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REVIEW ARTICLE

Clinical antihypertensive efficacy and safety of *Moringa oleifera* Lam. (Moringaceae) leaf: a systematic review

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Abstract

In low- and medium-income countries (LMICs) where access to medicines is challenging, hypertension prevalence is increasing, justifying the need to integrate traditional herbal medicines like *Moringa oleifera* into mainstream clinical practice. This review examines clinical studies in literature, starting from 2011, on the efficacy and safety of *Moringa oleifera* in hypertension treatment. Outcomes including effects on blood pressure, other cardiovascular risks, blood biochemistry, and adverse drug events were extracted from the articles. The quality of evidence was assessed with the risk of bias in non-randomised studies of interventions (ROBINS-1) tool. A total of 295 articles were identified, of which 16 were included for review. All but one were non-randomised studies. Regarding clinical efficacy, three articles, (n=131) showed that in normotensive patients, Moringa treatment has an acute BP-lowering effect but repeated doses failed to demonstrate a BP-lowering effect (3 articles, n=82). In hypertensive populations (3 articles, n=112) Moringa supplementation had BP-lowering effects. In terms of clinical safety (2 articles, n=66) there are non-significant changes in blood biochemistry including alanine aminotransferase, creatinine and blood urea nitrogen in normotensive patients. Regarding treatment tolerability, there was no incidence of adverse events (2 articles, n=209) while others reported minor gastrointestinal upset and changes in appetite and sleep patterns (2 articles, n=103). Limited literature using non-randomised trial designs shows that *Moringa oleifera* leaf supplementation lowers blood pressure in persons with hypertension. *Moringa oleifera* leaf appears safe in normotensive patients.

Keywords: *Moringa oleifera* leaf; Hypertension; Clinical efficacy; Clinical safety; Systematic review

INTRODUCTION

Hypertension, a dangerous cardiovascular risk factor, is a leading cause of diseases globally [1]. In low and medium-income countries (LMICs) where access to medicines is challenging, the prevalence of hypertension is increasing [2-4]. For example, in Nigeria, national estimates of hypertension prevalence indicate a rising trend. Hypertension prevalence rose from 11.2% in 1997 [5] to 28.0% in 2010 [6], and to 30.6% in 2021 [7], largely due to changes in dietary and lifestyle factors.

The World Health Organisation promotes evidence-based development and integration of traditional medicine especially herbal medicine into the mainstream health systems of nations to help expand medicine

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access for prevalent health conditions [8]. In Nigeria, the development and integration of traditional herbal medicines into the national healthcare system for priority diseases like hypertension are part of the core mandates of the recently created Traditional, Complementary and Alternative Department in the Federal Ministry of Health [9]. A rich database of clinical data on herbal medicine is crucial for facilitating traditional herbal medicine integration.

Moringa oleifera leaf is popular in the traditional treatment of hypertension in many parts of the world including Nigeria [10-14]. *Moringa oleifera* Lam. (Moringaceae) is native to Asia, and naturalised in many parts of the world including Nigeria [15]. An increasing body of evidence from animal studies indicates that *Moringa oleifera* leaf has an antihypertensive effect, mediated through antioxidant mechanisms [13,16-18]. The favourable preclinical evidence supports the need to determine the antihypertensive effect of *Moringa oleifera* in clinical trials. Research evidence on the clinical antihypertensive effectiveness of *Moringa oleifera* leaf is needed to advance the plant material for possible integration to complement medicine access, especially in LMICs. Okorie and colleagues [13] reviewed articles on the antihypertensive effects of *Moringa oleifera*, focusing on the bioactive components of the herbal remedy and its role in interfering with the hypertension pathophysiologic pathway. While such information is crucial for supporting clinical investigation of the herbal remedy, it is limited in addressing the clinical effectiveness data required for policy and clinical decision-making.

This study reviews existing clinical literature on *Moringa oleifera* efficacy and safety in hypertension treatment. The goal of the review is to synthesise the current knowledge on *Moringa oleifera* role in clinical hypertension. The question this review seeks to answer is: in persons with hypertension, does treatment with *Moringa oleifera* compared to comparators have different effects on hypertension treatment outcomes? The gaps in existing knowledge on the clinical antihypertensive effectiveness of *Moringa oleifera* are being addressed in an ongoing effort to determine the clinical effects of the herbal remedy in hypertension.

METHODS

Search strategy. A systematic review of published related articles on clinical antihypertensive efficacy and safety of *Moringa oleifera* leaf was carried out through the electronic search of different databases including PubMed, Google Scholar, and Cochrane databases. The search was limited to articles published between 2011 and 2020 to retrieve current articles related to the subject matter. The article search employed the keywords: '*Moringa oleifera*' in the title/abstract, combined with 'hypertension' 'blood pressure' cardiovascular, 'clinical' or safety.

Eligibility criteria. Articles were included for review if they fulfilled the following specific criteria: (a) studies written in English; (b) they examined *Moringa oleifera* leaf's antihypertensive effects in humans, and (c) they examined the safety of *Moringa oleifera* leaf in humans. Specific exclusion criteria were: (a) studies that utilised a cross-sectional design; and (b) articles such as reviews and editorials that do not report primary data research.

Data extraction and quality. The outcome of the literature review indicated that some previous related studies had been conducted. The characteristics of the identified articles which met the inclusion criteria were examined according to (a) article reference; (b) the study's objectives; (c) the study's design; (d) the study program (e) the study's population; and (f) effects of the study on any of the following: blood pressure, any other

cardiovascular risk parameter, incidence of adverse events, and health-related quality of life (HRQoL). The internal validity of the studies' conclusions was analysed using the tool described by Sterne and colleagues [19] for assessing the risk of bias in intervention studies.

RESULTS AND DISCUSSION

Overview of studies included in the review. The search yielded 259 publications in total. Applying the inclusion and exclusion criteria, 243 articles were excluded leaving 16 articles, that were reviewed (Figure 1) The reviewed articles consisted of studies conducted in 10 countries namely Nigeria (4), India (3), Barbados (2), Algeria (1), Cameroun (1), Indonesia (1), Mauritius (1), Thailand (1), USA (1), and Zambia (1). Twelve and 6 articles examined at least the clinical antihypertensive effect and safety of *Moringa oleifera* leaf respectively. Two studies addressed both the clinical efficacy and safety of *Moringa oleifera* leaf.

Trial designs utilised by the reviewed articles for evaluating clinical antihypertensive effects of *Moringa oleifera* leaf products were comparative non-randomised open-label trial designs (9 articles), and single-group designs (2 articles). Only one article used a randomised placebo-controlled blinded trial design to examine the blood pressure effect of *Moringa oleifera* leaf powder in a diabetic normotensive population. Based on the study population, the total sample for the clinical antihypertensive studies were 112 hypertensive adults from 3 studies; 69 adults with at least 2 cardiovascular risk factors from one study; 36 diabetic normotensives from 1 study; and 252 healthy normotensives from 7 studies. Three articles reported single-dose effects while the remaining 9 reported repeated-dose antihypertensive results of *Moringa oleifera* leaf.

Articles that assessed the clinical safety of *Moringa oleifera* leaf products utilised non-randomised comparative open-label (2 articles), single group (2), and randomised placebo-controlled (2 articles) trial designs. The safety studies sample consisted of 30 healthy adults (one article); 140 overweight adults (one article), 63 diabetic adults (2 articles); 69 adults with at least 2 cardiovascular risk factors (one article); and 54 children within the ages of 4 and 18 years (one article). All the studies were done in normotensives except one article that examined *Moringa oleifera* leaf's safety in participants with at least 2 cardiovascular risk factors.

Clinical antihypertensive efficacy of *Moringa oleifera* leaf. The main goal of antihypertensive treatment is reducing cardiovascular complications with associated mortality. However, in short-term clinical trials of antihypertensive medications, the blood pressure effect is used as a sufficient outcome measure of clinical efficacy. Furthermore, the effect of the trial agent on other cardiovascular risk factors is often advanced as an additional consideration of its effectiveness [20].

Effect on blood pressure. The blood pressure effect of *Moringa oleifera* leaf treatment in normotensives was evaluated by 7 studies (Table 1). Three studies examined the effects of *Moringa oleifera* leaf acute treatment and reported a statistically significant drop in blood pressure compared to control in healthy normotensives [21-23]. The results of these studies suggest a blood pressure-lowering efficacy of *Moringa oleifera* leaf acute treatment in normotensives. However, the finding is biased as the employment of non-randomised and unblinded designs implies the effect can be attributed to alternative explanations other than *Moringa oleifera* leaf treatment alone [19,24].

Four studies evaluated the blood pressure effect of *Moringa oleifera* leaf

repeated dose treatment in normotensive adults and reported inconsistent results. Reductions in blood pressure were statistically non-significant in 3 studies [25-27]. These results suggest a lack of blood pressure-lowering effect by repeated doses of Moringa leaf treatment in normotensives. None of these studies used a statistically powered sample size to evaluate the blood pressure effect; therefore, the lack of blood pressure effect might be due to type 2 error [19,24]. In contrast, Venkatesan [28] reported a statistically significant reduction in mean arterial pressure (MAP) in adult normotensive athletes treated with Moringa leaf powder for 8 weeks. Though this study was not statistically powered to detect a specified change in blood pressure, being on exercise might have interacted with Moringa treatment to amplify the reported blood pressure-lowering activity.

Three studies assessed the blood pressure effect of Moringa leaf supplementation in a hypertensive population and reported that the herbal remedy has blood pressure-lowering effects in hypertensive adults [29-31], with one article examining the blood pressure effect of the herbal remedy in persons with cardiovascular risk factors (Table 2). Fombang and colleagues [30] reported that the blood pressure-lowering effect of Moringa leaf supplementation was more pronounced in the obese, compared to the non-obese populations.

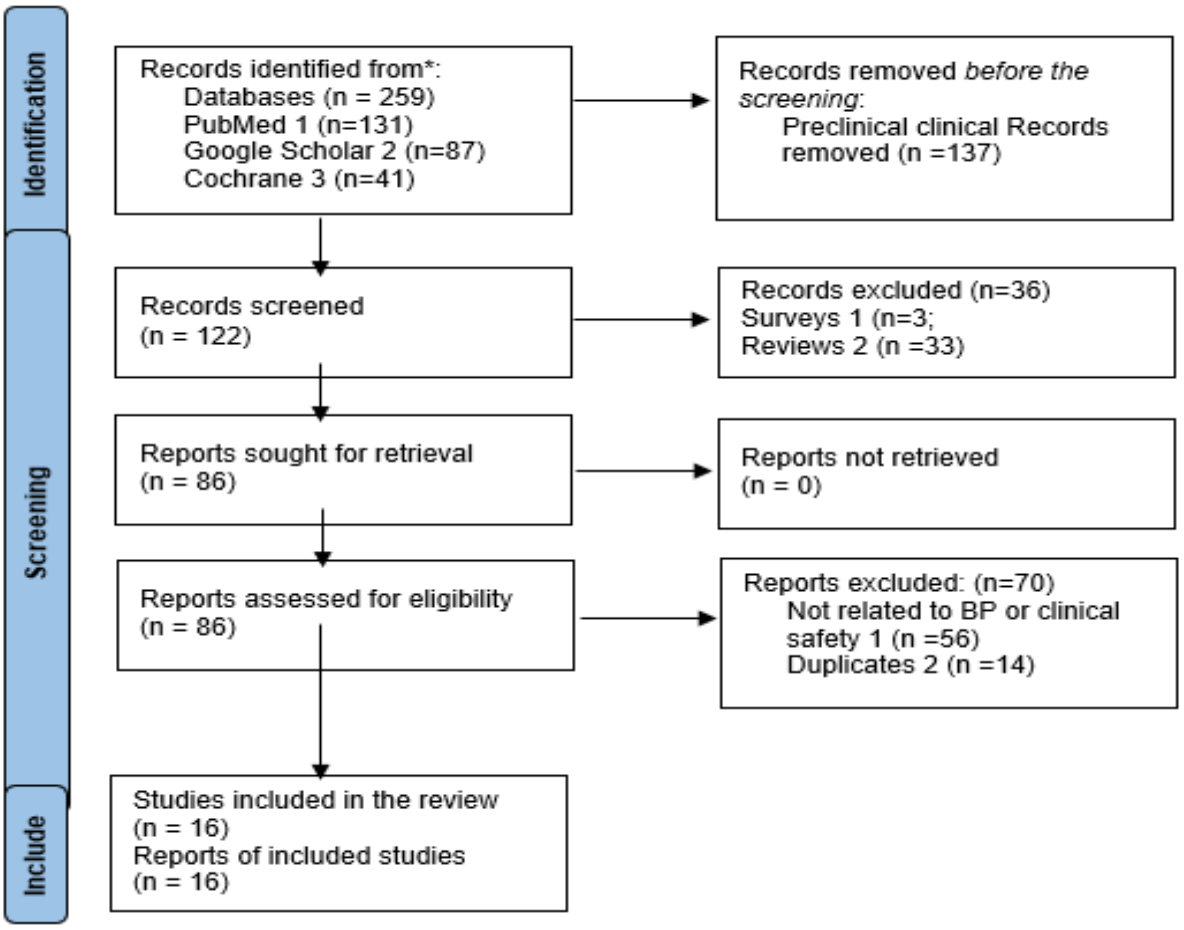

Figure 1: PRISMA chart for the articles reviewed

Table 1: Articles on blood pressure and cardiovascular effects of *Moringa oleifera* in normotensive adults

Reference	Objectives	Design	Population	Program	Findings	Threats to internal validity
[21]	To determine the acute effect of graded doses of Moringa leaf on systemic and intraocular blood pressure	Comparative groups, open-label trial	40 normotensive adults	Moringa leaf aqueous extract at 28.5, 57, and 85.7 mg/Kg start	Treatment reduces intraocular and systemic blood pressure in a dose-dependent fashion	Selection and measurement biases
[22]	To determine the effects of acute administration of Moringa leaf powder on blood pressure	Comparative, open-label trial	50 healthy adults	75 mg/Kg start Moringa leaf powder	Treatment lowers blood pressure	Selection and measurement biases
[23]	To compare the acute effect Moringa containing meals, to normal meals on blood pressure	The placebo-control trial, open-label	41 healthy adults	120 g Moringa leaf meal start	Treatment lowers blood pressure in healthy adults	Measurement bias
[25]	To compare the lipid, BMI, and blood pressure effects of graded doses of Moringa leaf powder	Open-label comparative groups trial	16 normotensive adults	0.03 g/day and 0.07 g/day doses of Moringa leaf powder for 14 days	Treatment has a nonsignificant reduction in blood pressure	Type 2 error, selection and measurement biases
[26]	To assess the effects of a combination product containing Moringa on blood pressure, blood glucose and **BCI**	Historical control trial design	30 healthy adults	Supplementation with a combination for 60 days (vitamin D3, banana leaf, green coffee, and Moringa leaf extracts) (Moringa extract = 200 mg per day)	Treatment has a nonsignificant reduction in blood pressure, and blood glucose and Significant improvement in BCI (negative)	Type 2 error, selection and measurement biases
[27]	To compare the effects of Moringa leaf powder to placebo on blood glucose	Randomised placebo control trial	36 diabetes mellitus patients	Moringa leaf powder capsule dosed at 8 g/day for 4 weeks	Treatment has non-significant changes in blood glucose	Type 2 error
[28]	To compare the effect of Moringa leaf with anuloma villoma on heart rate, mean arterial pressure	Open-label 3 comparative groups design	45 normotensive athletes	8 weeks supplementation with Moringa leaf powder alone, and combined with anuloma villoma	Moringa alone, and with annolma reduce mean arterial pressure, and heart rate	Measurement bias, interaction with anuloma villoma
[32]	To determine the effects of Moringa leaf powder on sodium, chloride and potassium ions	Single group pretest and posttest trial	30 healthy adults of either sex	5 g Moringa leaf powder for 7 days	Lowers sodium and chloride ion	History and maturation effects

Table 2: Articles on blood pressure and cardiovascular effects of *Moringa oleifera* in hypertensive adults

Reference	Objectives	Design	Population	Program	Findings	Threats to internal validity
[29]	To compare the blood pressure effects of supplementation with Moringa leaf powder herbal combination	Non-randomised, open-label trial design	20 adults with hypertension on their usual medicine	Supplementation with 20 g per day for 60 days with Moringa containing product (Moringa = 4 g/day)	Supplementation decreases both Systolic and diastolic blood pressure relative to the control group	Selection and measurement biases
[30]	To determine the body BMI, blood pressure and urinary output effects of supplementation with Moringa leaf powder in obese and non-obese hypertensive adults	Matched comparative, open-label trial	60 hypertensive adults	Supplementation with a diet containing Moringa leaf powder 30 g/day for 6 months	Supplementation lowers BMI, and diastolic blood pressure in an obese group; and increases urinary output in both obese and non-obese groups.	Selection and measurement biases
[31]	To determine the effect of Moringa leaf on blood pressure, high-density and low-density lipoproteins	Comparative open-label trial	32 adults with hypertension and hypercholesterolemia	Supplementation with Moringa leaf extract compared to captopril for 13 days	Moringa leaf extract lowers blood pressure and low-density lipoprotein and increases high-density lipoprotein	Selection and measurement biases
[32]	To examine the effect of a combination consisting of Moringa leaf, *Bryophyllum pinnatum* and vitamin C on blood pressure, blood glucose, and lipid profile	Single group	66 adults with at least 2 cardiovascular risk factors	Capsule containing vitamin C (700 mg), *Bryophyllum pinnatum* (25 mg) and Moringa (25 mg) 1/day for 6 months	Diastolic blood pressure dropped significantly only in female participants, lowers blood glucose, improves high-density lipoprotein,	History and maturation effects

Similarly, Sparman [32] reported a blood pressure-lowering effect of Moringa leaf supplementation in a population having at least two cardiovascular risk factors.

These reports suggest Moringa leaf supplementation has a blood pressure-lowering effect in persons with hypertension. However, the blood pressure-lowering evidence is of poor quality due to the methodological deficiencies of the three studies, especially the non-use of randomisation and blinding. Non-use of randomisation and blinding in allocating participants to study arms and study treatments respectively, imply that the blood pressure-lowering evidence is susceptible to alternative explanations apart from Moringa leaf supplementation [19].

Furthermore, Omolaso, Seriki and Adegbite [33] reported reductions in sodium and chloride electrolytes in normotensives, while Fombang and colleagues [30] reported increased urination in hypertensives supplemented with Moringa leaf powder.

These results suggest that Moringa leaf has a diuretic effect which might contribute to its apparent blood pressure-lowering efficacy.

Table 3: Articles on safety and tolerability effects of *Moringa oleifera* in normotensive adults

Reference	Objectives	Design	Population	Program	Findings	Threats to internal validity
[26]	To assess the effects of a combination product containing blood chemistry, health-related quality of life, and adverse events	Historical control trial design	30 healthy adults	Supplementation with a combination for 60 days (vitamin D3, banana leaf, green coffee, and Moringa leaf extracts) (Moringa extract = 200 mg per day)	Treatment has a non-significant effect on blood chemistry, no incidence of adverse events, and improves health-related quality of life.	Type 2 error, selection and measurement biases
[27]	To compare the effects of 4 g/day for 4 weeks of Moringa leaf powder, with a placebo on suspected adverse events	Randomised placebo control trial	36 Therapy-naïve type 2 diabetes mellitus patients	Moringa leaf powder capsule dosed at 8 g/day for 4 weeks	Treatment has non-significant changes in ALT, AST, creatinine and BUN	Type 2 error
[34]	To compare the effects of acute Moringa leaf-containing meal on taste acceptability in adults	Open-label cross-over trial design	17 Diabetic and 10 healthy adults,	A meal containing 20 g Moringa leaf power start	Moringa leaf powder has a low colour and taste acceptability rating,	Selection and measurement biases
[37]	To compare the tolerability effects of Moringa leaf-containing preparation to a placebo	Randomised, placebo-control trial	140 overweight adults	Moringa-containing herbal combination 900 mg/Kg for 16 weeks (Moringa content = 540 mg/Kg)	Moringa treatment improves mood with no adverse reaction.	Applicability of results to a hypertensive population
[38]	To assess the effects of a Moringa leaf-containing preparation on suspected adverse events and sexual drive	Single group design	69 adults with at least 2 cardiovascular risk factors	Capsule containing vitamin C (700 mg), *Bryophyllum pinnatum* (25 mg) and Moringa (25 mg) 1/day for 6 months	The moringa-containing product affects sleep patterns, appetite and gastrointestinal upsets. It also improves libido in males.	History and maturation effects
[39]	To assess the effects of Moringa leaf on and suspected adverse events in children	Matched-control, open-label design	54 girls aged between 4-18 years	Moringa leaf powder 14 g/day for 30 days	Supplementation leads to a minor incidence of diarrhoea,	Selection bias

Effects on other cardiovascular risk factors. The reviewed articles reported other cardiovascular effects of Moringa treatment in addition to blood pressure (Table 2). Reports on the blood glucose effect of Moringa leaf treatment are inconsistent. Two articles reported the blood glucose-lowering effect of Moringa acute treatment in healthy adults [22,23]. However, Leone and colleagues [34] reported acute blood glucose reduction only in a diabetic population. All the 3 articles used non-randomised open-label designs; thus, the findings are susceptible to the influence of biases [19]. Nonetheless, a randomised blinded trial design by Taweerutchana and colleagues [27] failed to demonstrate a significant blood glucose lowering effect of Moringa leaf treatment in treatment-naïve type 2 diabetic persons.

In regards to serum lipid profile and body mass index (BMI), reviewed articles show that Moringa treatment decreases lipid profile, body composition index (BCI) and BMI in obese persons [25,30]. However, the effects of Moringa treatment on lipid profile, BCI and BMI are not clear in nonobese persons [25,26,30].

Clinical safety of *Moringa oleifera* leaf. Some of the reviewed literature evaluated the clinical safety of Moringa leaf products. Safety outcome measures assessed include blood chemistry, suspected adverse events and health-related quality of life (HRQoL). The reviewed articles contained outcomes addressing the clinical safety and tolerability of *Moringa oleifera* leaf (Table 3).

Effects on blood chemistry. Blood chemistry parameters including alanine aminotransferase and creatinine levels are usually employed as indicators of hepatic and renal safety respectively during drug trials. This is because the liver and kidney are the major organs involved in drug metabolism and excretion; hence, they are usually the targets of the toxic effects of administered medications [35,36]. Two articles examined the clinical effects of Moringa leaf on blood chemistry including alanine aminotransferase (ALT), aspartate transaminase (AST), creatinine and blood urea nitrogen (BUN) in normotensives [26,27]. These studies reported statistically nonsignificant changes in serum biochemicals including ALT, AST, creatinine and BUN. These results suggest *Moringa oleifera* leaf has no adverse effects on the liver and kidney in normotensive adults. These studies were conducted in non-hypertensives; therefore, there is a limitation in extending this finding to a hypertensive population [19,24].

Effect on adverse events and quality of life. Four articles reported the effect of Moringa leaf treatment on the incidence of adverse events in normotensives. Two of the articles reported no incidence of adverse events in healthy overweight adults [37] and normotensive diabetic adults [27]. Both of these articles used a randomised blinded trial design. In addition, minor gastrointestinal upset and changes in sleep and appetite were reported in adults with cardiovascular risk factors [38] and malnourished children [39]. These results suggest that Moringa leaf treatment has good tolerability in normotensives. However, there is a limitation in extending this finding to a hypertensive population.

Two articles examined the effect of Moringa leaf treatment on HRQoL in normotensives. These studies reported improvements in mood [37], and quality of life [26]. Similarly, a third article reported improved male libido in adults with cardiovascular risk factors [40]. These reports indicate the apparent tolerability of Moringa leaf in humans, even though the taste of the leaf powder was reported to have low acceptability [34].

Summary of literature review. The review articles revealed the following current knowledge regarding the antihypertensive efficacy of *Moringa oleifera* leaf treatment in humans. In

normotensive patients results from five studies suggest *Moringa oleifera* leaf has a blood pressure-lowering effect on acute treatment in adults. However, this blood pressure-lowering effect is inconsistent in repeated doses of *Moringa oleifera* leaf in normotensive adults. In persons with hypertension, results from three studies suggest that *Moringa oleifera* leaf supplementation has a blood pressure-lowering effect. Results from two studies suggest that *Moringa oleifera* leaf treatment has a diuretic effect, mediated partly through depleting serum sodium and chloride ions, that might contribute to the apparent blood pressure-lowering effect.

Results from two studies indicate *Moringa oleifera* leaf treatment has no adverse effects on normotensive adults' renal and hepatic blood chemistry. Results from one article suggest that *Moringa oleifera* leaf treatment improves the health-related quality of life in normotensive adults. Results from two articles show that gastrointestinal upset and changes in appetite and sleep patterns are the minor adverse events associated with *Moringa oleifera* leaf treatment use in humans.

While existing literature contributes to the understanding of the clinical antihypertensive efficacy and safety of *Moringa oleifera*, the following gaps warrant attention for further research. The existing research on *Moringa oleifera* leaf's role in hypertension treatment has not addressed quality issues of the herbal preparations used in clinical trials. Quality parameters like microbial load and heavy metal contamination are invaluable for participants' safety [41]. The concentration of putative antihypertensive constituents in *Moringa oleifera* leaf products employed in clinical trials is another quality parameter that has not been addressed. Knowledge of the strength of the active constituents is valuable for inter-study comparisons since the same dose of *Moringa oleifera* leaf powder can have significantly different amounts of putative active constituents based on growing and processing factors [24].

Existing knowledge on the clinical blood pressure-lowering effect of *Moringa oleifera* leaf remains open to alternative explanations due to the methodological limitations of the study designs. The non-randomised clinical trial (NRT) design employed in the studies does not allow attribution of the clinical blood pressure-lowering effect to *Moringa oleifera* leaf treatment alone. Confounding factors (participants' demographics such as age, gender, overweight/obesity and duration of hypertension diagnosis) can also be attributed to the reported BP-lowering effects [19,24]. In addition, the open-label nature of the studies does not allow for isolating the effects of *Moringa oleifera* leaf from biases from participants (placebo effect), researchers, and outcome assessors [24]. Evidence-based medicine (EBM) is defined as ''the employment of the best available evidence with clinical expertise and patient value''. EBM considers findings generated from RCT and systematic review of RCTs as high-level evidence for treatment effectiveness. RCT-generated treatment effects data are prioritised in the meta-analysis of treatment effectiveness of interventions [19,42].

The major mechanism advanced for the *Moringa oleifera* BP-lowering effect is an anti-oxidant action [17,43]. However, the effects of *Moringa oleifera* leaf treatment on antioxidant activity outcomes in human hypertension have not been addressed. This is important as the World Health Organisation recommends that during the clinical investigation of an herbal remedy, the choice of outcome measures should reflect the proposed mechanism of action of the herbal product [44]. Another gap in the literature is the lack of research that addressed the clinical safety and tolerability of *Moringa oleifera* leaf treatment in a hypertensive population. Evidence-based decisions regarding the use and regulations of medicines require clinical safety data and clinical efficacy

data in assessing intervention effectiveness [44].

Conclusion. In conclusion, existing literature using non-randomised trial designs supports the clinical antihypertensive efficacy of *Moringa oleifera* leaf. There is a need to investigate *Moringa oleifera* leaf's role in treating hypertension using randomised controlled trial designs. This will strengthen the internal validity of the evidence. *Moringa oleifera* is inexpensive to cultivate and associated with minor adverse events. This may complement access to medicines for hypertension especially in low-and-medium-income countries.

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