

To defend against oxidant-induced cellular damage and lipid dysregulation, cells must employ a variety of antioxidant methods

because of the possibility of attack by oxidants (Suntres, 2002). A good source of such antioxidants is in the peels of orange fruits. The waste part of citrus fruits, mostly consisting of peels and seeds, is used in the treatment of various diseases, such as diabetes and high blood pressure (Chen *et al*., 2017; Hammad *et al*., 2018). Orange (*Citrus sinensis L*.) peels, contain a wide range of bioactive chemicals, such as flavonoids, phenolic acids, carotenoids, and vitamin C, and these chemicals have strong antioxidant capabilities and have been investigated for potential health advantages (Duysak and Kılıç, 2024). Several studies have looked into the effectiveness of orange peel extracts in reducing oxidative stress and related chronic disorders (Shehata *et al*., 2021; Shrinath *et al*., 2023; Silla *et al*., 2025). These extracts have demonstrated promising antioxidant activity, scavenging ROS and protecting cells from oxidative damage. Extracts of orange peel may aid in the prevention and management of chronic illnesses by lowering oxidative stress, strongly associated with the pathophysiology of neurodegenerative illnesses such as Alzheimer's and Parkinson's (Teleanu *et al*., 2022). Orange peel extracts have been extensively shown to possess neuroprotective effects, which may help reduce oxidative damage and maintain brain function due to it's lipid lipid-modulating activity (El-Beltagi *et al*., 2022). Studies show orange peel extract reduces triglycerides and total cholesterol, as well as increases High-Density Lipoprotein (HDL) levels in hypercholesterolemic and diabetic rats. This may be due to the presence of polymethoxylated flavones (PMFs) in peels, which inhibit hepatic lipid synthesis enzymes (e.g., HMG-CoA reductase) and enhance LDL receptor activity (Hammad *et al*., 2018). Citrus flavonoids, including hesperidin and nobiletin, have been shown in preclinical research to influence lipid metabolism via triggering the AMPK and PPARγ signalling pathways (Matsuzaki *et al*., 2022). This study aims to investigate the potential lipid-modulating properties of orange peel extract in paraquat-exposed mice.

Materials and methods

Sample collection, preparation and extraction

Extract Preparation

Orange (*Citrus sinensis)* peels were used in the course of this experiment. They were locally obtained from roadside fruit vendors in Abraka, Delta State, identified by the Department of Botany, Delta State University, Abraka, Nigeria and assigned a voucher number (DELSUH011). The peels were washed in water and air-dried for two weeks and then ground to a fine powder using a Waren blender. The powder was dissolved in ethanol using a ratio of 1g: 5ml of ethanol at 60^{o}C and allowed to stand for 48 hours. It was filtered using a muslin cloth to obtain the crude extract, and then concentrated using a water bath at 50ºC. The resultant extracts were preserved at 4◦C for further use.

Experimental Animal

Thirty adult albino male mice, aged six – seven weeks old, weighing between 20 – 25g were purchased from the animal house of the College of Medicine, Delta State University, Abraka. The animals were housed in cages constructed of stainless steel and plastic throughout the study, which was done at the Biochemistry Laboratory, Delta State University, Abraka, Nigeria. The mice were acclimatized for two weeks, fed on livestock feed and had access to water freely. Ethical approval was granted by the Faculty of Science Research and Ethics Committee (REC/FOS/2025/3), and all experiments were performed in accordance with the NIH Guideline for the Care and Use of Laboratory Animals.

Experimental Design

After acclimatization, the animals were divided into six (6) groups. Each group was

housed separately in well-ventilated plastic cages lined with clean husk bedding to provide an absorbent and stress-minimising environment, these beddings were replaced every 3 days. Throughout the treatment period of twenty-one (21) days, animals were provided with growers' mash (Top Feed, Premier Feed Mills Co. Ltd) and clean drinking water ad libitum to ensure optimal nutrition and hydration. Crude Orange peel ethanol extract (OPE) was prepared at two doses - 100 mg/kg/bwt and 200 mg/kg/bwt, a stock of OPE was prepared by dissolving the extract first in Tween-20 (emulsifier to help the oils in OPE and water mix). While paraquat was prepared at 10 mg/kg/bwt. The dose of OPE used for this study was selected based on results obtained from pilot studies carried out in the laboratory, while that of PQ was in line with the other literature (Abd El-Aziz *et al*., 2022).

The experiment groups were organized as follows:

Group 1: Control (Distilled water and Tween 20)

Group 2: OPE 100mg/kg b.w.

Group 3: OPE 200mg/kg b.w.

Group 4: PQ 10mg/kg b.w., *i.p*

Group 5: OPE 100mg/kg b.w. + PQ 10mg/kg, *i.p*

Group 6: OPE 200mg/kg b.w. + PQ 10mg/kg, *i.p*

Key: OPE = Orange Peel Ethanol Extract; PQ = Paraquat; *i.p* = intraperitoneally

Mice in group 1 received the vehicle used in dissolving OPE (Distilled water and Tween 20). The mice in groups 2 and 3 were given orange peel extract orally at indicated doses at two-day intervals. Mice in group 4 also received paraquat intraperitoneally, twice a week, one injection every 5 days throughout the study period. Cotreatment groups (5 and 6) received only OPE for the first 10 days of the study before paraquat was administered for the remaining half (remaining 10 days) of the study. This was done to determine the protective role of OPE on PQ-induced damage. The period of administration was 21 days.

Collection of Tissue Sample

At the end of the 21-day experiment period, the mice were fasted for 12 hours (7 pm to 7 am), and thereafter, they were sacrificed for the collection of blood samples and dissected for the collection of the brain. Blood samples were collected from mice and put into plain tubes to allow the separation of serum. Tubes were centrifuged at 2500 rpm for 15 minutes, and supernatants were stored in a freezer at 4 ºC until required. Brain tissue was rinsed in cold saline, and 0.5 g of wet brain tissue was homogenized in 4.5ml of normal saline. The homogenates were centrifuged at 2500 rpm for 15 minutes, and supernatants were stored in a freezer at 4 ºC until required.

Biochemical assay

Triglyceride levels were determined using the SPECTRUM Diagnostics Liquizyme kit (GPO-PAP-enzymatic colorimetric method), Total cholesterol levels were determined using SPECTRUM Diagnostics liquizyme kit (CHOD-PAP-enzymatic colorimetric method), High Density Lipoprotein (HDL) was estimated using the precipitation method (Fossati and Prencipe, 1982). and Low-Density Lipoprotein Cholesterol (LDL-C) levels were determined using the other lipid profile markers with the formular: LDL-C = Total Cholesterol – HDL – (Triglyceride/5)

Statistical analysis

Data points are represented as Mean ±SEM. The results were analyzed using one-way analysis of variance (ANOVA) on GraphPad Prism® software version 9.3.1 and levels of significance for all tests were set at $P< 0.05$.

Results and Discussion

Indicators of lipid profile measured included were total cholesterol, HDL, LDL, and triglycerides (TG). A study by Akinloye *et al*., (2013) found that a rise in PQ concentration is closely followed by a rise in triglycerides and cholesterol through investigations on the dose-dependent effects of PQ on these markers and organ histology involved in biotransformation. Thus, the severity and prognosis of acute paraquat poisoning can be accurately predicted by these biomarkers. These findings also indicate that PQ may put an animal at risk for coronary heart disease, as evidenced by the marked rise in triglyceride and cholesterol levels (Akinloye *et al*., 2013)(Figure 1a and 1b). Paraquat exposure has been found to be associated with increased levels of triglycerides and cholesterol in cardiovascular diseases. Triglycerides build up in tissues because they cannot be transferred when these lipoproteins are not generated (Sadava *et al*., 2011). Increased oxygen radical production may be the cause of the observed increased cholesterol level, which is also consistent with the finding that PQ treatment in rats results in elevated cholesterol levels (Sadava *et al*., 2011). A previous study by Tong *et al*., 2022 found that PQ exposure resulted in significant lipid metabolism disorders in the midbrain of mice. Their findings indicate that following 8 weeks of PQ treatment, the analysis demonstrated a substantial change in the levels of long-chain fatty acids based on the fraction of fatty acid chain lengths in each subclass of lipids, showing that PQ exposure changes the lipid profile in the mouse midbrain and causes lipid metabolism problems. Additional studies to determine the modified lipid contents and compositions discovered that six distinct lipid categories (Glycerophospholipids, sphingolipids, glycerides, glycolipids, fatty acyl acids, and steroids) contained 27 significantly changed subclasses (Tong *et al*., 2022).

The pathophysiology of neurodegenerative disorders, including Alzheimer's Disease (AD) and Parkinson's Disease (PD), is intimately linked to dysregulation of lipid metabolism in the brain. Exposure to environmental contaminants such as PQ disrupts the synthesis or breakdown of lipids in the brain, according to numerous in vivo or in vitro studies (Zhang *et al*., 2020). Results from this study showed that orange peel extract improved lipid profile biomarkers; triglycerides (TG), total cholesterol, high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL) in the brain (Figure 1a) and serum (Figure 1b) in experimental mice. This result is in tandem with the work of Hammad *et al*., (2018). In this study, orange peel positively regulated diabetic-induced lipid abnormalities. They demonstrated that all orange peel-treated groups had significantly lower serum levels of triglycerides and total cholesterol (Hammad *et al*., 2018). *Citrus sinensis*-fortified biscuits have also been found to decrease serum cholesterol, triglycerides, and LDL cholesterol levels while increasing HDL cholesterol (Youssef *et al*., 2013).

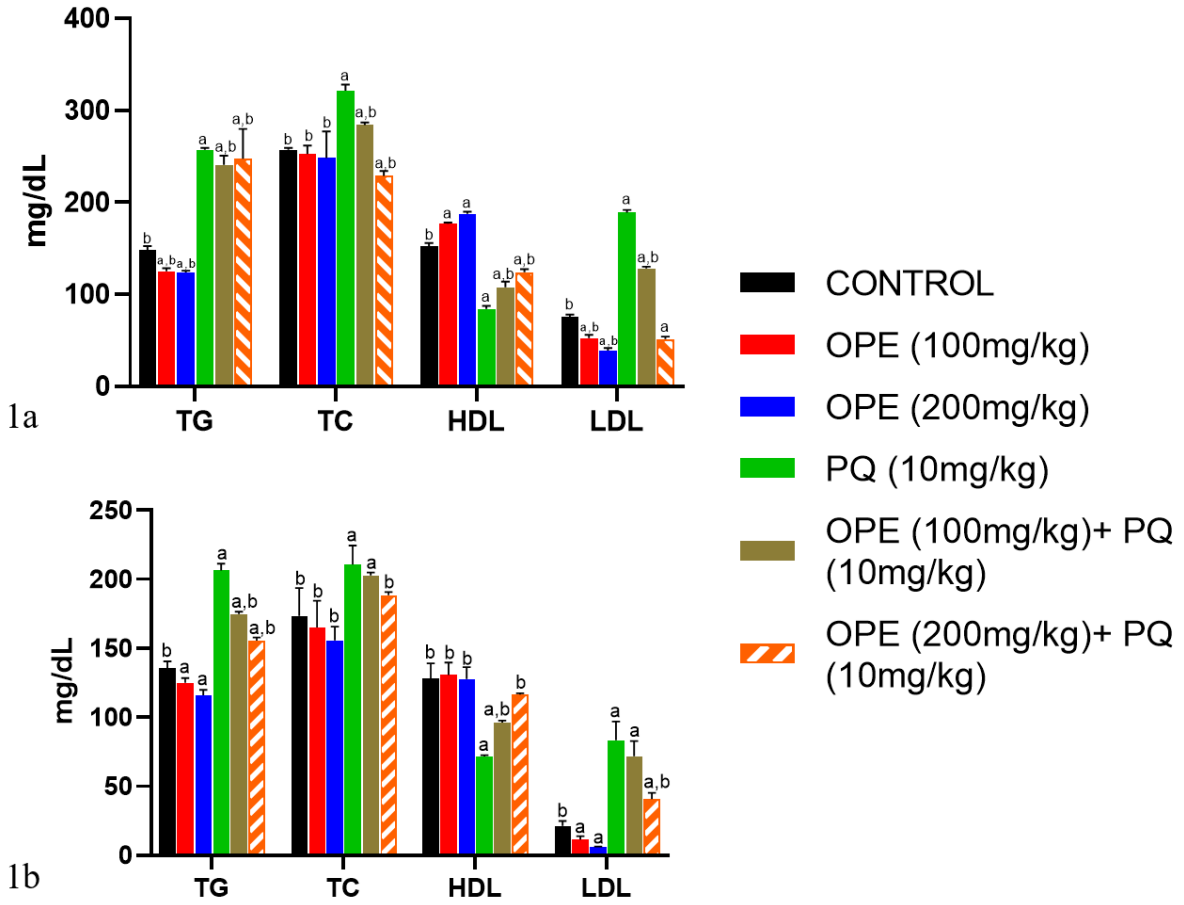

Figure 1: Effect of OPE on brain (Figure 1a) and serum (Figure 1b) lipid profile in paraquat-exposed mice after a 2-week treatment period. Data points are expressed as mean ± standard deviation (n=5). [a]($p<0.05$) are considered significant compared with the control group. [b]($p<0.05$) are considered significant compared with the PQ (10 mg/kg) group. **OPE**: Orange Peel Ethanol Extract; **PQ**: Paraquat; **TG**: Triglyceride; **TC**: Total Cholesterol; **HDL**: High Density Lipoprotein; **LDL**: Low Density Lipoprotein

Results from this study show that there were significant increases ($p<0.05$) in levels of TG, TC, and LDL-C in the brain and serum of mice in PQ groups, as well as a decrease ($p<0.05$) in HDL-C levels compared to the control group. The administration of OPE at both doses significantly decreased ($p<0.05$) TG, TC and LDL-C levels, while it increased ($p<0.05$) HDL-C in cotreatment groups when compared with PQ (10 mg/kg b.w.). However, the dose of 200 mg/kg b.w. was found to be more effective in the serum. These findings are consistent with those of Youssef *et al*., (2013), who found that fortified biscuits containing powdered citrus peels decreased serum cholesterol, triglycerides, and LDL cholesterol levels, all of which are known to raise the risk of heart disease and contribute to conditions like diabetes and obesity. Additionally, fortified biscuits increased HDL cholesterol, which is advantageous since it can offset the high levels of bad cholesterol (LDL cholesterol) without having the same negative side effects as other prescription medications (Youssef *et al*., 2013). Another study also found that Citrus sinensis peels reduced the levels of various serum lipids in male mice, including total cholesterol

(TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and very low-density lipoprotein cholesterol (VLDL-C) (Parmar and Kar, 2008).

OPE's lipid-modulating activity is primarily attributed to its ability to inhibit hepatic lipid synthesis. Studies show orange peel extract reduces Triglycerides (TG) by 15–35%, total cholesterol by 10–30% and increased High-Density Lipoprotein (HDL) levels by 10–20% in hypercholesterolemic and diabetic rats. This may be due to the presence of polymethoxylated flavones (PMFs) in peels, which inhibit hepatic lipid synthesis enzymes (e.g., HMG-CoA reductase) and enhance LDL receptor activity. Also, Pectin in peels can bind to bile acids, reducing cholesterol reabsorption (Hammad *et al*., 2018). Numerous citrus flavonoids, including hesperidin and nobiletin, have been shown in preclinical research to influence lipid and blood glucose metabolism via triggering the AMPK and PPARγ signalling pathways (Matsuzaki *et al*., 2022).

Conclusion

This study provides preclinical evidence which suggests that orange peel ethanol extract ameliorated lipid dysregulation caused by paraquat exposure via mechanisms related to inhibition of inflammation and inhibition of hepatic lipid synthesis. Hence, further studies are recommended to explore its molecular mechanisms and potential for clinical application.

Conflict of Interests

The authors declare no conflict of interest.

Authors' Declaration

The authors of this article say that the ideas and work in it are their own and that they will be responsible for any claims that come up because of this article.

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