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INVESTIGATION OF THE EFFECT OF FRUITS RICH IN ANTIOXIDANTS ON DEPRESSION CAUSED BY DEXAMETHASONE IN RATS

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ABSTRACT: Objective: Major Depressive Disorder (MDD) is a psychological disease with a growing global burden. Oxidative stress has been shown to be a causative mechanism of MDD. This research 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. **Method:** Thirty (30) rats were grouped into 5: Group 1 (positive control), Group 2 (treated with 2.6 mg/kg body weight Dexamethasone only), Group 3 (treated with 2.6 mg/kg b.w. Dexamethasone and 10.53ml/kg b.w. of watermelon juice), Group 4 (treated with 2.6 mg/kg body weight Dexamethasone, and 10.53ml/kg b.w. of carrot and mango juice) and Group 5 (treated with Gingko Biloba). The lipid profile and C-reactive protein (CRP) were determined using blood samples. Brain homogenate was used to determine oxidative stress parameters SOD, GPx, GSH, MDA, and serotonin levels. **Results:** Results of the research showed a significant increase in HDL and a significant decrease in LDL, TAG and MDA levels in Group 4. A significant increase was observed in SOD and GSH levels in Group 3. Results also showed a significant decrease in CRP levels in Group 3 and Group 4. There was also a significant increase in serotonin levels in Group 3. **Conclusion:** The study showed that watermelon, carrot, and mango fruits alleviate oxidative stress parameters which may help reduce the effects of oxidative stress-induced depression in affected individuals.

INTRODUCTION: Major depressive disorder (MDD) is a diverse disease affecting one in five persons and is a top cause of debility worldwide [1]. The lifetime occurrence of MDD ranges from 20% to 25% in women and 7% to 12% in men [2].

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Depression is an important determinant of life quality and persistence, accounting for about 50% of psychiatric sessions and 12% of hospital admissions [2].

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 is unresponsive to these treatments [3].

Recently, many studies have indicated that oxidative stress might play a vital role in the molecular mechanism of major depressive disorder [4]. Oxidative stress is an etiological factor in the onset of various metabolic dysfunctions [5]. There are proven facts that uncontrolled oxidation leads to generate excessive reactive oxygen species (ROS), a causative agent of many ailments that can be addressed through antioxidants/phytochemicals-rich diets [5] Oxidative stress is defined as a persistent imbalance between oxidation and anti-oxidation, which leads to the damage of cellular macromolecules. Higher oxidative stress is indicative of greater reactive oxygen species circulating the body. Antioxidants counteract the damaging effects of oxidative stress. Lower antioxidant status indicates fewer circulating antioxidant molecules to offset the oxidation of molecules [6].

Some studies have demonstrated that oxidative stress markers in the peripheral blood, red blood cells (RBC), mononuclear cells, urine, cerebrospinal fluid and post-mortem brains of depressed patients were abnormal [6]. Interestingly, the brain appears to be more susceptible to ROS/RNS because of the high content of unsaturated fatty acids, high oxygen consumption per unit weight, high content of key ingredients of lipid peroxidation (LP) and scarcity of antioxidant defence systems. A recent meta-analysis pooling data from studies with different oxidative stress markers suggests oxidative stress is increased and antioxidant defences are decreased in depression [7]. Products of oxidative damage found in patients of depression include products from lipid peroxidation, and protein and DNA damage [7].

When present in excess, ROS inflict damage, affecting cellular constituents with the formation of pro-inflammatory molecules, such as malondialdehyde, 4-hydroxynonenal, neoepitopes and damage-associated molecular patterns promoting immune response, and ultimately leading to cell death [4]. An increase in cortisol levels, activated by the hypothalamic-pituitary-adrenal axis, is one well-accepted explanation for the relationship between psychological distress, such as depression, and physical disease [8]. Patients with major depressive disorder and generalized anxiety disorder had higher MDA and lower vitamin E levels than those of healthy controls [9]. Dexamethasone is a potent synthetic glucocorticoid that is used to test the integrity of the hypothalamic-pituitary-adrenal axis [10]. GC drugs and elevated cortisol levels can cause psychiatric disorders including depression [11]. Dexamethasone induces depression-like phenotypes in mice by differentially altering gut microbiota and triggering macroglia activation [12].

Fruits rich in carotenoids [13], beta-carotene specifically [14], anthocyanins [15] and lycopene [16] have been proposed for the prevention of chronic, neurodegenerative diseases due to their antioxidant and anti-inflammatory properties. Examples of such fruits are Mango, Carrots and Watermelon which have been chosen for their local availability and ease of access.

METHODS:

Chemicals: All reagents which were used for this research were of analytical grade. Ethanol, distilled water, concentrated H_2SO_4, Sodium dodecyl sulphate.

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.

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.

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.

Experimental Animals: Thirty adult Albino rats weighing 180-200 g were used in the study. The rats were housed 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.

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- treated with 2.6 mg/kg body weight Dexamethasone only.

Group 3: Treated with 2.6 mg/kg b.w. Dexamethasone and 10.53ml/kg b.w. of watermelon juice.

Group 4: treated with 2.6 mg/kg b.w. Dexamethasone and 10.53ml/kg b.w. of carrot and mango juice during the period of 2 weeks.

Group 5: Received 2.6mg/kg b.w. Dexamethasone and 0.2mg/kg Gingko Biloba for a period of 2 weeks. Treatments were administered orally and with the aid of a feeding tube.

Sample Preparation: The samples were crushed and filtered to pass a 0.5 mm sieve. The extracted juice was weighed and administered at 10.53ml/kg body weight to the rats.

Collection of Blood Sample: After the administration for two 2 weeks, the rats were anaesthetized 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.

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 HDL, LDL, TAG, CRP, and Serotonin levels were determined using the method of Friedwald [17], Tietz [18], Albers [19], Jollow [20], and Ursini [21] respectively. SOD, GSH and GPx activities were determined according to the method of the IFCC [22] and Jollow [20] respectively.

Technique for Data Analysis: Data obtained was analyzed by one-way analysis of variance (ANOVA) with the help of SPSS version 20.0 statistical software. $P<0.05$ is considered significance for all values using F – the test and T-test to determine the significance of differences in Group results and Duncan's multiple range test to locate points of significant differences following the methods outlined by Bailey (1981).

RESULTS:

Effect of Treatment on Lipid and Lipoprotein Profile (HDL, LDL, TAG, Total Cholesterol): The result of the lipid and lipoprotein profile is shown in **Table 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 1: EFFECT OF TREATMENT ON LIPID AND LIPOPROTEIN PROFILE (HDL, LDL, TAG, TOTAL CHOLESTEROL)

Group	HDL (mg/dl)	LDL (mg/dl)	TAG (mg/dl)	Total Cholesterol (mg/dl)
Group 1	63.26±2.61[a]	12.51±1.86[a]	106.14±4.58[a]	97.00±3.02[a]
Group 2	33.68±3.98[d]	38.15±2.49[d]	120.70±0.86[c]	95.97±2.44[d]
Group 3	71.14±2.72[a]	9.14±2.14[a]	95.58±5.18[b]	99.40±3.35[a]
Group 4	73.07±3.97[b]	3.48±0.30[c]	67.98±2.48[d]	90.15±2.25[c]
Group 5	59.78±2.05[a]	10.01±2.31[a]	103.22±5.60[a]	90.43±3.32[a]

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

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 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 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	1.67±0.52[a]	51.15±2.34[a]	3.60±0.37[a]	3.69±0.27[a]
Group 2	0.07±0.01[c]	43.03±2.71[b]	3.15±0.12[a]	5.45±0.45[b]
Group 3	3.82±0.27[d]	57.03±2.41[a]	7.97±0.89[d]	2.99±0.15[a]
Group 4	2.50±0.59[a]	54.89±2.96[a]	4.18±0.15[a]	1.93±0.40[d]
Group 5	2.03±0.17[a]	52.45±4.54[a]	4.69±0.85[a]	3.22±0.97[a]

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.

Effect of Treatment on C-Reactive Protein (CRP) and Serotonin: Table 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 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: EFFECT OF TREATMENT ON C-REACTIVE PROTEIN AND SEROTONIN LEVELS

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

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.

DISCUSSION: Findings from this study showed an increase in High-Density Lipoprotein (HDL) following treatment with carrot and mango. Carotenoids contained in these fruits could explain the observed increase in HDL. Low HDL has been shown to be a strong independent risk factor for increased oxidative stress [24], consumption of mangoes and carrots could therefore reduce the risk for increased oxidative stress. Mango fruit which this group was treated with is rich in carotenoid compounds, of which β-carotene accounts for 60% of the total carotenoids in the fruit [25]. Orange carrots which this group was treated with as well are one of the richest dietary sources of provitamin A carotenoids - β-carotene [26]. Studies have shown an increase in plasma HDL levels associated with the consumption of β-carotene [27].

This study showed a decrease in Low-Density Lipoprotein (LDL) in following treatment with carrot and mango compared to controls. Carotenoids contained in these carrots and mangoes could explain the observed decrease in LDL. β-carotene is transported in circulation by incorporation into the hydrophobic core of various lipoprotein particles such as LDL [28]. Studies have shown significant dose-related decreases in serum total concentrations of LDL resulting from beta-carotene supplementation [29] which correlates with the observed results.

Results from this study showed a significant decrease in Triacylglycerol (TAG) levels following treatment with watermelon, carrot and mango. Triacylglycerols are the form in which fat energy is stored in adipose tissue. Beta-carotene contained in carrot and mango has shown antihyperlipidemic effects in rat studies [30], which this study confirms. Lycopene found in watermelon has shown lipid-lowering properties, reducing the total and LDL cholesterol, TAG level, LDL oxidation, and synthesis of dysfunctional HDL [31], these antioxidants act as scavengers of lipophilic radicals.

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 [32]. 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 [33]. A study by Oberoi and Sogi [34] has reported watermelon as the fruit containing the highest bioavailable lycopene which is about 60%

more than that found in tomatoes this could explain the results reduction of TAG shown in the results. This study showed a significant increase in Superoxide Dismutase (SOD) and reduced glutathione (GSH) activity following treatment with watermelon juice. Studies show that lycopene contained in watermelon can significantly restore antioxidant enzymes including SOD, and reduced glutathione (GSH) in hypertensive patients [35]. Lycopene has also been found to be effective in increasing GSH levels in coronary artery disease [36]. A study by Kim [37] 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. MDA levels decreased significantly following treatment with mango and carrot fruits. β-carotene has been found to decrease MDA levels and increase the activities of SOD and GPx [38] which correlates with the results from this study.

C-reactive protein (CRP) is a commonly used acute-phase reactant marker of inflammation in the body [39]. CRP is an acute inflammatory protein that increases up to 1,000-fold at sites of infection or inflammation [40]. The administration of Dexamethasone in this study significantly increased the blood CRP but results showed a significant decrease in CRP levels following treatment with watermelon, carrot and mango. β-carotene and lycopene contained in these fruits have also shown potent anti-inflammatory activity in some studies by suppressing Cox2, Nos2, and Tnfa gene expression [41]. Results from this study showed that treatment with watermelon, carrot and mango increased the serotonin levels non-significantly ($p>0.05$).

CONCLUSION: Watermelon, carrot and mango fruits contain important antioxidants. These fruits showed ameliorative effects on the lipoprotein and lipid profile measured as well as on biochemical markers of oxidative stress. These effects may synergistically help to reduce the oxidative stress pathway implicated in depression. It is recommended that further research be conducted to determine the mechanism of action of oxidative stress in depressive episodes.

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