https://dx.doi.org/10.4314/dujopas.v10i2b.28
ISSN (Print): 2476-8316
ISSN (Online): 2635-3490
Dutse Journal of Pure and Applied Sciences (DUJOPAS), *Vol. 10 No. 2b June 2024*

Effects of Co-administration of *Moringa oliefera* Leaf Tea with Standard Drug on Diabetic and Hypertensive Co-morbidity Patients

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Abstract

Treatments of diabetes and hypertension have remained a great challenge due to complications of toxicities and drug resistance associated with the chemotherapeutic regimens. Hence the need to explore the use of supplements in the management of diabetic patients. This study aimed to evaluate the effects of Moringa oleifera leaf tea (MOT) supplements on the glucose and haematological parameters in diabetes and hypertension co-morbidity patients. Fifty (50) patients of either sex diagnosed with the comorbidity of diabetes and hypertension were randomly assigned into five groups each consisting of ten patients (n=10) each. Group 1 served as the positive control, Group 2 as the negative control, Group 3 received normal control treatment plus MOT , Group 4 was treated with a reference drug, and Group 5 received the reference drug in combination with MOT. Administration was done for 14 days and thereafter, blood samples were collected for the assay of advanced glycation end product (AGEs), Advanced Oxidation Protein Product (AOPP), Glucose Index (Random, fasting and post prandial blood sugars) and haematological indices. The result revealed a significant decrease ($p<0.01$) in the level of AGEs and AOPP among patients treated with MOT compared to patients served with standard drug only and groups treated with standard drugs and control. There was a significant ($p<0.01$) reduction in the haematological parameters of all the groups treated with the standard drugs. However, there was a significant increase in the haematological parameters of the groups co-administered with MOT when compared with the control groups with only standard drugs. In conclusion, co-administration of M. oleifera leaf tea to patients suffering from diabetes-hypertension comorbidity treatment regimens can

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mitigate the adverse effects of the drugs by the reduction of glycemic parameters while improving the haematological parameters.

Key words: *Moringa oleifera*, Diabetes, Hypertension, Supplements, Co-Mobidity

INTRODUCTION

Diabetes mellitus is a group of metabolic disorders that presents phenotypically with hyperglycaemia resulting from defects in insulin secretion, insulin action, or both (Ta, 2014). The aetiologies of diabetes mellitus are complex interaction of genetics, environmental factors and life-style choices (Suneja, Christian and Chandra, 2018). The World Health Organization (WHO) has recommended the development of oral hypoglycaemic agents especially from medicinal plants as herbal natural remedies to treat diabetes mellitus due to their effectiveness and safety (Santosh *et al.,* 2008).

Traditionally, the management of diabetes has followed a stepwise pathway, comprising lifestyle modifications (regular food intake, weight management, moderate alcohol intake and exercise), proceeding to the use of one oral antidiabetic agent, followed by a combination of two or more oral agents before insulin is considered (Du and Sun, 2019; Slek *et al*., 2020).

There is considerable heterogeneity within the diabetic population with regards to the development and progression of diabetic complications (Cole and Florez, 2020). Although poor glycaemic control is clearly a major risk factor for complications, not all such controlled people with diabetes develop complications (Yozgatli *et al*., 2018). Conversely, some individuals develop complications despite relatively good glycaemic control (Mathur *et al.,* 2015). A diagnosis of diabetes, however, immediately increases a person's risk of developing irreversible clinical complications arising from microvascular (small blood vessel) and macrovascular (large blood vessel) diseases (Horton and Barrett, 2021).

Over the past decade the management of hypertension has changed with the recognition that there is no threshold below which elevated blood pressure causes no threat to health (Unger *et al*., 2020). However, research over the past decade has shown that even mildly elevated blood pressure levels can contribute to cardiovascular risk and other health complications over time (Bergmark *et al*., 2018). This recognition has led to a shift in hypertension management guidelines, with more emphasis on early detection and intervention to control blood pressure levels, even if they are only slightly elevated (Wilkins, 2018).

Moringa oleifera (MO) is grown for its nutritious pods, edible leaves and flowers and can be utilized as food, medicine, cosmetic oil or forage for livestock. Its height ranges from 5 to 10 m (Jattan *et al*., 2021). However, *M. oleifera* leaves are the most widely studied and they have shown to be beneficial in several chronic conditions (Abdull Razis *et al.,* 2014), including hypercholesterolemia, high blood pressure, diabetes, insulin resistance, non-alcoholic liver disease, cancer and overall inflammation. *M. oleifera* has been recognized as containing a great number of bioactive compounds (Sain *et al*., 2016; Jattan *et al*., 2021). The most used parts of the plant are the leaves, which are rich in vitamins, carotenoids, polyphenols, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins and saponins (Sivakumar *et al*., 2018). The high number of bioactive compounds might explain the pharmacological properties of *M. oleifera* leaves. Many studies, *in vitro* and *in vivo*, have confirmed these pharmacological properties (Leone *et al*., 2015).

People in many developing countries (particularly in Africa) have been using *M. oleifera* to treat and manage the symptoms of diabetes for years (Fatoumata *et al*., 2020). This is primarily because of its natural benefits (Abd El-Hack,*et al*., 2018). It has been shown to naturally boost the immune system, which usually becomes compromised in those who suffer from type I and type II diabetes (Alegbeleye *et al*., 2018; Arshad *et al*., 2021). It has also been shown to possess many key anti-inflammatory benefits (Arshad *et al*., 2021). There are no negative side effects associated with the use of *M. oleifera,* meaning that it is a safe, natural way for people to manage their blood sugar and other complications associated with diabetes (Alegbeleye *et al*., 2018; Arshad *et al*., 2021).

There is no satisfactory treatment for diabetes neither for hypertension. Once a person develops diabetes, he will suffer from the condition for the rest of his or her life (WHO, 2016). Treatments of diabetes and hypertension have remained a great challenge due to complications associated with the chemotherapeutic regiments are associated with toxicities and drug resistance (Chung *et al*., 2020). Hence, there is a need to explore the use of supplements in managing diabetic and hypertensive patients. Therefore, this study aimed to investigate the effect of MO tea supplements on biochemical and haematological parameters in diabetes and hypertension co-morbidity patients.

MATERIALS AND METHODS

Study Area
The research was undertaken at Adewole Cottage Hospital Ilorin, Kwara State, Nigeria between April to July 2021.

Ethical Clearance
An ethical approval was granted by the Ethical Review Committee of Kwara State Ministry of Health, Ilorin, Nigeria in accordance with institutional guidelines. An approval number MOH/KS/EU/777/490 was assigned (Appendix I).

Study Participants
Participants who had type-2 diabetes co-existing with hypertension, aged between 20 and 70 years were recruited for this study. They were patients under specific treatment monitoring (Tabs Metformin 1 g morning and night and Tabs Amlodipine 5 mg daily) scheme with the doctors in the Cottage Hospital and their consent were soughed before administration. Fifty patients (50) patients were recruited for the study.

Chemicals and Reagents
All the chemicals and reagents used were of analytical grade.

Moringa oleifera Tea bags
Moringa oleifera tea is a product of Uva Halpewatte Estate Limited, Sri Lanka. Each tea bag per serving contains 2 g *Moringa oleifera* leaves.

Experimental Design
Patients of either sex were divided into five (5) groups of five (5) Patients each as follows:
Group-I: (Positive Control) patients with no ailment and no treatment
Group-II: (Negative control) diagnosed patients without treatment
Group-III: (Positive Control + MO tea) patients with no ailment but were given MOT

Group-IV: (Reference Drug) Patients diagnosed with co-morbidity and under management with Standard drug (Tabs Metformin and Amlodipine)
Group-V: (Reference drug + *M. oleifera* tea) patients diagnosed of co-morbidity and under management and were given *M. oleifera* tea.
The administration was done for 14 days. Thereafter, blood samples were collected and biochemical parameters were evaluated.

Sample Collection
Blood samples were collected by licensed Phlebotomist at the cottage hospital. Blood samples were withdrawn into plain, lithium heparin, and EDTA coated sample bottle, then centrifuged at 3000 rpm for 15 minutes using standard procedures (Pal, 2006) to obtain clear serum which was used for the analysis. Blood samples in the EDTA bottles were used for haematological assay.

Determination of Glucose concentration
Determination of blood glucose was done by glucose – oxidase principle (Beach and Turner, 1958) using one touch basic instrument and results were expressed in mg/dL and then converted to mmol/L.

Determination of Advanced Glycation End Product (AGE) and Advanced Oxidation Protein Product (AOPP)
The AGEs concentrations were estimated Spectro-fluorometrically according to the method described by Kalousva *et al*. (2002). The fluorescence intensity was recorded at 440 nm emission and 350 nm excitation. AOPP levels were determined Spectro-Photometrically according to the method of Kalousva *et al*. (2002)

Statistical Analysis
The results were expressed as the mean ± standard error of the mean (S.E.M). Differences between groups was determined by one-way analysis of variance (ANOVA) using SPSS version 20. The $p<0.01$ is considered statistically significant.

RESULTS
Effect of *M. oleifera* tea on advanced Glycation End Products
There was significantly ($p<0.01$) higher concentration of AGE in the serum of the untreated, reference drug and referenced drug + MO group when compared with the control. Whereas, there was no significant difference between the group treated with only MOT and the control. However, the increased concentration observed in the untreated group was significantly ($p<0.01$) reduced in the MOT treated group when compared with both the untreated group and groups that was administered only the reference drugs (Table 1).

Table 1: Advanced glycation end-products (AGEs) of the Experimental Patients

Treatment groups	AGEs (fluorescence intensity) p-value 0.01
Positive Control	176.16 +22.28[a]
Negative Control	256.79 ±25.60[d]
Positive Control + MO tea	177.15 ± 22.76[a]
Reference Drug	243.75 ± 28.61[c]
Reference Drug + MO tea	233.75 ± 25.50[b]

Effects of MO tea on Advanced Oxidation Products in Experimental Patients

Advanced oxidation protein products (AOPP) concentration was a significantly ($p<0.01$) higher in the untreated group, group treated with reference drug and group treated with both reference drug and MOT when compared with the control. Whereas, there was no significant difference between the group treated with only MOT and the control. However, the increased concentration observed in the untreated group was significantly ($p<0.01$) reduced in the group treated with both reference drug and MOT when compared with both the untreated group and groups that was administered only the Reference drugs (Table 2).

Table 2: Advanced oxidation protein products (AOPP) in the experimental

Treatment Groups	AOPP (µmol/L)
Positive Control	48.71±12.14[a]
Negative Control	77.56±12.15[d]
Positive Control + MO tea	46.47 ±15.41[a]
Reference Drug	75.06±10.02[c]
Reference Drug + MO tea	65.09 ±10.21[b]

Effects of MO Tea Supplement on Glucose Index

The result on Table 3 revealed that Random blood sugar (RBS), fasting blood sugar (FBS) and postpradial glucose level was significantly higher ($p<0.01$) in untreated patients compared with the control. Whereas, these parameters were not significantly ($p<0.01$) different from the control in the Positive Control + MOT while patients with Reference drug are higher than that of reference drug + MO tea (Table 3).

Table 3: Glucose Index in the Experimental patients

Treatment **Reference Value**	RBS Ref (6.1– 11.1)	FBS (2.5 – 6.1)	POSTPRANDIAL (6.1 - 11.1)
Positive Control	7.45±2.45[b]	4.44±2.10[a]	6.44±1.87[a]
Negative Control	22.65±2.8[b]	20.45±2.20[b]	25.55±2.82[b]
Positive control + MOT	7.12±1.22[a]	4.14±2.44[a]	5.76±1.27[a]
Reference Drug	12.8±.2.12[d]	10.16±2.45[c]	13.44±1.22[c]
Reference Drug + MOT	10.17±1.43[c]	6.14±2.20[b]	12.66±1.20[c]

Data are expressed as Mean ±SD., ABF= after breakfast, FBS= fasting blood sugar

Effects of *Moringa oleifera* tea on Haematological Parameters

There was significant ($p<0.01$) reduction in values of the white blood count (WBC), red blood count (RBC), packed cell volume (PCV), haemoglobin (HGB), mean cell haemoglobin concentration (MCHC), mean concentration haemoglobin (MCH), platelets (PLT) and mean corpuscular volume (MCV) of all the groups co-administered with drugs and MOT and group administered with standard drugs alone compared with the Positive control. However, there was a significant ($p<0.01$) reduction in the parameters of positive control treated with only MOT whereas no significant difference ($p>0.01$) between the positive control and the negative control (untreated group) (Table 4).

Table 4: Effects of *Moringa oleifera* leaf tea on Hematological Parameters of Diabetics/Hypertension Co-morbidity patients

Treatment	WBC ($x10^9$/L)	RBC ($x10^{12}$/L)	HGB (g/dL)	PCV (%)	MCHC (g/dL)	MCH (Pg)	PLT ($x10^9$/L)	MCV (fL)
Positive Control	8.76±1.87^a	6.27±0.41^a	13.5±0.17^a	39.16±2.74^a	29.98±1.02^a	32.66±1.13^a	506.72±27.18^a	69.56±1.21^a
Negative Control	8.66±2.0^a	6.5±0.52^a	13.6±0.18^a	40.1±2.84^a	29.84±1.50^a	32.52±1.15^a	605.56±25.21^a	66.50±1.52^a
Positive Control + MO tea	7.56±0.32^b	5.27±0.40^b	9.5±0.17^b	28.16±2.74^b	28.96±0.54^{ab}	31.36±0.61^{ab}	639.54±16.33^b	57.1±1.58^b
Reference Drug	6.46±0.32^c	4.27±0.40^c	9.5±0.17^c	28.16±2.73^{bc}	25.76±1.29^c	41.26±0.68^d	452.82±17.68^c	46.3±1.08^c
Reference Drug + MO tea	7.56±0.32^b	4.47±0.40^c	8.5±0.16^c	27.16±2.74^c	26.78±1.64^c	37.64±1.13^c	513.28±5.18^c	49.72±2.36^c

Values are Mean ± SEM. RBC- Red Blood Count, MCHC-Mean Cell Haemoglobin Concentration, MCH- Mean Ce ll Haemoglobin, MCV- Mean Corpuscular Volume, HGB-Haemoglobin, PCV-Packed Cell Volume, PLT-Platelets, WBC- White Blood Count.

Effects of *Moringa oleifera* tea on the blood pressure

There was a significant ($p>0.01$) reduction in the SBP, DBP and MAP of all groups treated with MOT. However, groups administered only the standard drugs had a significantly higher value than the groups which had the drug together with MOT. Moreover, the untreated groups had significantly ($p<0.01$) higher values than all other treatment groups (Table 5).

Table 5: Effects of *Moringa oleifera* leaf tea on blood pressure of Diabetics/Hypertension Co-morbidity patients

Treatment groups Ref. Value	SBP (100-135 mmHg)	DBP (60-85 mmHg)	MAP (60-100 mmHg)
Positive Control	122±10^a	71±12^a	88±12^a
Negative control	152±22^d	92±20^d	113±17^d
Positive Control + MO tea	120±12^a	60±12^b	88±12^a
Standard drug	142±15^c	92±10^d	109±11^c
Standard drug + MO tea	138±20^b	88±14^c	105±10^b

DISCUSSION

Previous studies have demonstrated the role of AGE and AOPP in the pathogenesis of various chronic diseases, including diabetes and cardiovascular diseases (Rasool *et al*., 2018; García-Sánchez *et al*., 2020). AGE and AOPP accumulation are associated with oxidative stress and inflammation, contributing to tissue damage and dysfunction (García-Sánchez *et al*., 2020). The observed increased in AGEs in negative control patients is an indication of disturbance in physiological systems (Suzuki *et al*., 2022). There is moderate production of AGEs under normal physiological conditions, but it is markedly accelerated under persistent hyperglycemic conditions due to increased glucose availability such as diabetes (Pérez-Burillo *et al*., 2019). The elevated blood glucose levels observed in this study corroborate this assertion (Table 5). AGEs are compounds that have undergone irreversible post-translational modifications due to reactions between sugars and amino groups on proteins and nucleic acids. The observed reduction in AGE and AOPP levels with MO tea supplementation aligns with the known antioxidant and anti-inflammatory properties of *M. oleifera* (Varadarajan and Balaji 2022). Previous research has shown that *M. oleifera* extracts possess potent antioxidant activity due to the presence of bioactive compounds such as polyphenols, flavonoids, and vitamins (Rocchetti *et al*., 2020; Lin *et al*., 2020).

Hyperglycemia accelerates formation of AGEs, which accumulate in the extracellular matrix of vessels and contribute to vascular damage in diabetes (Vlassara *et al*., 2014). High glucose concentrations are associated with reactive oxygen species formation and oxidative stress by different molecular mechanisms, such as an increased flux through the polyol and glucosamine pathways, activation of protein kinase C and NADPH oxidase (Jakuš *et al*., 2014). This is evident with the increased superoxide dismutase (SOD), catalase (CAT) and malondialdehyde (MDA) in the study of Lambe *et al.* (2023). Co-administration of MO leaf tea with standard drug in diabetic/ hypertensive patients showed significant decrease in AGEs and AOPP compared to diabetic/hypertensive patient treated with standard only.
These findings support the hypothesis that MO tea supplementation can mitigate oxidative stress and inflammation (Varadarajan and Balaji 2022), thereby reducing the formation and accumulation of AGE and AOPP (Vlassara *et al*., 2014).

Elevated blood glucose levels, as indicated by random blood sugar (RBS), fasting blood sugar (FBS), and postprandial glucose levels, are hallmark features of diabetes mellitus (Supabphol, *et al*., 2021). Controlling blood glucose levels is essential for the management of diabetes and prevention of complications (Zhang *et al*., 2018).

The observed reduction in glucose indices with MO tea supplementation suggests a potential antidiabetic effect. Previous studies have reported hypoglycemic properties of *Moringa oleifera* extracts, attributed to various mechanisms including improved insulin sensitivity, enhanced glucose uptake, and inhibition of carbohydrate digestion enzymes (Ahmad *et al.,* 2019; Vargas-Sánchez *et al.,* 2019). These findings support the assertion that MO tea supplementation may offer benefits in glycemic control and diabetes management.

Hematological abnormalities, such as alterations in white blood cell count (WBC), red blood cell count (RBC), and hemoglobin levels, are commonly observed in chronic diseases and may reflect underlying inflammation, oxidative stress, or nutritional deficiencies (Singh and Bhatta, 2018). Assessment of hematological parameters can be used to explain blood relating functions of a plant extract or its products (Ware, 2020). The significant reduction in hematological parameters in the groups co-administered with drugs and MO tea suggests potential ameliorative effects on systemic inflammation and oxidative stress. *Moringa oleifera* is known for its nutritional richness, including high levels of vitamins, minerals, and amino acids, which may contribute to improved hematological profiles (Zaher *et al*., 2020). These findings support the assertion that MO tea supplementation may exert positive effects on hematological parameters, possibly through its nutritional and antioxidant properties. These is also in relation to the findings of Lambe and Bewaji (2022) which reported the positive effect of *M. oliefera* leaf supplement on heamatological parameters.

Hypertension is a major risk factor for cardiovascular diseases and is often associated with oxidative stress, endothelial dysfunction, and inflammation (Incalza *et al*., 2018). Lowering blood pressure levels is crucial for reducing the risk of cardiovascular events (Shaito *et al*., 2022).

The significant reduction in systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) with MO tea supplementation suggests a potential antihypertensive effect (Shaito *et al*., 2022). Previous studies have reported vasodilatory and antihypertensive properties of *M. oleifera* extracts, attributed to bioactive compounds such as quercetin and chlorogenic acid (Okorie *et al*., 2019; Alia *et al*., 2022). These findings support the assertion that MO tea supplementation may contribute to blood pressure regulation and cardiovascular health.

CONCLUSION

Findings from this study revealed that co-administration of *M. oleifera* leaf tea with diabetes-hypertension comorbidity standard drugs can reduce the adverse effects of the drugs and aid the reduction of glycemic parameters while improving the haematological parameters. Hence, *M. oleifera* tea is one of the promising products to control diabetes and hypertension comorbidity. However, further research, including randomized controlled trials and mechanistic studies, is warranted to validate these findings and elucidate the underlying molecular mechanisms.

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