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Evaluation of the Effect of Antioxidant-Rich Fruits against Depression Induced By Dexamethasone in Rats

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ABSTRACT

Major Depressive Disorder (MDD) is a psychological disease with a growing global burden exacerbated by the COVID-19 pandemic. Studies have shown MDD to be caused by seemingly variable but intertwined molecular mechanisms. Current evidence connects oxidative stress to several psychiatric disorders, including anxiety and major depression, although the mechanism(s) and pathway(s) involved are not fully understood. This evaluation therefore explored the pathway of depression via oxidative stress and aimed to evaluate the effect of antioxidant-rich fruits (mango, carrots and watermelon) on oxidative stress markers in rats treated with Dexamethasone to induce depression.

30 subjects were grouped into 5: Group 1 (positive control) – no treatments given, Group 2 was treated with Dexamethasone only, Group 3 was treated with Dexamethasone and watermelon juice, Group 4 was treated with Dexamethasone and carrot and mango juice and Group 5 was treated with Dexamethasone and Gingko Biloba.

Blood and homogenate brain samples were used to determine oxidative stress parameters (SOD, GPx, GSH, MDA), the lipid profile (HDL, LDL and TAG) and the levels of glucose, C-reactive protein and serotonin.

Results showed a significant ($p<0.01$) increase in High-Density Lipoprotein (HDL) and a significant decrease in Low-Density Lipoprotein (LDL), Triacylglycerol (TAG) and Malondialdehyde (MDA) levels in the group treated with the juice of carrot and mango compared to the positive control. A significant increase was observed in Superoxide Dismutase (SOD) and reduced glutathione (GSH) levels in the group treated with watermelon juice at ($p<0.001$). Results also showed a significant decrease in C-Reactive Protein (CRP) levels in the groups treated with watermelon and, carrot and mango, respectively. Treatment with watermelon and, carrot and mango juice did not significantly increase serotonin levels.

Findings revealed that oxidative stress markers linked to depression improved with watermelon juice, the lipid profile improved with carrot and mango juice, and the acute-phase reactant marker of inflammation decreased in groups treated with watermelon and carrot and mango.

I. INTRODUCTION

Major depressive disorder (MDD) is a diverse disease affecting one in five persons and is a top cause of debility worldwide (Filatova et al., 2021). The lifetime occurrence of MDD ranges from 20% to 25% in women and 7% to 12% in men (Wang et al., 2017). Depression is an important determinant of life quality and persistence, accounting for about 50% of psychiatric sessions and 12% of hospital admissions (Wang et al., 2017). MDD can occur at any age. Depression causes severe suffering and disruption of life and, if untreated, can be terminal. Till this time, pharmacological, psychological and physical intercessions are the mainstay of the treatment of MDD. However, a significant populace with depression are unresponsive to these treatments (Wu et al., 2021).

Several studies have recently indicated the vital role played by oxidative stress in the molecular mechanism of major depressive disorder (Bakunina et al., 2015). The emergence of numerous metabolic dysfunctions is etiologically linked to oxidative stress (Butt et al., 2009). Uncontrolled oxidation has been shown to produce excessive reactive oxygen species (ROS), which is a known cause of a number of illnesses that can be treated with diets high in phytochemicals and

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antioxidants (Butt et al., 2009) A chronic imbalance between oxidation and anti-oxidation, which results in the harming of cellular macromolecules, is referred to as oxidative stress. Greater levels of reactive oxygen species in the blood indicate higher levels of oxidative stress. The harmful effects of oxidative stress are offset by antioxidants. A reduced antioxidant state denotes a lower level of circulating antioxidant molecules to counteract molecular oxidation (Lui et al., 2015). Some studies have demonstrated that oxidative stress markers in the red blood cells (RBC), urine, peripheral blood, mononuclear cells, cerebrospinal fluid and post-mortem brains of depressed patients were abnormal (Lui et al., 2015). The high concentration of unsaturated fatty acids, high oxygen consumption per unit weight, high concentration of essential components of lipid peroxidation (LP), and dearth of antioxidant defense systems, interestingly, appear to make the brain more vulnerable to ROS/RNS. According to a recent meta-analysis that combined information from studies using various oxidative stress markers, oxidative stress is enhanced and antioxidant defenses are reduced in depression (Palta et al., 2014).

Overproduction of ROS damages cellular components, causing the synthesis of pro-inflammatory chemicals including malondialdehyde and 4-hydroxynonenal as well as damage-associated molecular patterns that trigger immunological response and ultimately result in cell death (Bakunina et al., 2015). The association between psychological distress, such as depression, and physical disease is generally recognized to be due to an increase in cortisol levels brought on by the hypothalamic-pituitary-adrenal axis (Barden 2004). In comparison to healthy controls, patients with major depressive disorder and generalized anxiety disorder had greater MDA and lower vitamin E levels (Bal et al., 2012).

A powerful synthetic glucocorticoid called dexamethasone is used to assess the health of the hypothalamic-pituitary-adrenal axis (Cynthia et al., 2013). Depression is one of the psychiatric illnesses that GC medications and high cortisol levels can cause (Mesripour et al., 2019). By differently changing the gut microbiota and inducing macroglia activation, dexamethasone causes depression-like behaviors in mice (Wu et al., 2021).

Fruits rich in carotenoids (Zuluaga et al., 2017), beta-carotene specifically (Kasperczyk et al., 2014), anthocyanins (Speer et al., 2020) and lycopene (Naz et al., 2014) have been suggested for the prevention of long-term, neurodegenerative illnesses because of their anti-inflammatory and antioxidant capabilities. Example of such fruits are Mango, Carrots, Watermelon and Gingko Biloba which have been chosen for their local availability and ease of access.

Around the world, about 280 million people suffer from depression, making it a common condition (IHME 2021). Depression may develop into a serious medical problem if it is recurrent and of moderate or severe degree. The worldwide Covid19 outbreak has caused a rise in anxiety and depression symptoms. More than 75% of people in low- and middle-income nations do not obtain medication despite there being established, efficient methods for mental diseases (Evans-Lacko et al., 2018). One of the obstacles to providing good care is a shortage of treatment resources, which can be overcome by using local alternatives in their place.

II. MATERIALS AND METHODS

2.1 Materials

2.1.1 Chemicals

All reagents which were used for this research were of analytical grade. Ethanol, distilled water, concentrated H2SO4, Sodium dodecyl sulphate.

2.1.2 Equipment

The equipment used for this research include; Rotor centrifuging machine, Syringes and needles, ELISA kit, cotton wool, Plain tubes, EDTA tubes, dissecting kit, analytical weighing balance, gloves, conical flasks, test tubes, feeding tubes, non-heparinised tubes, filter paper and separating funnel.

2.1.3 Study Area

This study was carried out in Keffi town which lies between longitude 8-5^{o}S and latitude 7^{o}N and above the sea level of latitude 630m. It is approximately 53km from the Federal Capital Territory, Abuja and 133km from the state capital Lafia (Awka, et al., 2007).

2.1.4 Materials

Watermelon, Mango and Carrot were purchased from Keffi market. The antidepressant Ginkgo biloba, and Dexamethasone Tablets used in this research study, were also purchased from the Keffi market.

2.1.5 Experimental Animals

Thirty adult Albino rats weighting 180-200 g were used in the study. The rats were housed

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6 rats per cage and allowed acclimatization to laboratory status for two weeks before the beginning of experiments according to Bawazir, (2018). These animals were maintained at room temperature and with a 12h light/12h dark cycle and allowed ad libitum access to feed and water. Ethical approval was obtained from NSUK Animal Care and Use Research Ethics Committee (NSUK-ACUREC). All experimental steps were made according to the ethical rules of NSUK-ACUREC, Nasarawa State University, Keffi.

2.2 Experimental Design

After the acclimatization, the animals were weighed and divided into 5 Groups with 6 animals each per Group:

Group 1: Positive Control –received feed and water only throughout the period of 2 weeks.

Group 2: Negative Control- received Dexamethasone throughout the period of 2 weeks.

Group 3: received Dexamethasone and watermelon during the period of 2 weeks

Group 4: received Dexamethasone and a juice of Mango and Carrot during the period of 2 weeks.

Group 5: received Dexamethasone and Gingko Biloba for a period of 2 Weeks.

Treatments were administered orally and with the aid of a feeding tube.

2.3 Method

2.3.1. Sample preparation

The samples were crushed and filtered to pass a 0.5 mm sieve. The extracted juice was weighed and administered per body weights to the rats.

2.3.2 Collection of Blood Sample

After the administration for two (2) weeks, the rats were anesthetized with diethyl ether and blood samples were collected with the aid of a capillary tube via an ocular vein puncture into a plain bottle for biochemical analysis.

2.4 Biochemical Analysis

Biochemical analysis was performed using Standardized diagnostic kits (Randox by Randox laboratories ltd. United Kingdom) according to the modified convention. The biochemical parameters including blood glucose levels, HDL, LDL, TAG, CRP, and Serotonin levels were determined using the method of Friendwald (1972), Tietz (1990), Albers (1978), Jollow et al., (1974), and Ursini (1995) respectively.

III. DATA PRESENTATION AND DISCUSSION

3.1 Result

3.1.1 Effect of Treatment on Lipid and Lipoprotein Profile (HDL, LDL, TAG)

The result of the lipid profile is shown in table 3.1.1. In the table, the HDL level was 63.26±2.61 in Group 1 (positive control). Administration of Dexamethasone in Group 2 (negative control) decreases the HDL level significantly ($p<0.001$). Treatment with watermelon juice in Group 3 shows a non-significant ($p>0.05$) increase in HDL level. However, there was a significant ($p<0.01$) increase in HDL in Group 4 treated with the mixture of carrot and mango.

The LDL level was 12.51±1.86 in the positive control Group. Administration of Dexamethasone in the negative control group increases the LDL level significantly ($p<0.001$). However, there was a non-significant ($p>0.05$) decrease in LDL when watermelon juice was treated. Furthermore, a significant ($p<0.01$) decrease in LDL occurred when the mixture of carrot and mango juice was used to treat the animals.

TAG level was 106.14±4.58 in Group 1 (positive control). The administration of Dexamethasone increases the TAG level significantly ($p<0.01$). However, treatment with watermelon and a mixture of carrot/mango juice reduced the TAG levels significantly at ($p<0.05$) and ($p<0.001$), respectively. No significant ($P>0.05$) difference was observed when the animals were treated with Ginkgo Biloba compared to the positive control.

Table 3.1.1: Effect of Treatment on Lipid and Lipoprotein Profile (HDL, LDL, TAG)

Group	HDL (mg/dl)	LDL (mg/dl)	TAG (mg/dl)
Group 1	63.26±2.61a	12.51±1.86a	106.14±4.58a
Group 2	33.68±3.98d	38.15±2.49d	120.70±0.86c
Group 3	71.14±2.72a	9.14±2.14a	
Group 4	73.07±3.97b	3.48±0.30c	

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95.58±5.18b
67.98±2.48d
Group 5
59.78±2.05a
10.01±2.31a
103.22±5.60a
Mean ± Standard Deviation, a = p>0.05, b = p<0.05, c = p<0.01 and d = p<0.001
Group 1 – Rats fed with feed and distilled water only (no treatment)
Group 2 – Rats treated with Dexamethasone only
Group 3 – Rats treated with Dexamethasone and watermelon juice
Group 4 – Rats treated with Dexamethasone and carrot and mango juice
Group 5 – Rats treated with Dexamethasone and Ginkgo Biloba

3.1.2 Effect of treatment on Brain in vivo Oxidative Stress Markers (SOD, GPx, GSH, MDA)

The antioxidant assay of the rat's brain homogenate is shown in table 4.1.2 The SOD activity was 1.67±0.52 in Group 1 (positive control). Administration of Dexamethasone decreased the SOD activity significantly at (p<0.01). However, treatment with watermelon juice increased the enzyme activity significantly (p<0.001) but had a non-significant (p>0.05) increase when treated with a mixture of carrot and mango juice.

GPx activity was 51.15±2.34 in Group 1 (positive control). Administration of Dexamethasone decreased the GPx activity significantly at (p<0.05). Treatment with watermelon and a mixture of carrot and mango juice produced a non-significant (p>0.05) increase in GPx activity.

GSH level was 3.60±0.37 in Group 1 (positive control). There was no significant (p>0.05) decrease when Dexamethasone was administered. Treatment with watermelon juice increased the GSH level significantly (p<0.001). However, there was a non-significant (p>0.05) increase in GSH level when treated with a mixture of carrot and mango.

MDA level was 3.69±0.27 in Group 1 (positive control). Administration of Dexamethasone increases the MDA level significantly (p<0.05). There was a non-significant (p>0.05) decrease in MDA level when treated with watermelon juice. However, there was a significant (p<0.001) decrease in MDA level when the animals were treated with a mixture of carrot and mango juice. There was no significant (P>0.05) difference when the animals were treated with Ginkgo Biloba compared to the positive control.

Table 3.1.2: Effect of Treatment on Brain in vivo Oxidative Stress Markers

Group
SOD (IU/L)
GPx (IU/L)
GSH (mg/dl)
MDA (mg/dl)
Group 1
Group 2
Group 3
Group 4
1.67±0.52a
0.07±0.01c
3.82±0.27d
2.50±0.59a
51.15±2.34a
43.03±2.71b
57.03±2.41a
54.89±2.96a
3.60±0.37a
3.15±0.12a
7.97±0.89d
4.18±0.15a
3.69±0.27a
5.45±0.45b
2.99±0.15a
1.93±0.40d
Group 5
2.03±0.17a
52.45±4.54a
4.69±0.85a
3.22±0.97a
Mean ± Standard Deviation, a = p>0.05, b = p<0.05, c = p<0.01 and d = p<0.001
Group 1 – Rats fed with feed and distilled water only (no treatment)
Group 2 – Rats treated with Dexamethasone only
Group 3 – Rats treated with Dexamethasone and watermelon juice
Group 4 – Rats treated with Dexamethasone and carrot and mango juice
Group 5 – Rats treated with Dexamethasone and Ginkgo Biloba

3.1.3 Effect of Treatment on C-Reactive Protein (CRP) and Serotonin

Table 4.1.3 shows the C-Reactive Protein (CRP) and Serotonin levels. The CRP level in the blood was 62.65±2.69 in Group 1 (positive control). Administration of Dexamethasone increased the blood CRP significantly (p<0.001). However, there was a significant decrease in CRP levels to (p<0.05) and (p<0.001) in the groups treated with watermelon and a mixture of carrot and mango, respectively. The serotonin level of the brain homogenate of the rats was 0.51±0.13 in

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Group 1. Administration of Dexamethasone had a non-significant ($p>0.05$) decrease in the serotonin level. However, treatment with watermelon and a mixture of carrot and mango increased the serotonin levels non-significantly ($p>0.05$). No significant ($P>0.05$) difference was observed when the animals were treated with Ginkgo Biloba compared to the positive control.

Table 3.1.3: Effect of Treatment on C-Reactive Protein and Serotonin Levels

Group	Group 1	Group 2	Group 3	Group 4
CRP (ug/ml)	62.65±2.69a	79.37±2.41d	56.66±2.82b	27.02±1.97d
Serotonin (per ml)	0.51±0.13a	0.33±0.05a	1.22±0.59d	0.64±0.25a
Group 5				
59.86±1.55a				
0.76±0.08a				

Mean ± Standard Deviation, a = $p>0.05$, b = $p<0.05$, c = $p<0.01$ and d = $p<0.001$
Group 1 – Rats fed with feed and distilled water only (no treatment)
Group 2 – Rats treated with Dexamethasone only
Group 3 – Rats treated with Dexamethasone and watermelon juice
Group 4 – Rats treated with Dexamethasone and carrot and mango juice
Group 5 – Rats treated with Dexamethasone and Ginkgo Biloba

3.2 Result Discussion

Results presented in Table 3.1.1 showed a significant ($p<0.01$) increase in High-Density Lipoprotein (HDL) in the group treated with the juice of carrot and mango compared to the positive control. HDL absorbs cholesterol in the blood and transports it back to the liver for excretion, high levels of HDL can lower the risk of heart disease and stroke (CDC 2022). Low HDL-C is a strong independent risk factor for cardiovascular disease, premature atherosclerosis and increased oxidative stress (Karabacak et al., 2022). Mango fruit is rich in carotenoid compounds, of which β-carotene accounts for 60% of the total carotenoids in the fruit (Saleem-Dar et al.,,,. 2016). Orange carrots are one of the richest dietary sources of provitamin A carotenoids - β-carotene (Klein et al., 2015). Studies have shown an increase in plasma HDL levels associated with the consumption of β-carotene (Marcelino et al., 2020).

Results showed a significant ($p<0.01$) decrease in Low-Density Lipoprotein (LDL) in the group treated with carrot and mango compared to controls. High levels of LDL cholesterol have been shown to increase the risk of heart disease and stroke (CDC 2022). β-carotene is transported in circulation by incorporation into the hydrophobic core of various lipoprotein particles such as LDL (Varsha and Loredana, 2013). Studies have shown significant dose-related decreases in serum total concentrations of LDL and TAG resulting from beta-carotene supplementation (Tsai et al., 1992).

Results showed a significant decrease in Triacylglycerol (TAG) levels in groups treated with watermelon and carrot and mango. Triacylglycerols are the form in which fat energy is stored in adipose tissue. Beta-carotene supplementation has shown antihyperlipidemic effects in rat studies (Silva et al., 2013). Lycopene has shown lipid-lowering properties, reducing the total and LDL cholesterol, triacylglyceride level, LDL oxidation, and synthesis of dysfunctional HDL (Mozos et al., 2018).

Oxidative balance is disrupted during the production of ROSs that successively generate double allylic hydrogen atoms and initiate the oxidation of lipids (Naz et al., 2014). Neutrophils then catalyze the synthesis of hypochlorous acid that causes oxidative injury in terms of cellular damage (Naz et al., 2014). In this situation, the body produces defence enzymes i.e., SOD and glutathione peroxidase (GPx). SOD acts as a first-line defence by producing singlet oxygen into hydrogen peroxide and then GPx and catalase enzymes convert hydrogen peroxide into water. Generally, these enzymes work in harmony but during ROS overproduction, an interruption may occur resulting in necrosis or apoptosis. In such cases, dietary lycopene, found in watermelon, can act as a therapeutic agent to combat excessive ROS production (Erdman et al., 2009). A study by Oberoi and Sogi, 2017 has reported watermelon as the fruit containing the highest bioavailable lycopene which is about 60% more than that found in tomato.

The antioxidant assay of the rats' brain homogenate is shown in Table 4.1.2. Results showed a significant increase in Superoxide Dismutase (SOD) and reduced glutathione (GSH) activity in the group treated with watermelon juice

at ($p<0.001$). Studies show that lycopene can significantly restore antioxidant enzymes including SOD, and reduced glutathione (GSH) in hypertensive patients (Bose and Agrawal, 2007). Lycopene has also been found to be effective in increasing GSH levels in coronary artery disease (Misra et al., 2006). Kim et al., (2011) examined the effect of lycopene in smoker men with low fruit and vegetable intake through a double-blind randomized controlled study. They concluded that lycopene significantly reduces oxidative stress and ameliorates endothelial function.

Results showed a significant ($p<0.001$) decrease in MDA levels in groups treated with carrot and mango juice. Mango fruit is rich in carotenoid compounds, of which β-carotene accounts for 60% of the total carotenoids in the fruit (Saleem-Dar et al., 2016). Orange carrots are one of the richest dietary sources of provitamin A carotenoids - β-carotene (Klein et al., 2015). β-carotene has been found to decrease MDA levels and increase the activities of SOD and GPx (Li et al., 2020).

C-reactive protein (CRP) is a commonly used acute-phase reactant marker of inflammation in the body (Zheng et al., 2019). CRP is an acute inflammatory protein that increases up to 1,000-fold at sites of infection or inflammation (Sproston and Ashworth, 2018). The administration of Dexamethasone increased the blood CRP to a highly significant ($p<0.001$) level but results showed a significant decrease in CRP levels to ($p<0.05$) and ($p<0.001$) in the groups treated with watermelon and carrot and mango, respectively. β-carotene and lycopene have shown potent anti-inflammatory activity in some studies by suppressing Cox2, Nos2, and Tnfa gene expression (Kawata et al., 2018). Treatment with watermelon and carrot and mango increased the serotonin levels non-significantly ($p>0.05$).

IV. SUMMARY, CONCLUSION AND RECOMMENDATIONS

4.1 Summary

Findings revealed that oxidative stress markers linked to depression improved with treatment with watermelon juice, the lipid profile improved with treatment with carrot and mango juice, and the acute-phase reactant marker of inflammation decreased in groups treated with watermelon and carrot and mango. Correlations have been made between the antioxidant content of these fruits and their effects on markers of oxidative stress.

4.2 Conclusion

We conclude that watermelon, carrot and mango ameliorated oxidative stress and inflammation induced by dexamethasone in rats.

4.3 Recommendation

Further studies are required to confirm the phytochemical content of these fruits on their direct effect markers of oxidative stress linked to depression.