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Exploring the Genotoxic Effects of *Moringa oleifera* Leaf Aqueous Extract on Rat Bone Marrow

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Abstract

Introduction: Moringa oleifera is the most popular herb, a plant known for its medicinal properties, and has gained major attention for its antioxidant, antidiabetic, and anti-inflammatory effects. *Moringa oleifera* is commonly used to treat infections, inflammation, and metabolic disorders. However, its potential impact on bone marrow genotoxicity remains unexplored. The purpose of this study is to explore the genotoxic effect of *Moringa oleifera* leaf aqueous extract on bone marrow of Albino Wistar rats by using a micronuclei assay.

Materials and Methods: For the evaluation of the genotoxic effect, aqueous extract of the *Moringa oleifera* leaves at doses of 100, 200, 500 mg/kg body weight (2 ml/rat) was administered orally to the treated groups for eight weeks. Dose-dependent effects on body weight of rats were observed weekly. Rats of all groups were sacrificed after 8th week for extraction of bone marrow from the femur bone. Micronucleus assay was performed for the genotoxicity assessment.

Results: The micronucleus assay revealed a statistically significant decrease in the frequency of micronucleated polychromatic erythrocytes (MNPCE) in 200 and 500 mg/kg dosage groups, whereas micronucleated normochromatic erythrocyte (MNNCE) count insignificantly spiked up in 500 mg/kg dosage group, compared to control group. Total polychromatic erythrocyte (PCE) counts displayed no significant treatment-related changes. In contrast, normochromatic erythrocyte (NCE) frequencies demonstrated variations among the treatment groups with a predominant significant increase in the 500 mg/kg dosage group. Furthermore, a dose-dependent decline in the PCE/NCE ratio was also observed, with the most prominent reduction seen in the 500 mg/kg dosage group.

Conclusion: Moringa oleifera may not have genotoxic effects at given doses. However, it may produce cytotoxicity at higher doses.

Keywords: Cytotoxicity, genotoxicity, micronucleated polychromatic erythrocytes (MNPCE), micronucleus assay, *Moringa oleifera*, normochromatic erythrocytes (NCE), polychromatic erythrocytes (PCE)

1. Introduction

Herbs have been commonly used as medicines and have become a significant part of the healthcare system. According to the World Health Organization (WHO), the use of medicinal plants is almost 80% worldwide[1]. Use of herbal medicine is increasing progressively due to their low cost and easy availability. Plants contain biologically active substances that exert beneficial effects[2], yet these may contain toxic substances that produce side effects and serious illness[3]. Herbal medicines are often considered as low risk. However, their potential health risks should be assessed carefully. Patients and physicians often lack exact information about their safety and efficacy[4]. Several factors of herbal medicines can cause toxicity such as the presence of toxic plant constituents, environmental contaminants (heavy metals and pesticides), adulterants, microbial contaminants (toxigenic fungi) that must be carefully assessed to ensure patient safety[5].

Moringa oleifera is commonly known as *drumstick tree*, *miracle tree* and *tree of life* due to its immense medicinal and non-medicinal benefits. It is rich in bioactive compounds, such as flavonoids, vitamins, and alkaloids. It is traditionally used to treat wounds, ulcers, pain, liver disease, heart disease, and for its anti-inflammatory, antioxidant, antiarthritic, anticancer and antidiabetic effects[6-9]. It must be noted that

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plants contain xenobiotic agents, which are hazardous and when these plants are used for medicinal purposes, they may produce adverse effects[10]. Numerous therapeutic plants contain bioactive chemicals that, when taken in large quantities or over an extended period of time, may have genotoxic, hepatotoxic, nephrotoxic, or carcinogenic effects[11,12]. Herbs that have been proven to cause DNA damage, mutagenesis, and organ toxicity include *Aristolochia* species (contains aristolochic acid)[13], Comfrey (contains pyrrolizidine alkaloids)[14], and *Aloe vera* (contains aloin and emodin)[15]. Even widely used herbs like Ephedra and *Ginkgo biloba* have the potential to cause genotoxicity by inducing oxidative stress[16]. Thus, it is essential to evaluate the benefits, risks and concentrations of active compounds found in these medicinal plants to ensure the safety and to counteract systemic toxicity or genotoxicity associated with these plants.

Serious health hazards associated with genotoxicity, or damage to genetic material, include bone marrow suppression, carcinogenesis, and mutagenesis. Because of its fast cellular turnover, the bone marrow is especially susceptible to genotoxic chemicals. Exposure to environmental toxins, pharmaceuticals, and radiation can lead to chromosomal aberrations, micronucleus formation, and DNA strand breaks, which may contribute to hematological disorders. With the increasing use of herbal medicines, it is essential to evaluate their potential hazards as well. While *Moringa oleifera* is widely recognized for its medicinal and antioxidant properties, its potential to cause or prevent bone marrow genotoxicity remains unclear. Therefore, the objective of the study was to evaluate the genotoxic implications of the sub-chronic consumption of aqueous extract of *Moringa oleifera* leaves on the bone marrow of albino Wistar rats.

2. Materials and Methods

2.1. Ethics statement

All experimental protocols followed the guidelines of the National Research Council (US) Committee for the Update of the Guide for the Care and Use of Laboratory Animals[17]. The experimental protocol was approved by the Departmental Research Committee (DRC), University of Karachi (approval no. DRC/KU/113/2023).

2.2. Plant material

Fresh *Moringa oleifera* leaves were collected locally and thoroughly washed with distilled water to remove dirt and contaminants. Then the leaves were shade dried at room temperature ~25°C for 10 days until completely dried. After drying, the leaves were crushed into a fine powder using an electric grinder.

2.3. Chemicals

Bone marrow smear slides were prepared and fixed in 100% methanol and were stained using 5% Giemsa solution (Merck). Hanks balanced salt solution (HBSS 1x, Gibco) served as a diluting agent.

2.4. Animals

Twelve male albino Wistar rats, each weighing 180-200 g and six weeks of age, were purchased from the animal facility center of Muhammad Ali Jinnah University. Each rat was healthy and showed no symptoms of any underlying illnesses. The rats were housed in standard cages (four per cage) with adequate bedding and provided *ad libitum* access to food and water. Prior to the start of the experiment, the rats were acclimatized to the laboratory setting over a period of one week. Throughout the study, the animals were housed in a regulated environment with an average temperature of 25°C and 12-hour light/dark cycle. Animals within each cage were uniquely identified by tail markings.

2.5. Study design

Following one-week acclimatization, the rats were randomly assigned to four groups: one control and three experimental groups. The control group (Group 1) received saline that was orally administered using a gavage needle. The experimental groups received orally administered *Moringa oleifera* leaf aqueous extract daily for eight weeks. Parameters, including body weight, behavioral changes, and bone marrow genotoxicity were systematically monitored. Any alterations in body weight, behavioral parameters and bone marrow genotoxicity in rats were monitored. To evaluate the safety profile of *Moringa oleifera* leaf aqueous extract, the animals were monitored daily for behavioral changes, while body weight and bone marrow genotoxicity were assessed and recorded at regular intervals.

2.6. Dose selection

Three different concentrations of *Moringa oleifera* leaf powder tea was given orally to the albino Wistar rats at dosages of 100 mg/kg, 200 mg/kg, and 500 mg/kg to experimental groups 2, 3 and 4 respectively, based on a previously published study[18]. The rats were given 2 ml of the solution, in accordance with the prescribed dosages. The doses were administered once daily by oral gavage for a total of eight weeks. Among the examined groups, there was no evidence of acute toxicity, abnormal behavior, or mortality.

- Group 1 (Control Group): Normal saline (0.9%)
- Group 2 (Treatment Group 1): 100 mg/kg *Moringa oleifera* extract
- Group 3 (Treatment Group 2): 200 mg/kg *Moringa oleifera* extract
- Group 4 (Treatment Group 3): 500 mg/kg *Moringa oleifera* extract

2.7. Body weight

Throughout the eight-week experimental period, each rat was weighed once-a-week to track physiological responses to various doses of *Moringa oleifera* extract.

2.8. Behavioral observations

Regular assessment and documentation of general health and behavior, focusing on their activity level, food and water intake, and clinical signs of stress were carried out.

2.9. Bone marrow genotoxicity

Rats were anesthetized following 8-week treatment period, and their bone marrow were taken. Standard techniques, including the micronucleus assay, were used to evaluate the following parameters in order to figure out the genotoxic effects of *Moringa oleifera*.

- Polychromatic erythrocyte (PCE) count
- PCE with nucleus count
- Micronucleated polychromatic erythrocyte (MNPCE) count
- Normochromatic erythrocyte (NCE) count
- Micronucleated normochromatic erythrocyte (MNNCE) count

2.10. Bone marrow smear preparation

Following euthanasia, the femur bone was immediately excised. The end of the proximal femur was cut to expose the marrow canal. A syringe needle containing few drops of HBSS was inserted into the marrow canal opening. The marrow was directly placed onto a pre-cleaned glass slide and smeared. Two smears were taken per animal and the slides were kept at room temperature for air drying. After drying and heat fixing, the slides were labeled and fixed in methanol (100%) for 10 minutes and air dried. Subsequently, all slides were stained with Giemsa (5%) for 20 minutes. Staining permitted visualization and differentiation between PCE and NCE. The stained slides were briefly immersed in distilled water for one minute and allowed to air-dry. Following staining, a single drop of oil immersion was added to the slides and were observed (zigzag orientation) and photographed at 100x magnification with the Optika digital microscope (Optika, B190 series).

2.11. Micronucleus assay

Each animal's genotoxic and antigenotoxic activity was evaluated using the frequency of MNPCE in 1000 PCE, with an optical microscope having 100x magnification. Further, bone marrow suppression was assessed using the PCE/(PCE+NCE) ratio, derived from a 200-erythrocyte count that provided a comprehensive view of the cytotoxic effects of *Moringa oleifera* leaf extract.

2.12. Statistical analysis

The statistical analysis was carried out using the SPSS version 27.0 package. Data were presented as mean±SD. One-way ANOVA followed by Tukey's post hoc test were used in order to compare the cytotoxic and genotoxic parameters in control and treated groups for multiple comparisons. Variables analyzed among the control and treatment groups were PCE, PCE with nucleus, MNPCE, NCE, and MNNCE count. A statistically significant p-value was set at $p<0.05$.

3. Results

3.1. Effect of Moringa oleifera on body weight of rats

Table 1 and Figure 1 present the body weight change in rats treated with different doses of *Moringa oleifera* aqueous extract (100, 200, and 500 mg/kg/day) over eight weeks. Initially, all the groups had similar body weights. Over time, the control group maintained a relatively stable weight, while the groups treated with 100 mg/kg/day and 200 mg/kg/day of *Moringa oleifera* demonstrated a gradual decline in weight. However, the 500 mg/kg/day group initially gained weight, showing an upward trend until week 6, followed by a reduction at week 8. Although an apparent decrease in body weight was observed in treated rats, these changes were not statistically significant when compared to the control group ($p>0.05$).

Table 1: Effect of *Moringa oleifera* extract on body weight of rats

Week	Group 1 Control	Group 2 *Moringa oleifera* (100 mg)	Group 3 *Moringa oleifera* (200 mg)	Group 4 *Moringa oleifera* (500 mg)	F	p-value
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD		
1	198.25 ± 8.15	191.25 ± 2.495	204.25 ± 6.637	212.5 ± 6.198	2.098	0.153
2	202.5 ± 7.942	193.5 ± 2.217	201 ± 9.789	209.75 ± 9.885	0.678	0.581
3	206 ± 7.164	191.5 ± 0.5	197.25 ± 11.585	209.5 ± 13.961	0.705	0.566
4	202.25 ± 7.814	186 ± 2.081	190.25 ± 10.435	207 ± 13.826	0.887	0.477
5	202 ± 13.0	181.66 ± 2.905	183.5 ± 11.434	207 ± 11.09	1.478	0.284
6	196 ± 21.0	176.34 ± 2.603	178.75 ± 10.757	213 ± 7.505	2.741	0.112
7	193.5 ± 20.5	174 ± 5.0	175.5 ± 10.835	209.67 ± 8.171	2.147	0.182
8	197.5 ± 21.5	171.5 ± 0.5	173.5 ± 11.651	211.34 ± 9.492	2.411	0.152

Values expressed as Mean±SD. One-way ANOVA followed by Tukey's post hoc test

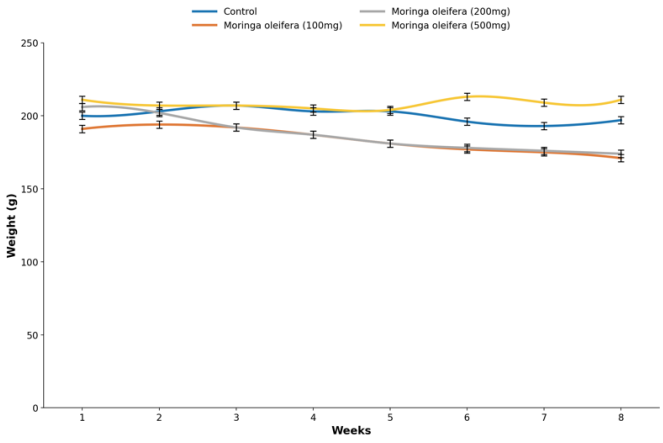

Figure 1: Weight changes in rats treated with *Moringa oleifera* aqueous extract

3.2. Micronuclei formation in treated and control rats

Table 2 and Figure 2 demonstrate the effects of *Moringa oleifera* at varying doses (100 mg, 200 mg, and 500 mg) on the formation of micronuclei in PCE and NCE in albino rats. The overall PCE count remained consistent across all experimental groups. Statistical analysis did not reveal any significant differences among these groups ($p\geq0.05$), indicating that *Moringa oleifera* supplementation did not notably alter PCE production (Table 2, Figure 3). In contrast, the number of PCEs containing nuclei demonstrated a slight upward trend with increasing *Moringa oleifera* doses. Compared to the control group, PCEs containing nuclei increased in the highest-dose group (500 mg). However, this increase did not reach statistical significance ($p>0.05$). Also, some cellular changes were observed but they were not pronounced enough to confirm a definitive effect (Table 2, Figure 3).

Table 2: Micronuclei formation in *Moringa oleifera* treated and control rats

Cells	Group 1 Control	Group 2 *Moringa oleifera* (100 mg)	Group 3 *Moringa oleifera* (200 mg)	Group 4 *Moringa oleifera* (500 mg)	F	p-value
PCE	940 ± 12.06	914.75 ± 13.38	940.25 ± 22.02	943.75 ± 7.66	0.83	0.503
PCE with nucleus	27 ± 6.09	29.75 ± 2.8	51.75 ± 17.67	46.5 ± 6.22	1.51	0.262
MNPCE	56 ± 19.98	58.25 ± 11.1	15 ± 3.741*	21 ± 7.416*	3.5	0.049
PCE total	1023 ± 15.13	1002.25 ± 0.85	1007 ± 5.19	1011.25 ± 2.28	1.2	0.35
NCE	57.5 ± 15.22	56.5 ± 17.056	19.5 ± 12.311	104.75 ± 19.52*	4.62	0.023
MNNCE	54	48.5	46.5	261.75	2	0.167
NCE total	111.5 ± 24.78	105 ± 11.64	66 ± 6.45	366.5 ± 150.07	3.25	0.06
PCE/NCE	9.17	9.54	15.25	2.75		

* Statistically significant ($p<0.05$) compared to control

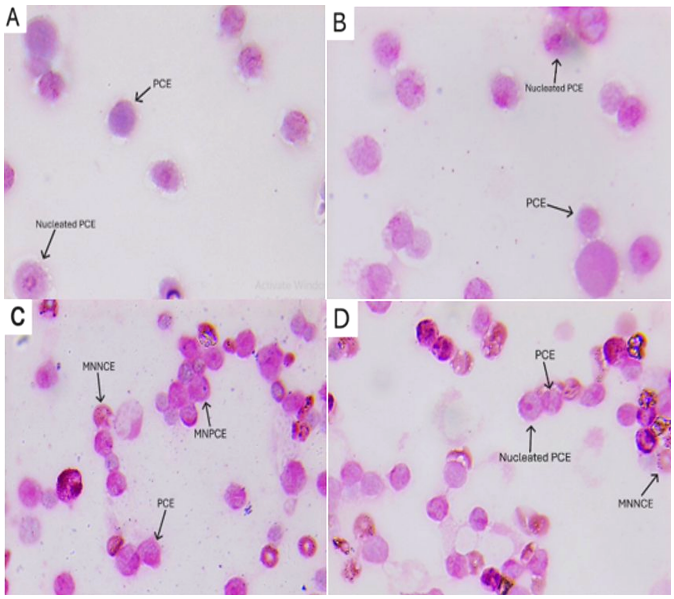

Figure 2: Photomicrographs of cells in rat bone marrow

(A) PCE and nucleated PCE in control group; (B) PCE and nucleated PCE in 100 mg *Moringa oleifera* treated group; (C) PCE, MNPCE and MNNCE in 200 mg *Moringa oleifera* treated group; (D) PCE, nucleated PCE and MNNCE in 500 mg *Moringa oleifera* treated group (Giemsa, magnification: 100x)

A more distinct pattern emerged in the case of MNPCE, where a significant reduction was observed following treatment with *Moringa oleifera* ($p<0.05$). The highest-dosage group (500 mg) of *Moringa oleifera* exhibited a considerable decrease than control group. This finding suggests that *Moringa oleifera* may play a protective role in reducing the occurrence of micronuclei in newly formed erythrocytes, potentially indicating a reduction in genetic damage (Table 2, Figure 3).

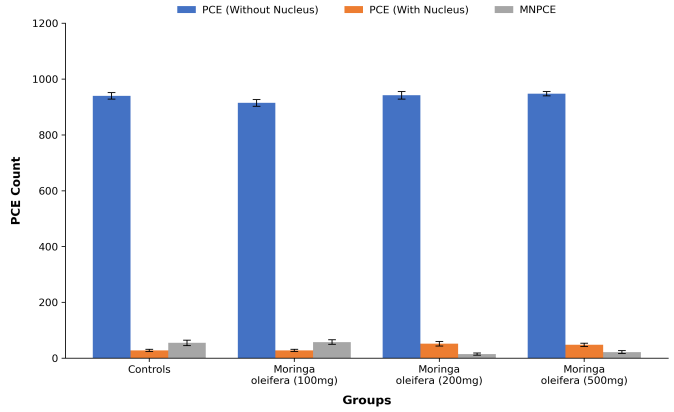

Figure 3: PCE count in *Moringa oleifera* treated and control groups

The analysis of NCE also revealed a significant elevation ($p<0.05$) in the treatment group of 500 mg/kg compared to the control group, thus further suggesting a biological response to *Moringa oleifera* administration. Additionally, MNNCE also exhibited a noticeable increase in the highest-dose group, although this result was not statistically significant ($p>0.05$) (Table 2, Figure 4).

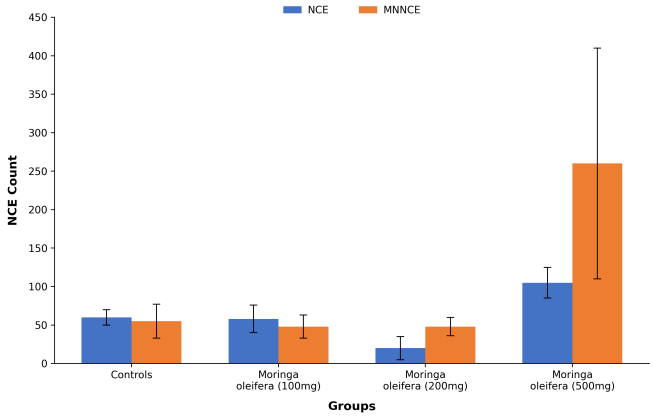

Figure 4: NCE count in *Moringa oleifera* treated and control groups

The ratio of PCE/NCE is an important parameter in genotoxicity studies. A decrease in this ratio indicates bone marrow toxicity or cytotoxic effects, while an increase suggests stimulation of erythropoiesis (Table 2). The PCE/NCE ratio increased at 200 mg/kg dosage group, indicating enhanced erythropoiesis. However, at 500 mg/kg, the ratio significantly declined, suggesting bone marrow suppression or cytotoxic effects at this high dose ($p<0.05$). The slight increase at 100 mg/kg suggests minimal impact on bone marrow function. This indicates that higher doses of *Moringa oleifera* might have toxic effects on bone marrow, leading to a reduction in PCEs.

4. Discussion

This study evaluated the impact of an aqueous extract of *Moringa oleifera* leaves on the genotoxicity of bone marrow in albino rats. *Moringa oleifera* is an herbal plant, most commonly consumed for its anti-hyperglycemic effects[6], boosting immunity[19], improving heart health, reducing inflammation[9], oxidative stress and in several other allopathic treatment strategies[7]. Despite the common belief that herbal medications are inherently safe with rare adverse effects, this assumption is not consistently supported by toxicological data as plants may contain biotoxins and consequently poisoning from medicinal plants can lead to serious illnesses. Therefore, it is crucial to evaluate the safety and efficacy of herbs[3]. Limited scientific research has been done on herbs regarding presence of near pharmaceutical concentrations of potent toxins, due to misidentification of the plants, incorrect preparation of the plant extracts, and administration by inadequately trained personnel. Therefore, this study provides significant insight on whether *Moringa oleifera* at typical dietary or supplemental doses exerts beneficial or detrimental effects (genotoxicity), particularly on bone marrow, which is a crucial site for hematopoiesis.

In this study, aqueous extract of *Moringa oleifera* was administered orally to albino rats in different concentrations (100, 200, and 500 mg/kg/day) for eight weeks. Administration of *Moringa oleifera* caused the body weights of rats to decline gradually in comparison to the control group, which maintained constant weight throughout the treatment period. Several *in vivo* and *in vitro* studies have been conducted to investigate the anti-obesity potential of *Moringa oleifera*, which indicated that inhibition of adipogenesis and inflammation, and improvement of lipid metabolism were the underlying mechanisms for weight reduction. These findings are in line with the present study, suggesting *Moringa oleifera* as a metabolic regulator that eventually leads to decreased body weight[20,21].

For the assessment of genotoxic effects of *Moringa oleifera*, micronucleus assay was performed, which showed a significant reduction in the MNPCE count in the 200 and 500 mg/kg treated groups compared to the control group. This indicates that *Moringa oleifera* does not possess genotoxic effects at these doses. This finding is consistent with other studies conducted on *Moringa oleifera* leaves, proposing its anti-mutagenic and anti-DNA damaging activities[22,23]. However, a study conducted on aqueous leaf extract of *Moringa oleifera* (3000 mg/kg) for 14 days, resulted in the significantly reduced MNPCE in bone marrow compared to 1000 mg/kg or controls[24,25].

In the current study, the PCE/NCE ratio showed an increase at 100 mg/kg and 200 mg/kg doses, which suggests enhanced erythropoiesis. Conversely, at high dose (500 mg/kg) of *Moringa oleifera*, this ratio was significantly decreased, suggesting bone marrow suppression or cytotoxic effects at the higher doses. Comparable results have been documented, showing significant genotoxicity in the bone marrow micronucleus test in rats after 14 days of *Moringa oleifera* aqueous leaf extract administration at 3000 mg/kg, while no genotoxic effect at 1000 mg/kg[24]. Another study reported that aqueous extract of *Moringa oleifera* at 1000 mg/kg for 28 days, was found to be toxic[26]. Similarly, a 13-week study on mice observed that *Moringa oleifera* leaf extract was safe at doses up to 500 mg/kg. However, a higher dose of 1000 mg/kg led to reduced food intake, weight loss, and signs of potential liver toxicity, suggesting that long-term use should be avoided at these doses[27]. The existing literature on toxicity studies of *Moringa oleifera* demonstrated that concentrations of 500 mg/kg and 1000 mg/kg may damage the liver and kidneys. In these studies, biochemical assays and histopathological analysis were used. However, genotoxicity and mutagenicity were not produced by the consumption of *Moringa oleifera* at a higher concentration (2000 mg/kg)[22]. Similarly, few investigations have documented that sub-acute administration (14 and 28-day repeated doses) of the aqueous extract of *Moringa oleifera* at 500 and 2000 mg/kg doses resulted in survival of all mice with no observable signs of systemic toxicity[28,29]. However, it is important to note that most of these existing evidences are extracted from subacute or short-term repeated-dose toxicity studies. Long-term chronic and sub-chronic studies specifically addressing the high-dose genotoxic effects of *Moringa oleifera* remain limited.

5. Limitations of the Study

Firstly, the relatively small sample size and lack of positive control group may restrict its sensitivity to identify subtle physiological variations. These findings should therefore be interpreted as preliminary, necessitating large-scale confirmatory studies to establish broader generalizability and robustness of the observed effects. Next, decrease in PCE/NCE ratio suggests bone marrow cytotoxicity, although this was not further validated by hematological analysis. Furthermore, the duration of the present study may not have been sufficient to observe the long-term effects of the herb. Long-term chronic genotoxicity studies (≥ 6 months) evaluating DNA damage and chromosomal aberrations are needed to strengthen the findings of this research.

6. Conclusion

The present study provides scientific evidence of relative safety of *Moringa oleifera* at moderate supplemental doses, as no genotoxic effects were observed at the particular doses. However, at high doses the PCE/NCE ratio significantly declined suggesting it may have bone marrow suppression or cytotoxic effects. The reduction in MNPCE suggests a potential protective effect, while the observed changes in NCE, MNNCE, and PCE/NCE ratio highlight the need for further investigation into the biological implications of *Moringa oleifera* supplementation. This study showed that *Moringa oleifera* may cause cytotoxicity at higher doses, therefore, excessive or prolonged high-dose use should be approached cautiously, especially in vulnerable

populations such as pregnant women or patients with renal or hepatic diseases. Therefore, more standardized in-depth studies on chronic use of *Moringa oleifera* along with the identification of substances that can damage DNA are needed.

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Conflict of Interest

TAK is on the Editorial Board of the SAAP Journal of Integrative Physiology.

Disclosure of AI Use

The AI tool, Claude (Sonnet 4.6) was used to format and enhance the quality of the tables and figures during the editorial phase.

Authors' Contributions

MI and TAK conceptualized and designed the study. SH was responsible for acquisition, analysis, and interpretation of the data. SH, MI and UF were responsible for drafting the article and critically revising it. MI and TAK approved the final version of the manuscript submitted to the journal.

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