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MORINGA OLEIFERA LEAF POWDER FOR TYPE 2 DIABETES: A PILOT CLINICAL TRIAL

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Abstract

Background: *Moringa oleifera* Lam. (Moringaceae) leaves are commonly used for diabetes in Mali. This pilot clinical study aimed to evaluate its effect on post-prandial blood glucose in preparation for a larger trial.
Methods: Diabetic patients and non-diabetic healthy volunteers (35 each) were asked to fast for 13 hours on three occasions. Blood glucose was measured before and after eating 100g of white bread (at 30, 60, 90, 120, 150 and 180 minutes). On their second and third study visits, they were given 1g and 2g respectively, of *M. oleifera* leaf powder, 30 minutes after eating the bread. The mean paired reduction in blood glucose at each time interval and the incremental area under the curve were calculated.
Results: Ingestion of *Moringa* powder had no effect on blood glucose in non-diabetic participants, but in diabetic patients, it lowered blood glucose at 90 minutes. There was a trend towards lower incremental area under the curve when diabetic patients took 2g of *Moringa*. No side-effects were reported by any participant.
Conclusions: *Moringa oleifera* leaf powder reduced post-prandial glycaemia in diabetic patients. A larger study is needed to define the optimal dose and to assess whether this translates into longer-term benefits.

Key words: *Moringa oleifera*; Type 2 diabetes; clinical trial

List of Abbreviations: 95% CI = 95% Confidence Interval, AUC = Area Under the Curve, BMI = Body Mass Index HbA1c = Haemoglobin A1c, IC50 = Inhibitory Concentration 50%, NIHR = National Institute of Health Research mmol/l = millimoles per litre, SD = Standard Deviation, SGLT-1 = sodium glucose transporter-1

Introduction

The prevalence of diabetes in Mali has increased six-fold from 0.27% in 2002-3 to 1.8% in 2017 (95% CI 1.4-4.2%) in adults aged 20-79 years (International Diabetes Federation, 2017; Liu *et al.*, 2012). Diabetes was the second most common reason for admission to the two university teaching hospitals in Bamako (Mali), and was also responsible for 40% of general medical consultations in 1996 (Santé Diabète Mali, 2012). A survey of 100 diabetic patients at Gabriel Touré University Hospital in 2006-7 showed that 71% of patients had a monthly income of less than US$100, but the average yearly treatment costs for diabetes were US$1169 (Sanogo *et al.,* 2015). This has been confirmed in a later study which found that total annual healthcare-associated costs for diabetic patients were $1127 compared to $308 for non-diabetic control patients, in a sample of 500 diabetic patients and 500 controls in Mali (Bermudez-Tamayo *et al.,* 2017). A further survey of 100 type 2 diabetic patients attending the University Hospital clinic in 2009 found that 65% were not complying with their medications; in 57% of cases this was due to cost, and in 20% due to poor access to medicines (Sanogo *et al.,* 2013). In rural areas, financial barriers to accessing medications are even greater; most of the population in Mali cannot easily access modern medicines and prefer to use herbal medicine as the first line.

Many herbal medicines are used for the treatment of diabetes, and the most widely-used modern antidiabetic medicine (metformin) is derived from guanidine and galegine, active compounds of the Western herbal remedy *Galega officinalis* (Simmonds and Howes, 2006). *Moringa oleifera* Lam. (Moringaceae) is widely used in the tropics as a herbal remedy for diabetes. In Bangladesh, an ethnobotanical survey showed that *M. oleifera* was one of the plants most frequently cited by traditional healers across 15 districts (Kadir *et al.,* 2012). In South Africa, 17% of Bapedi healers of Limpopo district use the raw seeds and leaves, cooked for 5-10 minutes, to treat diabetes mellitus (Semenya *et al.,* 2012). In Senegal, *M. oleifera* was used by nearly 66% of diabetic patients interviewed at a university teaching hospital (Dièye *et al.,* 2008). The most popular use of *M. oleifera* is as medicine for treating diabetes and regulating blood pressure through the consumption of the fresh or dried leaves. These uses are common knowledge throughout Senegal (Yousefian, 2012), and have also been reported in Nigeria (Popoola and Obembe, 2013). In Ugandan rural communities, the use of *Moringa* leaves to treat diabetes mellitus was cited by 90% of respondents (Kasolo *et al.,* 2010).

M. oleifera, commonly referred to as the "drumstick tree" because of its large seed-pods (figure 1), is native to the western sub-Himalayan regions of India, Pakistan, Bangladesh and Afghanistan, but has been cultivated for food and medicine in tropical Asia, sub-Saharan Africa, Latin America and the Caribbean (Fahey, 2005; Jahn *et al.,* 1986; Morton, 1991). The consumption of the leaves, pods and flowers as food is very common. In West Africa, the leaves and sometimes the flowers, are eaten in a peanut sauce, whereas the immature pods are not frequently consumed but rather pressed for oil and used as medicine (Yousefian, 2012). In India, the immature pods are cooked in curries as vegetables, the mature pods are used in soups and stews and the drumstick pulp is used in various dishes (Pandey *et al.,* 2011). The leaves are also widely used as vegetable, condiment and in salads. The leaves are rich in protein, essential amino acids, iron, copper, calcium, Vitamin C and carotenoids (Fahey, 2005; Fuglie, 2002) so have been promoted as a nutritional supplement for malnourished children, lactating women and people with osteoporosis (Pandey *et al.,* 2011).

Therefore, various non-governmental organisations and governments have supported large scale planting of *Moringa* (Hirt and Lindsey, 2008; Thurber and Fahey, 2009; Yousefian, 2012). As would be expected for a food, *M. oleifera* leaves are non-toxic. This has been confirmed by laboratory experiments. The aqueous extract of *M. oleifera* leaves was administered orally to 30 male Wistar rats and even at doses of 2000 mg/kg, no mortality ensued (Adedapo *et al.,*2009). Sub-acute toxicity was assessed by administering daily doses of up to 1600 mg/kg to male rats, and no signs of serious toxicity were observed on biochemical or haematological tests, or on histopathology of the organs (Adedapo et al., 2009). The safety of *M. oleifera* leaves has been confirmed in other studies (Isitua and Ibeh, 2013).

Figure 1: *Moringa oleifera* tree *(Photo: Merlin Willcox)*

In vitro studies

A water extract of dried Moringa leaf strongly inhibited the activity of intestinal sucrase (IC_{50} 0.98mg/ml) and weakly inhibited the activity of maltase and pancreatic α-amylase (22.3% and 5.3% respectively, at 5mg/ml). It also inhibited the activity of pancreatic cholesterol esterase (IC_{50} 4.34 mg/ml) (Adisakwattana and Chanathong, 2011).

A methanol extract at a concentration of 250 µg/ml inhibited α-amylase activity by 68% (Leone *et al.,* 2018). *Moringa oleifera* water, ethanol and methanol extracts have a dose-dependent α-D-glucosidase inhibition activity (Togola, 2014). *Moringa* leaf contains a high concentration of quercetin-3-glucoside (Q3G) (Ndong *et al.,*¬ 2007) which competitively inhibits sodium (Na+) dependent mucosal uptake of glucose via SGLT-1 (sodium glucose transporter-1) in the small intestine (Cermak *et al.,* 2004).

In vivo studies

Several studies in diabetic rats have shown that *M. oleifera* leaf extracts have antidiabetic properties. An ethanolic leaf extract of *M. oleifera* was one of the most potent among 30 hypoglycaemic medicinal plants from indigenous folk medicines for lowering blood glucose level in alloxan-induced diabetic albino rats (Kar *et al.,* 2003).

M. oleifera leaf tablets reduced blood glucose by 54.4%, compared to 40% in those who received glibenclamide, while the negative control groups had an increased blood glucose level with time (Momoh *et al.,*2013).

M. oleifera leaf powder significantly improved glucose tolerance and lowered fasting plasma glucose in diabetic rats (Jaiswal *et al.,*2009). *M. oleifera* significantly decreased postprandial blood glucose levels in both Wistar and Goto-Kakizaki (GK) rats (Ndong *et al*., 2007). This study suggests that *M. oleifera* leaves increase glucose tolerance, though the effect was greater in GK rats than in Wistar rats.

Other parts of the plant also have antidiabetic properties: an alcoholic bark extract prevented dexamethasone-induced insulin resistance in peripheral tissues of rats (Sholapur and Patil, 2013). A methanol extract of the pods reduced blood sugar levels in diabetic rats (Gupta *et al.*, 2012) and a hydroalcoholic flower extract had significant activity against hyperglycemia in diabetic rats (Sunilkumar, 2011).

Clinical studies

There have been three clinical trials to study the hypoglycaemic effect of Moringa leaf in diabetic patients. The first studied the effect of 50g of cooked leaves on post-prandial blood glucose after a standard meal, compared to bitter gourd and curry leaves, in six type 2 diabetic patients who were not taking any medication (William *et al.,* 1993).

The meal including Moringa leaves was followed by a significantly reduced incremental area under the glucose curve, unlike the other two vegetables, suggesting that Moringa does indeed have hypoglycaemic properties over and above the reduction in glycaemic index seen with any vegetable or fibre in the diet. The insulin levels were not raised compared to the other foods, suggesting that the mechanism of action is not an increase in insulin secretion.

A second trial measured HbA1c and post-prandial blood glucose levels after three months in 30 patients with type 2 diabetes who took a Moringa leaf tablet after breakfast and after dinner every day, in addition to sulphonylureas, compared to 30 control patients without Moringa (Giridhari *et al.,* 2011). The experimental group had a significant reduction of HbA1c (from 7.8% to 7.4%) and in postprandial blood glucose, whereas there was no significant change in the control group.

More recently, a trial in 17 diabetic patients found that 20g of dried Moringa leaf powder significantly reduced post-prandial glucose in diabetic patients after eating a standard meal, but that this significantly reduced the acceptability of the meal due to the bitter taste (Leone *et al*., 2018). The authors, therefore, recommended trials with lower doses of Moringa. All these trials are small and have methodological flaws, so there is a need for better evidence on the effectiveness and optimal dosage of Moringa leaf powder in diabetic patients.

Aims and Objectives

We aimed to conduct a pilot study of the effect of *Moringa oleifera* leaf powder on postprandial blood glucose in diabetic patients and non-diabetic controls. The objectives were to test whether it was possible to recruit and retain patients to such a study, and to inform sample size calculation for a definitive study. This study was approved by the Institut National de Recherche en Santé Publique in Mali.

Materials and Methods

Preparation of plant material

The youngest leaves (at the tips of the branches) were harvested early in the morning at the start of the rainy season in June 2014, in Bamako district (Mali). The plant was identified by the Head Botanist of the Department of Traditional Medicine (Seydou Dembélé), and a voucher specimen has been deposited in its herbarium (Number 1391/DMT). The leaves were washed with tap water, dried in the shade, then pounded and sifted to give a fine powder.

The powder was stored in hermetically sealed glass jars and kept in a dry area. The dose was determined by

weighing the dose normally given by traditional healers – this was approximately one gram. We decided to test this, and double this dose, to look for a dose-response effect.

Participants

We recruited 70 participants (35 with diet-controlled type 2 diabetes, and 35 non-diabetic) from Bamako and Kati. Diabetic patients were excluded if they were pregnant, if they had any cardiac, respiratory, renal or liver disease; if their fasting blood glucose was <7.0 mmol/l, if their post-prandial glucose was <11.0 mmol/l, or if they had any allergy to Moringa leaf powder. Non-diabetic participants were recruited from among the relatives of the diabetic patients, and from the staff of local schools.

Study procedures

Participants came on three occasions, at least 15 days apart. On all occasions, they were asked to fast for 13 hours before the test. Participants were weighed, and body mass index was calculated. Fasting blood glucose was measured with a hand-held glucometer (Infopia Element, USA), following which the patient ate 100 g of white bread, with water. On the first occasion, nothing else was administered, and blood glucose was measured again 30, 60, 90, 120, 150 and 180 minutes after eating the bread. On the second occasion, participants were given 1g of *Moringa oleifera* leaf powder with 75 ml water, 30 minutes after eating the bread (after the first post-prandial measurement of blood glucose). On the third occasion, they took 2 g of *Moringa oleifera* leaf powder with 75 ml in the same way. Patients were asked about any symptoms.

Analysis

Data was recorded on paper forms, and then entered into a database using Epi-info version 3.5.4 (CDC, Atlanta, USA). After completing data entry, data were exported and analysed using SPSS 20 (IBM). A paired t-test was used to compare mean post-prandial blood glucose at 60, 90 and 120 minutes, with and without different doses of *Moringa*. The results were analysed separately for the patients with diabetes, and the healthy controls. The primary outcome measure was defined as the mean paired difference in blood glucose at 90 minutes, with and without *Moringa* at the two different doses.

As a secondary outcome measure, positive incremental area under the curve was calculated for all glucose measurements from baseline to 180 minutes in accordance with FAO/WHO's '*Joint Guidelines on glycaemic index testing of foods*' and the International Standard *'ISO 26642/2010: Food Products – determination of the glycaemic index (GI) and recommendation for food classification*'. Repeated measures ANCOVA was used to compare treatments across time-points, recognising that responses were clustered within individual participants. This analysis was carried out in Stata v14.

Sample size for a definitive study was calculated using NQuery, assuming 90% power, and using the difference in the positive incremental area under the curve and standard deviation estimated during this pilot study.

Ethical issues

The research followed guidelines of the Declaration of Helsinki and Tokyo. The protocol received ethical approval from the ethics committee of the National Institute for Public Health Research (INRSP) in Bamako, Mali (decision No 12/13 CE-INRSP, 6th November 2013). The study was explained to participants, who were given an information sheet and allowed an opportunity to ask questions. If they agreed to participate, they were asked to sign a consent form. Participants were compensated for the time and travel to each appointment.

Results
Participants

Baseline characteristics are summarised in Table 1. The diabetic group was on average slightly older, included more women, and had a higher BMI than the non-diabetic group. It was feasible to recruit and retain patients to this study.

Table 1: Baseline characteristics of participants

	Diabetic (n=35)	Non-diabetic (n=35)
Mean age in years (SD)	45.8 (10.6)	50.1 (11.6)
Number of women (%)	25 (71%)	14 (40%)
Mean BMI (SD)	29.6 (4.4)	24.5 (3.8)
No of obese patients, BMI>30 (%)	18 (51%)	3 (9%)
Mean baseline fasting glucose, mmol/l (SD)	9.1 (2.7)	5.4 (0.7)

Effect of Moringa on blood glucose

In diabetic patients, blood glucose was on average about 1mmol/l lower after ingesting Moringa than it was after eating the same meal without Moringa (Table 2 and Figure 3). The difference reached statistical significance at 90 minutes when the dose was 1g, and at 120 mins when the dose was 2 g. In non-diabetic participants, there was no significant difference in blood glucose, except in the group that took 2 g, at 60 minutes; this reduction was lower than in diabetic patients (0.58 mmol/l). No side-effect was reported by any participant.

Table 2: Mean paired difference in blood glucose (mmol/l) at different time intervals after eating 100g white bread without Moringa, compared to white bread 100 g with Moringa 30 minutes later (* $p<0.05$, paired t-test)

Group	Dose of Moringa	60 mins (95% CI)	90 mins (95% CI)	120 mins (95% CI)
Non-diabetic	1 g	0.07 (-0.57 to 0.72)	-0.03 (-0.55 to 0.50)	0.11 (-0.31 to +0.52)
	2 g	0.58 (0.19 to 0.98)*	0.17 (-0.31 to 0.66)	0.15 (-0.32 to + 0.61)
Diabetic	1 g	0.70 (-0.39 to 1.78)	1.26 (0.07 to 2.46)*	0.76 (-0.26 to +1.80)
	2 g	1.04 (-0.21 to 2.29)	1.04 (- 0.18 to 2.27)	1.25 (0.24 to 2.26)*

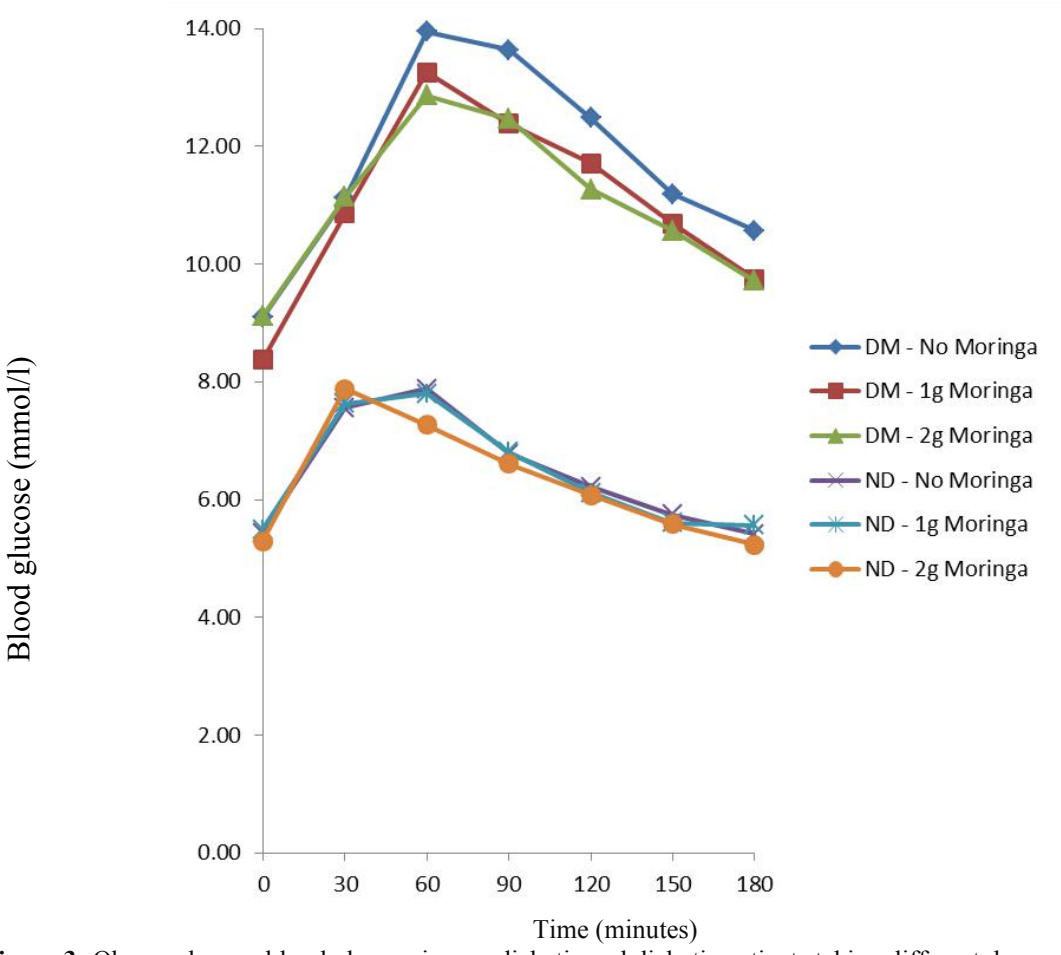

Figure 3: Observed mean blood glucose in non-diabetic and diabetic patients taking different doses of Moringa. (DM= Diabetic; ND = Non-Diabetic)

There were no significant differences between the control and Moringa treatments in the positive incremental area under the curve (AUC) for the whole study population controlling for age, sex, BMI and whether the participant was diabetic (Table 3). There was a trend towards a dose-response effect, with a larger reduction for diabetic patients who took 2 g of Moringa compared to when they took no Moringa (by 92 mmol min/l) but this difference was not statistically significant.

Table 3: Positive incremental area under the curve (mmol min/l)

Group		Mean positive incremental area under the curve (SD)	Difference compared to control (95% CI)
Non-diabetics	Control	222.77 (108.29)	
	1 g Moringa	301.29 (453.67)	78.52 (-51.54, 208.59)
	2 g Moringa	221.82 (125.28)	-0.94 (-131.01, 129.12)
Diabetics	Control	552.79 (344.47)	
	1 g Moringa	549.83 (318.29)	-2.96 (-121.70, 115.77)
	2 g Moringa	461.41 (414.88)	-91.38 (-210.11, 27.35)

The sample size calculation, using a simple crossover design to detect a difference between 2 g of *Moringa oleifera* leaf powder and control, for a difference in the positive incremental area under the curve of 92 and a standard deviation of 360, suggests that a full study would require 82 diabetic patients.

Discussion

Principal findings

We were able to recruit and retain diabetic patients to a trial examining the effect of *Moringa oleifera* leaf powder on post-prandial glucose. We were able to collect the primary outcome measure (post-prandial glycaemia, measured from a finger prick); administration of Moringa appears to reduce the post-prandial rise in blood glucose in diabetic patients but not in healthy controls. The duration of effect may be greater and longer after taking 2 g of *Moringa oleifera* leaf powder than after taking 1g. A larger study of 82 diabetic patients is needed to confirm this effect. No adverse effects were reported.

Strengths and limitations

This was a small pilot study, and because of logistical difficulties, healthy volunteers were not perfectly matched by age and sex to the diabetic patients. We used glucometers rather than venous blood samples to measure glucose, because of limited resources and practical considerations. Nevertheless it is unlikely that these factors could have caused the observed differences in blood glucose. *Moringa* leaf powder was administered 30 minutes after the bread, but in future studies it would be better to administer it at the same time as the food (which is the traditional practice, and which would fit with the putative mechanism of action). It would also be good to escalate the dose further beyond 2 g to evaluate whether there would be a larger and more significant effect, while maintaining acceptability.

In future studies it would be better to use the positive incremental area under the curve as the primary outcome measure.

Implications

This pilot study supports the results of previous research which also show that *M. oleifera* leaf powder lowers blood glucose. It is particularly interesting that this effect only seemed to occur in diabetic patients. Future studies are needed to confirm this, to study whether a larger dose would have a greater effect, and to evaluate the effect of its daily use over a period of several months, on glycated haemoglobin. It would also be interesting to evaluate its effect on blood cholesterol, since preclinical studies suggest that *M. oleifera* may also have cholesterol-lowering effects (Ghasi *et al.,* 2000). Diabetic patients are at increased risk of cardiovascular disease, and cholesterol is a major risk factor for this.

M. oleifera leaves are primarily a food, part of the normal diet in many tropical countries, so are particularly interesting as a potential dietary intervention for patients with diabetes, because it is possible to increase the dose significantly with no risk of toxicity. Giving the leaf powder in capsules could avoid the issue with acceptability of the taste. While awaiting results of further research, there would be no harm in encouraging diabetic patients to incorporate *M. oleifera* into their daily diet (if they do not already do so).

Conclusions

Moringa oleifera leaf powder, administered 30 minutes after a food bolus, seemed to reduce post-prandial blood glucose in diabetic patients only, but not in non-diabetic volunteers. A definitive trial would need 82 diabetic patients to demonstrate whether there is a statistically significant difference in the area under the curve. Further research is also needed to assess whether this translates into reductions in HbA1c after use of Moringa for three or more months, and reductions in long-term complications of diabetes.

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