***Therapeutic potential of various edible vegetable extracts for managing DL-methionine-induced hyperhomocysteinemia and oxidative stress in Wistar rats***

**ABSTRACT**

*Hyperhomocysteinemia, a metabolic disorder characterized by elevated plasma homocysteine levels, is associated with oxidative stress and an increased risk of cardiovascular diseases. This study investigated the therapeutic potential of vegetable extracts in mitigating DL-methionine-induced hyperhomocysteinemia and oxidative stress in rats. Plasma homocysteine levels and oxidative stress markers, including malondialdehyde (MDA), superoxide dismutase (SOD), and glutathione (GSH), were assessed. The results showed that hyperhomocysteinemia significantly increased plasma homocysteine and MDA levels while decreasing SOD and GSH (p < 0.05). Treatment with vegetable extracts, particularly S. oleracea and B. oleracea , resulted in a significant reduction in homocysteine and MDA levels, along with an increase in SOD and GSH concentrations (p < 0.05). Pearson’s correlation analysis further demonstrated a strong association between homocysteine and oxidative stress markers. These findings suggest that dietary supplementation with folate- and antioxidant-rich vegetables may serve as an effective strategy for managing hyperhomocysteinemia and reducing oxidative damage.*

***Keywords****: Hyperhomocysteinemia, Oxidative Stress, Antioxidants, Homocysteine Metabolism, Vegetable Extracts, Folate, Vitamin B6, Lipid Peroxidation*

**1.0 INTRODUCTION**

Hyperhomocysteinemia is a metabolic disorder characterized by raised plasma homocysteine levels [1]. It is linked with increased risks of cardiovascular diseases, neurodegenerative disorders, endothelial dysfunction, and oxidative stress [2-4]. Homocysteine is an intermediate product in the methionine metabolism pathway and is normally converted to either cysteine via transsulphuration or methionine via remethylation [5, 6]. Alterations in these metabolic pathways, often due to deficiencies in folate, vitamin B6, or vitamin B12, result in the accumulation of homocysteine in the blood [7, 8].

DL-methionine, a synthetic form of L-methionine, an essential amino acid, serves as a precursor for homocysteine synthesis [9]. When DL-methionine is excessively consumed, it can overload the transsulfuration and remethylation pathways [10], leading to hyperhomocysteinemia [11]. Hence, dietary interventions that promote homocysteine clearance may offer a natural and effective approach to mitigating hyperhomocysteinemia [12]. For instance, several vegetables that are rich in B vitamins, antioxidants, and sulphur compounds have been known to aid homocysteine metabolism [13]. This study, therefore, aims to study the therapeutic potential of various edible vegetable (*S. oleracea*, *B. oleracea,* garlic, and carrot) extracts for managing DL-methionine-induced hyperhomocysteinemia and oxidative stress in wistar rats.

**2.0 MATERIALS AND METHODS**

**2.1. Sample Collection**

Four different edible vegetables, namely spinach (*Spinacia oleracea*), broccoli (*Brassica oleracea var. italica*), garlic(*Allium sativum*), and carrot(*Daucus carota*) were purchased from a fruit garden store located in D-Line, Port Harcourt, Rivers State, Nigeria and were identified and confirmed at the Herbarium of the Department of Plant Science and Biotechnology of the University of Port Harcourt, Rivers State, Nigeria.

**2.2 Preparation of Plant Extracts**

The plant materials were thoroughly washed under running tap water to eliminate dirt, dust, and pesticide residues, followed by triple rinsing with distilled water. *A. sativum* bulbs were peeled before washing. To preserve bioactive compounds, the plant materials were dried using appropriate methods, for instance, *S. oleracea* and *B. oleracea* were air-dried in the shade at room temperature (25 ± 2°C) for 7–10 days, while *A. sativum* and *D. carota* were sliced and oven-dried at 40°C for 48 hours. Once dried, they were ground into a fine powder using an electric blender, passed through a 250 µm sieve for uniformity, and stored in airtight amber glass bottles at 4°C until extraction. For ethanolic extraction, 50 g of powdered plant material was macerated in 200 mL of 70% ethanol at room temperature for 48 hours with occasional stirring. The extract was then filtered and concentrated using a rotary evaporator at 40°C to remove excess solvent. The concentrated extracts were dried under vacuum, weighed, and stored in airtight amber bottles at 4°C until further analysis.

**2.3. Study Design and Animal Model**

The study was conducted using forty-two (42) male Wistar rats (8–10 weeks old), housed under controlled temperature (22 ± 2°C) and humidity (55 ± 5%) with a 12-hour light-dark cycle. Rats were provided a standard diet and water ad libitum.

**2.4. Experimental Groups**

The rats were divided into six groups (n = 7 per group):

|  |  |
| --- | --- |
| Group | Treatment |
| Group 1 (Control) | Standard diet, no DL-methionine |
| Group 2 (Hyperhomocysteinemia) | DL-methionine (1 g/kg/day) |
| Group 3 | DL-methionine + *S. oleracea* extract (200 mg/kg/day) |
| Group 4 | DL-methionine + *B. oleracea*  extract (200 mg/kg/day) |
| Group 5 | DL-methionine + *A. sativum* extract (150 mg/kg/day) |
| Group 6 | DL-methionine + *D. carota* extract (200 mg/kg/day) |

**2.5. Induction of Hyperhomocysteinemia**

Hyperhomocysteinemia was induced by orally administering DL-methionine (1 g/kg/day) for six weeks. Rats with plasma homocysteine levels of ≥ 20 µmol/L after the induction period were selected for the study.

**2.6. Blood Sample Collection**

At the end of the experiment, rats were anesthetized with ketamine (80 mg/kg) and xylazine (10 mg/kg). Blood was collected via cardiac puncture using a sterile syringe, then centrifuged at 3,000 rpm for 10 minutes. Plasma samples were stored at −80°C for homocysteine measurement, while serum was used for oxidative stress marker analysis.

**2.7. Biochemical Analysis**

**2.7.1. Total Homocysteine Measurement**

Plasma total homocysteine levels were measured using High-Performance Liquid Chromatography (HPLC) with a fluorescence detector for high sensitivity and specificity as described by Minniti et al. [14]. Protein precipitation was carried out by adding trichloroacetic acid (10% w/v) to the plasma, followed by centrifugation. The supernatant was then derivatized using S-adenosylmethionine (SAM)) as a fluorescence reagent. Samples were injected into an HPLC system equipped with a C18 reversed-phase column and eluted with a mobile phase containing phosphate buffer (pH 2.1) and methanol (5–10%) at a flow rate of 1 mL/min. A series of homocysteine standard solutions (ranging from 5 to 50 µmol/L) were prepared and analyzed under the same HPLC conditions to generate a linear calibration curve (R² > 0.99). The peak areas of the plasma samples were then interpolated onto this standard curve (figure 1) to determine their respective homocysteine concentrations. All measurements were conducted in triplicates. Results were expressed in µmol/L as shown in Table 1.

Table 1. Total Homocysteine concentrations and their corresponding HPLC peak areas.

|  |  |
| --- | --- |
| Homocysteine Concentration (µmol/L) | Peak Area (Arbitrary Units) |
| 5 | 0.25 |
| 10 | 0.50 |
| 20 | 1.02 |
| 30 | 1.55 |
| 40 | 2.10 |
| 50 | 2.65 |

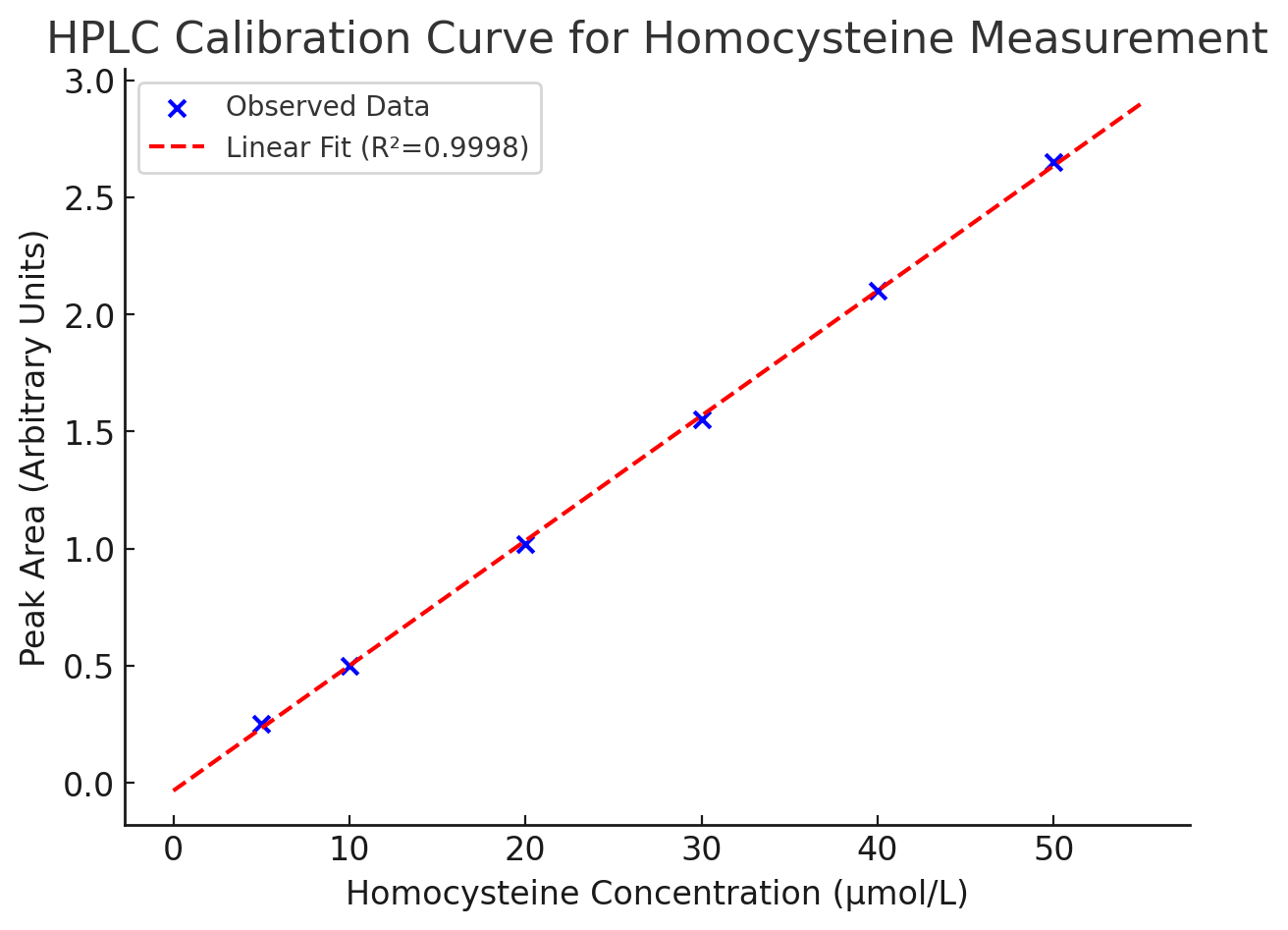


Fig. 1. HPLC calibration curve for the determination of homocysteine concentration**s.**

**2.7.2. Estimation of Oxidative Stress Markers**

* **Malondialdehyde (MDA) Levels**

MDA levels were measured using the Thiobarbituric Acid Reactive Substances (TBARS) assay to assess lipid peroxidation, following a modified method by Merino de Paz [15]. Plasma (0.2 mL) was mixed with 1 mL of 10% trichloroacetic acid (TCA) and 1 mL of 0.67% thiobarbituric acid (TBA), then heated at 95°C for 15 minutes. After cooling on ice and centrifugation at 3,000 rpm for 10 minutes, absorbance was recorded at 532 nm using a UV-visible spectrophotometer. MDA levels were expressed in nmol/mL using a tetramethoxypropane (TMP) calibration curve.

* **Superoxide Dismutase (SOD) Activity**

SOD activity was determined based on its ability to inhibit epinephrine autoxidation, using a modified method by Otitoju and Onwurah [16]. Plasma was combined with 0.05 M sodium carbonate buffer (pH 10.2) and 0.1 mM EDTA, followed by 0.1 mM epinephrine. Absorbance was measured at 480 nm, and activity was expressed in U/mL.

* **Glutathione (GSH) Levels**

GSH levels were quantified using Ellman’s reagent (DTNB) following Alisik et al. [17]. Plasma was deproteinised with 5% sulphosalicylic acid and incubated with DTNB in phosphate buffer (pH 7.4). The resulting 5-thio-2-nitrobenzoic acid (TNB) chromophore was measured at 412 nm, and GSH levels were expressed in µmol/mL using a standard curve.

**2.8. Statistical Analysis**

Data were analysed using GraphPad Prism 9.0 and reported as mean ± standard deviation (SD). Group comparisons were performed using one-way ANOVA followed by Tukey’s post hoc test. Pearson’s correlation was used to assess relationships between homocysteine and oxidative stress markers (MDA, SOD, and GSH). A p-value < 0.05 was considered statistically significant.

**2.8. Statistical Analysis**

Experimental data were analyzed using GraphPad Prism 9.0 and presented as mean ± standard deviation (SD). Statistical significance between groups was assessed using one-way analysis of variance (ANOVA), followed by Tukey’s post hoc test for multiple comparisons. Pearson’s correlation analysis was performed to evaluate relationships between homocysteine levels and oxidative stress markers (MDA, SOD, and GSH). A p-value < 0.05 was considered statistically significant. Graphical representations, including bar charts, were generated to illustrate variations among study groups.

**3.0. RESULTS**

**3.1. Effect of Vegetable Extracts on Plasma Homocysteine Levels**

Plasma homocysteine levels were significantly higher in DL-methionine-induced hyperhomocysteinemia rats compared to the control group (p < 0.05). Treatment with vegetable extracts significantly reduced homocysteine levels, with *S. oleracea* and *B. oleracea* demonstrating the most pronounced reductions (p < 0.05 vs. untreated hyperhomocysteinemia group). Table 2 presents the plasma homocysteine concentrations across treatment groups.

Table 2: Plasma Homocysteine Levels (µmol/L) in Different Treatment Groups

|  |  |
| --- | --- |
| Group | Plasma Homocysteine (µmol/L, Mean ± SD) |
| Group 1 (Control) | 6.2 ± 0.5 |
| Group 2 (Hyperhomocysteinemia) | 18.5 ± 1.2 \* |
| Group 3 | 10.3 ± 0.9 \* |
| Group 4 | 9.8 ± 1.1 \* |
| Group 5 | 12.5 ± 1.3 \* |
| Group 6 | 14.1 ± 1.2 \* |

*Significant difference compared to control, p < 0.05.*

**3.2. Effect of Vegetable Extracts on Oxidative Stress Markers**

The three markers of oxidative stress (MDA, SOD, and GSH) were significantly different in the hyperhomocysteinemia group compared to the control group (p < 0.05). Treatment with vegetable extracts lowered MDA levels while increasing SOD and GSH, with B. oleracea and S. oleracea exhibiting the most pronounced effects (p < 0.05). A summary of the results is provided in Table 3.

Table 3: Effect of Vegetable Extracts on Oxidative Stress Markers

|  |  |  |  |
| --- | --- | --- | --- |
| Group | MDA (nmol/mL, Mean ± SD) | SOD (U/mL, Mean ± SD) | GSH (µmol/mL, Mean ± SD) |
| Group 1 (Control) | 1.5 ± 0.2 | 8.2 ± 0.5 | 5.4 ± 0.3 |
| Group 2 (Hyperhomocysteinemia) | 4.3 ± 0.5 \* | 4.1 ± 0.4 \* | 2.1 ± 0.3 \* |
| Group 3 | 2.6 ± 0.3 \* | 6.3 ± 0.5 \* | 4.2 ± 0.4 \* |
| Group 4 | 2.4 ± 0.4 \* | 6.8 ± 0.6 \* | 4.5 ± 0.5 \* |
| Group 5 | 3.1 ± 0.4 \* | 6.5 ± 0.5 \* | 3.8 ± 0.4 \* |
| Group 6 | 3.5 ± 0.5 \* | 5.9 ± 0.6 \* | 3.5 ± 0.5 \* |

*Significant difference compared to control, p < 0.05.*

**3.3. Correlation between Homocysteine and Oxidative Stress Markers**

Pearson’s correlation analysis showed a significant positive correlation between homocysteine and MDA levels (r = 0.72, p < 0.05), indicating that higher homocysteine levels leads to lipid peroxidation. In contrast, homocysteine levels were negatively correlated with SOD (r = −0.68, p < 0.05) and GSH (r = −0.71, p < 0.05), suggesting that elevated homocysteine impairs antioxidant defense mechanisms. These correlations are summarised in Table 4.

Table 4: Correlation between Homocysteine and Oxidative Stress Markers

|  |  |  |
| --- | --- | --- |
| Parameter | Homocysteine (r-value) | p-value |
| MDA | 0.72 | < 0.05 |
| SOD | -0.68 | < 0.05 |
| GSH | -0.71 | < 0.05 |

*Significant correlations, p < 0.05.*

**4.0. DISCUSSION**

**4.1 Effect of Vegetable Extracts on Plasma Homocysteine Levels**

This study confirms that DL-methionine-induced hyperhomocysteinaemia raises plasma homocysteine levels and intensifies oxidative stress, marked by increased malondialdehyde (MDA) and reduced superoxide dismutase (SOD) and glutathione (GSH). Treatment with vegetable extracts, especially with *S. oleracea* and *B. oleracea*, significantly lowered homocysteine levels (p < 0.05), suggesting that dietary interventions may help counteract hyperhomocysteinaemia-related oxidative damage [18].

B vitamins, including folate, vitamin B6, and vitamin B12, play an important role in lowering homocysteine levels, which helps in the primary prevention of cardiovascular disease by reducing endothelial dysfunction and oxidative stress [19-21].

Folate (vitamin B9), abundant in these vegetables, supports homocysteine remethylation, reducing its accumulation [22-24]. Additionally, vitamins B6 and B12, essential in homocysteine metabolism, may contribute to this effect [24, 25]. The observed reduction in homocysteine aligns with previous studies demonstrating the benefits of folate-rich diets in managing hyperhomocysteinaemia [26, 27].

**4.2 Oxidative Stress and Antioxidant Enzyme Activity**

Elevated homocysteine levels are known to induce oxidative damage through the generation of reactive oxygen species (ROS), which disrupt cellular antioxidant defense mechanisms [28, 29]. In this study, the significant increase in malondialdehyde (MDA) levels in the DL-methionine group (p < 0.05) suggests that excess methionine intake contributes to oxidative stress by elevating homocysteine levels, which in turn promotes lipid peroxidation. This aligns with previous findings that link hyperhomocysteinemia to enhanced oxidative damage and impaired antioxidant defense mechanisms [30]. However, the reduction in MDA levels following vegetable extract treatment, particularly with S. oleracea and B. oleracea, highlights their potential in counteracting oxidative damage through antioxidant properties [31].

Antioxidant enzyme activity plays a crucial role in mitigating oxidative stress [32]. The observed decrease in SOD and GSH levels in the DL-methionine group is indicative of impaired antioxidant defense [33]. The significant improvement in SOD and GSH levels after treatment with vegetable extracts (p < 0.05) suggests that bioactive compounds present in these vegetables enhance endogenous antioxidant mechanisms. *B. oleracea* and *S. oleracea* extracts were the most effective in restoring SOD and GSH, which aligns with previous research highlighting their high antioxidant content, including flavonoids, polyphenols, and vitamins C and E [34]. These antioxidants help neutralize ROS and improve cellular defense against oxidative stress, as previously demonstrated by Pisoschi et al. [35].

**4.3 Correlation between Homocysteine and Oxidative Stress Markers**

The correlation analysis further reinforces these findings. The positive correlation between homocysteine and MDA (r = 0.72, p < 0.05) underscores the link between hyperhomocysteinemia and oxidative stress, while the negative correlations of homocysteine with SOD (r = -0.68, p < 0.05) and GSH (r = -0.71, p < 0.05) highlight its detrimental impact on antioxidant defense. These results confirm that homocysteine accumulation disrupts redox homeostasis, which can be mitigated through dietary antioxidants [36]. Similar correlations have been reported in previous studies, where high homocysteine levels were associated with increased oxidative damage and compromised antioxidant capacity [37].

**5.0. CONCLUSION**

This study provides strong evidence that vegetable extracts, particularly from *S. oleracea* and *B. oleracea,* effectively reduce plasma homocysteine levels and improve oxidative stress markers in DL-methionine-induced hyperhomocysteinemia. The presence of folate, vitamins B6 and B12, as well as antioxidant compounds in these vegetables, likely contributes to their beneficial effects. The findings suggest that dietary supplementation with these vegetables may serve as a therapeutic strategy for managing hyperhomocysteinemia and its associated oxidative damage. Future studies should explore the underlying molecular mechanisms and potential clinical applications of these findings.

Disclaimer (Artificial intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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