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Evaluation of the effect of antioxidant-rich fruits against depression induced 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 is 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.

Keywords: *Depression, Antioxidants, Oxidative Stress, Watermelon, Mango*

Plain English Summary

This research investigated the effects of watermelon, carrot, and mango fruits on the lipid and lipoprotein profile and biochemical oxidative stress markers in rats treated with Dexamethasone to induce depression. Results from this study showed an improvement in the investigated profiles and markers indicating that the antioxidants found in these fruits can reduce oxidative stress.

Background

Major depressive disorder (MDD) is a multifaceted mental health condition that impacts a considerable segment of the global population. It manifests as persistent feelings of sadness, hopelessness, and disinterest in activities once enjoyed, often accompanied by physical symptoms such as changes in appetite and sleep patterns. MDD can significantly impair an individual's daily functioning, affecting their relationships, work or school performance, and overall quality of life. Despite its prevalence and debilitating effects, MDD remains a challenging condition to treat effectively. While various therapeutic approaches, including pharmacological and psychotherapeutic interventions, are available, a significant proportion of individuals with MDD do not achieve full remission with existing treatments. This highlights the need for continued research and innovation in the development of novel therapeutic strategies to address the complexities of MDD and improve outcomes for affected individuals., with profound implications for individual well-being and societal functioning. Studies indicate that MDD affects approximately one in five individuals and ranks among the leading causes of disability worldwide. The prevalence of MDD varies between genders, with higher rates observed in women compared to men. Despite its prevalence and impact, MDD remains a challenging condition to treat effectively [1-2]. Traditionally, the treatment of MDD has relied on pharmacological, psychological, and physical interventions. However, a substantial proportion of individuals with MDD do not respond adequately to these conventional treatments. This treatment resistance underscores the need for a deeper understanding of the underlying mechanisms contributing to MDD and the development of novel therapeutic approaches [3-5]. Recent studies have suggested that oxidative stress may play a role in the underlying molecular mechanisms of MDD. This imbalance arises from an excess of reactive oxygen species (ROS) production relative to the body's antioxidant capacity, resulting in harm to cellular structures. This oxidative damage can affect various biological processes and has been linked to the onset and progression of several metabolic dysfunctions. Research has revealed irregularities in oxidative stress markers across diverse biological specimens among individuals diagnosed with MDD, encompassing peripheral blood, red

blood cells, mononuclear cells, urine, cerebrospinal fluid, and post-mortem brain tissue. Notably, the brain is especially susceptible to oxidative stress due to its heightened oxygen consumption, abundance of unsaturated fatty acids, and constrained antioxidant defenses [6-7].

Meta-analyses have reinforced the connection between oxidative stress and MDD by revealing heightened oxidative stress and diminished antioxidant defenses in depressed individuals. Additionally, biomarkers indicating oxidative damage, including lipid peroxidation byproducts, protein oxidation, and DNA damage, have been observed in MDD patients, underscoring the potential involvement of oxidative stress in the disorder's pathophysiology. Excessive levels of reactive oxygen species (ROS) can lead to cellular damage and trigger inflammatory responses, ultimately contributing to various pathological conditions, including major depressive disorder (MDD). The formation of pro-inflammatory molecules, such as malondialdehyde and 4-hydroxynonenal, as well as the release of damage-associated molecular patterns, promotes immune activation and cell death. Studies have shown that individuals with MDD and generalized anxiety disorder often exhibit elevated levels of malondialdehyde and reduced levels of antioxidants like vitamin E compared to healthy individuals.

The hypothalamic-pituitary-adrenal (HPA) axis, responsible for managing the body's stress response, serves a pivotal function in linking psychological distress with physical health. Elevated cortisol levels, triggered by HPA axis activation during stress, have been linked to the onset of psychiatric conditions, such as depression. Synthetic glucocorticoids like dexamethasone, used to assess HPA axis function, can induce depression-like symptoms by altering gut microbiota and triggering inflammation in the brain [8-10]. In light of these findings, there is growing interest in the potential of antioxidants to mitigate oxidative stress and inflammation associated with MDD. Fruits rich in carotenoids, beta-carotene, anthocyanins, and lycopene have garnered attention for their antioxidant and anti-inflammatory properties, which may have neuroprotective effects. Mangoes, carrots, and watermelons are examples of such fruits, chosen for their accessibility and potential benefits in combating oxidative stress and inflammation [10-14]. Further research is needed to better understand the mechanisms underlying the relationship between oxidative stress, inflammation, and MDD, as well as to evaluate the efficacy of antioxidant interventions in the prevention and treatment of depression. By harnessing the potential of antioxidants found in natural sources like fruits, there may be opportunities to develop adjunctive therapies that complement existing treatments for MDD and improve patient outcomes [14-16].

Methods

Chemicals

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

Equipment

The equipment used for this research includes a rotor centrifuging machine, Syringes and needles, ELISA kit, cotton wool, Plain tubes, EDTA tubes, a 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°S and latitude 7°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 between 180-200 g, were utilized for the study. They were housed in groups of six rats per cage and given a two-week acclimatization period in laboratory conditions before the commencement of experiments, as per the protocol outlined by Bawazir (2018). The rats were kept at room temperature with a 12-hour light/12-hour dark cycle and provided ad libitum access to food and water throughout the study period. Ethical approval for the study was obtained from the NSUK Animal Care and Use Research Ethics Committee (NSUK-ACUREC), and all experimental procedures were conducted in accordance with the ethical guidelines set forth by NSUK-ACUREC at Nasarawa State University, Keffi.

Experimental Design

Following the acclimatization period, the animals were weighed and then divided into five groups, each containing six animals.Group 1: Positive Control –received feed and water only throughout 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 2 weeks

Group 5: received 2.6mg/kg b.w. Dexamethasone and 0.2mg/kg Gingko Biloba for a period of 2 weeks

The treatments were administered orally using 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 two-week administration period, the rats were anesthetized using diethyl ether, and blood samples were collected via an ocular vein puncture using a capillary tube. The blood samples were then transferred into plain bottles for biochemical analysis.

Biochemical Analysis

Biochemical analysis was conducted using standardized diagnostic kits (Randox by Randox Laboratories Ltd., United Kingdom) following a modified protocol. 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

The data obtained was analyzed using one-way analysis of variance (ANOVA) in SPSS version 20.0 statistical software. A significance level of $P < 0.05$ was considered for all values using the F-test, with additional post-hoc analysis conducted using the T-test to determine the significance of differences between groups. Duncan's multiple range test was employed to identify specific points of significant differences, following the methodology 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 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 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 is 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 carrots 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 perturbed when reactive oxygen species (ROS) are produced, leading to the generation of double allylic hydrogen atoms and initiating lipid oxidation processes. Neutrophils contribute to this oxidative injury by catalyzing the synthesis of hypochlorous acid, which further damages cells. To counteract this oxidative stress, the body produces defense enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). SOD serves as the first line of defense by converting superoxide radicals into hydrogen peroxide, which is then metabolized into water by GPx and catalase enzymes. While these enzymes normally work synergistically, ROS overproduction can disrupt this balance, leading to cellular necrosis or apoptosis. In such cases, dietary lycopene, abundant in watermelon, can serve as a therapeutic agent to mitigate excessive ROS production. Research by Oberoi and Sogi has highlighted watermelon as a particularly rich source of bioavailable lycopene, surpassing even tomatoes by approximately 60%. This finding may explain the observed reduction in TAG levels, suggesting the potential benefits of watermelon consumption in oxidative stress management [32-34].

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 demonstrated efficacy in increasing glutathione (GSH) levels in individuals with coronary artery disease, as evidenced by a study (36). Furthermore, research conducted by Kim (37) investigated the impact of lycopene supplementation in men who were smokers with low fruit and vegetable intake. Through a double-blind randomized controlled trial, it was found that lycopene supplementation significantly reduced oxidative stress and improved endothelial function. These findings underscore the potential therapeutic role of lycopene in mitigating oxidative stress-related conditions and promoting cardiovascular health [36-37].

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) serves as a widely utilized marker for acute-phase reactions and inflammation within the body (39).

As an acute inflammatory protein, CRP levels can surge by 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 CoX_2, NoS_2, 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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