Therapeutic potential of *Moringa oleifera* leaves in chronic hyperglycemia and dyslipidemia: a review

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Moringa oleifera (*M. oleifera*) is an angiosperm plant, native of the Indian subcontinent, where its various parts have been utilized throughout history as food and medicine. It is now cultivated in all tropical and sub-tropical regions of the world. The nutritional, prophylactic, and therapeutic virtues of this plant are being extolled on the Internet. Dietary consumption of its part is therein promoted as a strategy of personal health preservation and self-medication in various diseases. The enthusiasm for the health benefits of *M. oleifera* is in dire contrast with the scarcity of strong experimental and clinical evidence supporting them. Fortunately, the chasm is slowly being filled. In this article, I review current scientific data on the corrective potential of *M. oleifera* leaves in chronic hyperglycemia and dyslipidemia, as symptoms of diabetes and cardiovascular disease (CVD) risk. Reported studies in experimental animals and humans, although limited in number and variable in design, seem concordant in their support for this potential. However, before *M. oleifera* leaf formulations can be recommended as medication in the prevention or treatment of diabetes and CVD, it is necessary that the scientific basis of their efficacy, the therapeutic modalities of their administration and their possible side effects be more rigorously determined.

Keywords: *Moringa oleifera*, cardiovascular disease, diabetes, phytotherapy, natural products

INTRODUCTION

Moringa oleifera, Lam (*M. oleifera*), also known as *Moringa pterygosperma* Gaertn, is a member of the Moringaceae family of perennial angiosperm plants, which includes 12 other species (Olson, 2002). Native of the sub-Himalayan northern parts of India, it is cultivated throughout tropical and sub-tropical areas of the world, where it is known by various vernacular names (Ramachandran et al., 1980), with drumstick tree, horseradish tree, and malunggay being the most commonly found in the literature.

Moringa oleifera is an edible plant. A wide variety of nutritional and medicinal virtues have been attributed to its roots, bark, leaves, flowers, fruits, and seeds (Ramachandran et al., 1980; Anwar et al., 2007; Kumar et al., 2010). Phytochemical analyses have shown that its leaves are particularly rich in potassium, calcium, phosphorous, iron, vitamins A and D, essential amino acids, as well

as such known antioxidants such as β-carotene, vitamin C, and flavonoids (Bennett et al., 2003; Aslam et al., 2005; Manguro and Lemmen, 2007; Amaglo et al., 2010; Gowrishankar et al., 2010).

The therapeutic use of *M. oleifera* parts in the Indian subcontinent dates back to Antiquity. In other parts of the world, in sub-Saharan Africa in particular, such a use appears not to have been known by the wide public, as it is being promoted by diverse organizations as an untapped opportunity (Thurber and Fahey, 2009; Torimiro et al., 2009). At the writing of this manuscript (April 2011), a search on the Internet, using the Google browser and the words moringa, drumstick, or malunggay as keys within page titles, reported nearly 90,000 websites. Most of these sites present this plant as a remedy to malnutrition and a vast range of ailments. On the Internet, *M. oleifera* is variably labeled as Miracle Tree, Tree of Life, Mother's Best Friend, God's Gift to Man, Savior of the Poor. In many regions of Africa, it is widely consumed for self-medication by patients affected by diabetes, hypertension, or HIV/AIDS (Dieye et al., 2008; Kasolo et al., 2010; Monera and Maponga, 2010). Yet, in a similar search of the PubMed database of biomedical publications, merely 163 papers were fetched; 76% of them were published in the last decade (**Figure 1**). A similar search through Google Scholar produced about 1250 articles; the vast majority of these were in scientific journals not indexed in PubMed, and a good number in non-peer-reviewed book chapters, patents, citations, or other documents. By comparison, green tea, another plant claimed to be medicinal for a range of illnesses (Schneider and Segre, 2009), 1972 and 7240 publications were retrieved in a similar search in PubMed and Google Scholar,
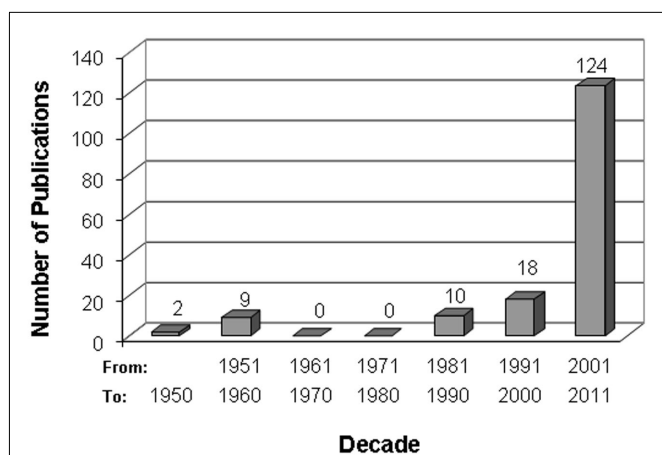
FIGURE 1 | Chronological trend of scientific publications on *M. oleifera*. The bibliographic search was conducted online in the PubMed database at www.pubmed.ncbi.nlm.nih.org/, using moringa, drumstick, or malunggay as title keywords. Article abstracts were reviewed for content and those unrelated to *M. oleifera* were discarded. Of the 163 PubMed articles retained, 64 (39.3%) were about the physiological effects of *M. oleifera* preparation in experimental animals, 30 (18.4%) on their water-cleansing properties as toxic metal absorbent or flocculent, 23 (14.1%) about their chemical composition, 22 (13.5%) about their antimicrobial efficacy, 5 (3.1%) about their antioxidant properties *in vitro*, 5 (3.1%) about their effects on cellular physiology *ex vivo*, 6 (3.1%) on their nutritional values, 3 (1.8%) about their therapeutic effects in humans, and 6 about various matters (review, genetics, biofuel, animal feed).

respectively. Clearly, in spite of the widely held "belief" in the health benefits of *M. oleifera*, the interest of the international biomedical community in the medicinal potential of this plant has been rather tepid.

This report is a review of current data on the therapeutic potential of *M. oleifera* in chronic hyperglycemia and dyslipidemia. Chronic hyperglycemia is an indicator of diabetes mellitus (DM), and chronic dyslipidemia a risk factor for cardiovascular disease (CVD). These metabolic disorders are global epidemics (Yusuf et al., 2001; Wild et al., 2004). In developing countries, they are on the way to becoming as major causes of morbidity and mortality as infectious diseases, due to the progressive transition in these countries to a lifestyle characterized, among other aspects, by greater access to dietary calories and less demand for calorie expenditure (Hossain et al., 2007; Aje and Miller, 2009). Geographically, many of developing countries are located in the tropical and sub-tropical regions of the world where *M. oleifera* grows and is cultivated. If validated by medical science, dietary consumption of this plant could be advocated in these and other countries as an inexpensive prophylactic strategy against DM and CVD.

The review covers peer-reviewed studies of the therapeutic potential of *M. oleifera* in these pathologies. It focuses on studies involving experimental animal models and human subjects, in which leaves were used as the medicinal parts of the plant. Leaves were generally administered *per os* (p.o.) as powders or aqueous or organic extracts thereof, and, for experimental animals, at body weight-adjusted doses. A therapeutic effect was defined as a beneficial change in specific biochemical parameters of disease.

The review includes five sections. The first two sections are concerned with the scientific evidence of *M. oleifera* efficacy at correcting chronic hyperglycemia or dyslipidemia. They each begin with a brief description of main aspects of glucose or lipid homeostasis and its pathogenic disruption, so that the therapeutic efficacy of the plant could be subsequently evaluated based on current biomedical understanding. The third section attempts to correlate the observed therapeutic effects with the presence in the leaves of physiological properties or chemical constituents experimentally proven to offer such metabolic benefits. The fourth section briefly examines what is known of the possible toxicity of *M. oleifera* leaves. The final section identifies obvious gaps in current knowledge and proposes potential avenues for future investigation.

METHODOLOGY

Two biomedical literature databases were searched: PubMed and Google Scholar (subsections: Biology, Life Science, Environmental Science, Medicine, Pharmacology, and Veterinary Science). The search was conducted using moringa or drumstick as a keyword within the title of the article. Articles dealing with *Moringa* varieties other than *oleifera* were excluded; as were articles in which the word drumstick referred to other subject matters (e.g., medical conditions or transcription factor) than the plant. All the remaining articles, including reviews, were critically read. Peer-reviewed articles presenting results of experimental studies, in animals or humans, on the therapeutic potential of *M. oleifera* leaf extract or powder in chronic hyperglycemia or hyperlipidemia were analyzed for inclusion in this review. The analysis focused on therapy subjects, galenic formulation, mode of administration, dosage, treatment duration, and measurable biochemical outcomes.

THERAPEUTIC POTENTIAL OF *M. OLEIFERA* IN CHRONIC HYPERGLYCEMIA

GLUCOSE HOMEOSTASIS

Glucose is a major fuel for animal cells. It is supplied to the organism through dietary carbohydrates and, endogenously, through hepatic gluconeogenesis and glycogenolysis. Glucose absorption from the gastrointestinal tract (GIT) into blood is regulated by a variety of neuronal signals and enterohormones (incretins), as well as by meal composition and the intestinal flora. Glucose homeostasis reflects a balance between glucose supply and its utilization. Physiologically, this balance is determined by the level of circulating insulin and tissue responsiveness to it. Insulin is secreted by pancreatic islet β cells. It stimulates glucose uptake and utilization by tissues, especially by liver, skeletal muscle, and adipose tissue. It also suppresses gluconeogenesis in hepatocytes, while stimulating lipogenesis and inhibiting lipolysis in adipocytes (Gerich, 2000).

HYPERGLYCEMIA

An individual is diagnosed as diabetic when his blood glucose level is chronically ≥ 126 mg/dL after an overnight fast, and ≥ 200 mg/dL 2 h after an oral glucose load of 75 g (oral glucose tolerance test, OGTT; Alberti and Zimmet, 1998). Age, genetics, environment, and lifestyle influence the development of this pathology. The relative importance of these factors and their combinatorial effects are not yet fully understood. Two types of DM are commonly recognized: type 1 DM (T1DM) results from autoimmune destruction

of pancreatic β cells and represents only 5% of all cases; type-2 DM (T2DM) is the most common form of the disease and the primary concern of this review.

In its early stages, T2DM is characterized by chronic hyperglycemia and hyperinsulinemia, due to loss of tissue sensitivity to insulin, and compensatory secretion of the hormone by islet β cells. Its progression involves a complex network of interacting cellular and physiological alterations leading to β cell failure. Glucotoxicity and lipotoxicity are the most commonly invoked mechanisms for this failure (Robertson et al., 2004).

Glucotoxicity arises from excessive uptake of glucose by islet β cells. The excess sugar drives glycation reactions and the mitochondrial electron transport chain, producing macromolecule-damaging reactive oxygen species (ROS), at levels beyond the antioxidation capacity of the cell. The ensuing oxidative stress impairs insulin synthesis and secretion, and initiates a cascade of cellular events that ultimately lead to apoptosis (Kaneto et al., 2007).

Lipotoxicity, on the other hand, results in part from the unresponsiveness of adipocytes to insulin, negating the ability of this hormone to stimulate uptake by these cells of non-esterified fatty acids (NEFA) that result from triglycerides (TG) lipolysis in circulation, and to inhibit lipolysis of endogenous TG to NEFA. Excess plasma NEFA impairs insulin secretion by β cells, stimulates gluconeogenesis by liver, and inhibits glucose disposal by skeletal muscle, further exacerbating hyperglycemia (Stumvoll et al., 2005). NEFA accumulation in the bloodstream is further aggravated by obesity, a condition characterized by an expanded adipose mass. Furthermore, adipose tissues, especially the visceral and deep subcutaneous ones, secrete pro-inflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor α (TNFα), which also contribute to tissue insensitivity to insulin.

Impaired TG storage into adipocytes facilitates the formation in the bloodstream of small, cholesterol ester-poor, TG-rich low-density lipoprotein (LDL) particles. Hyperglycemia promotes glycation of these particles, a modification that extends their half-life in circulation. These particles are prone to oxidation and are potent initiators of atherogenesis and its vascular damages (discussed in more detail below). Diabetes-associated neuropathy, retinopathy, and nephropathy are some of the consequences of these damages (Dokken, 2008).

Underlying these complex physiological changes are molecular alterations in the relative levels of expression and post-translational modifications of a wide variety of gene products, including surface receptors, second messengers and transcriptional factors.

EVIDENCE OF ANTI-HYPERGLYCEMIC PROPERTIES OF *M. OLEIFERA*

Moringa oleifera parts have been used in folk medicine for the treatment of diabetes (Dieye et al., 2008). Five studies aimed at verifying these properties using leaves were identified in the scientific literature: two were conducted in experimental animals (Ndong et al., 2007b; Jaiswal et al., 2009) and three in T2DM patients (William et al., 1993; Kumari, 2010; Ghiridhari et al., 2011). They are summarized in **Table 1**.

Animal studies

In the study by Ndong et al. (2007b), Goto-Kakizaki (GK) Wistar rats were used as model of DM. GK rats spontaneously develop early glucose intolerance associated with impaired insulin secretion (Bisbis et al., 1993; Abdel-Halim et al., 1995). In an OGTT, overnight fasted Wistar controls or GK male rats were given 2 g/kg of body weight (kg-bw) glucose by oral gavage, without or with 200 mg/kg-bw of *M. oleifera* leaf powder. To determine blood glucose levels, vein blood was collected before gavage and at different times afterward up to 120 min. Areas under the curves (AUC) were derived from the time courses of these levels. In the absence of treatment, fasting plasma glucose levels (FPG) and their postprandial levels (PPPG) at 120 min were greater ($\sim$1.4× and 2.2×, respectively) in GK rats than in control rats. Treatment with *M. oleifera* leaf powder resulted in a lower glycemic response in GK and control rats. However, in GK rats, the treatment reduced

Table 1 | *Moringa oleifera* experimental therapy for chronic hyperglycemia.

A. ANIMAL MODELS					
Species	**Inducer**	**Plant part (extract)**	**Protocol[a]**	**Corrective outcomes**	**Reference**
Rat	STZ	Leaf (water)	100–300 mg/kg-bw; p.o., single dose; 8 h	↓FPG; ↑glucose tolerance (OGTT)	Jaiswal et al. (2009)
Rat (GK)	–	Leaf	200 mg/kg-bw; p.o., single dose; 2 h	↑glucose tolerance (OGTT); ↑stomach content	Ndong et al. (2007b)
B. HUMAN T2DM PATIENTS (FPG > 9 mmol/L)					
Exper. N	**Contr. N**	**Plant part (formulation)**	**Protocol**	**Corrective outcomes (in the experimental group)**	**Reference**
6	6	Leaf (meal)	50 g/meal; p.o. single; 1 or 2 h	↓PPPG/FPG	William et al. (1993)
46	9	Leaf (tablet)	8 g/day; p.o., daily; 40 days	↓FPG; ↓PPPG	Kumari (2010)
30	30	Leaf (tablet)	2 tablets/day; p.o., daily; 1, 2, 3 months	↓HbA$_{1c}$; ↓PPPG	Ghiridhari et al. (2011)

Exper. N, number of subjects in the experimental (treated) group; Contr. N, number of subjects in the control (untreated) group. The other abbreviations are explained in the text.

[a]*The protocol brief description is given in three lines: line 1, dose; line 2, mode of administration and frequency; line 2, duration of treatment before assessment.*

AUC values by 23% ($P < 0.05$); it did not significantly affect these values in control rats. These observations suggested that *M. oleifera* treatment improves plasma glucose disposal only in the diabetic rats.

In the study by Jaiswal et al. (2009), prediabetes and diabetes were induced in Wistar rats by intraperitoneal (i.p.) injection of 55 mg/kg-bw of streptozotocin (STZ), a cytotoxic drug that selectively destroys islet β cells (Like and Rossini, 1976). Based on FPG (mg/dL), STZ-treated rats were classified as sub-diabetic (∼88 mg/dL), mildly diabetic (∼190 mg/dL), and severely diabetic (∼300 mg/dL). A *M. oleifera* aqueous extract was administered to overnight fasted animals by oral gavage, at 100, 200, or 300 mg/kg-bw. FPG was determined before treatment (baseline) and at various time points post-treatment. An OGTT was conducted 90 min after the last time point. In normal rats, *M. oleifera* treatment lowered FPG at all doses in time- and concentration-dependent manners. Six hours after administration, 200 mg/kg-bw of *M. oleifera* extracts lowered FPG by about 26% ($P < 0.05$), compared to baseline levels or the levels in untreated mice. In an OGTT, at the same dose, a 30% fall in PPPG was observed after 3 h, in normal, sub-diabetic, and mildly diabetic rats. A 21-day treatment of severely diabetic rats with the *M. oleifera* extract at a daily dose of 300 mg/kg-bw reduced FPG and PPPG by 69 and 51%, respectively, relative to untreated controls. In all the above experiments, the hypoglycemic effect of the plant extract was comparable to that of the anti-diabetic drug Glipizide administered at 2.5 mg/kg-bw.

Human studies
In a controlled study with untreated T2DM patients, William et al. (1993) examined how *M. oleifera* addition to a standardized meal, taken after an overnight fast, affected the 1- and 2-h PPPG, relative to the standard meal alone or a 75-g oral glucose load. *M. oleifera* was compared to bitter gourd (*Momordica charantia*) and curry leaves (*Murraya koenigii*). Compared to the glucose load, standard meals with or without vegetable supplements induced a significantly lower rise in PPPG (glycemic response) as derived from AUCs. However, when leaf-supplemented meals were compared to standard meals, only the *M. oleifera* leaf-supplemented meal elicited a lower response (-21%, $P < 0.01$). Plasma insulin AUCs did not differ significantly between the two meals, suggesting that the hypoglycemic effect of *M. oleifera* leaf supplementation was not due to increased insulin secretion.

Kumari (2010) examined the hypoglycemic effect of *M. oleifera* leaf dietary consumption over a 40-day period in T2DM patients, 30–60 years of age, not on anti-hyperglycemic medication. The experimental group included 46 subjects, 32 men, and 14 women; the control group of 9 subjects included 4 men and 5 women. Daily meals were comparable among these groups in terms of relative content of food types (e.g., cereals, green leafy vegetables, fruits, etc.) and nutrients (e.g., proteins, fat, fiber, minerals, etc.) as well as calories. The experimental group received a daily dose of 8 g *M. oleifera* leaf powder. FPG and PPPG at the end of the protocol (final) were compared to baseline levels. Final values did not differ much from baseline in the control group. They were significantly reduced in the experimental group (FPG: -28%, $P < 0.01$; PPPG: -26%, $P < 0.05$).

More recently, Ghiridhari et al. (2011) studied a group of 60 T2DM patients, age 40–58 years, BMI 20–25 kg/m^2, on sulfonylurea medication and a standardized calorie-restricted diet. The patients were equally divided into an experimental and a control groups. Patients in the experimental group were prescribed two *M. oleifera* leaf tablets/day, one after breakfast, the other after dinner for 90 days. *M. oleifera* leaf powder constituted 98% (w/w) of the tablet content, but the average weight of tablets was not specified, making the total daily dose unclear. Blood glycated hemoglobin (HbA$_{1c}$) was measured before and after the regimen. PPPG was determined before the regimen and every 30 days afterward. In the control group, HbA$_{1c}$ and PPPG progressed downwardly with time, but the change was not significant. In the experimental group, in contrast, relative to the baseline, HbA$_{1c}$ decreased by 0.4% point (from 7.8 ± 0.5 to 7.4 ± 0.6; $P < 0.01$). Compared to the starting levels (210 ± 49 mg/dL), PPPG in the experimental group progressively decreased with treatment duration, by 9% after 30 days, 17% after 60 days, and 29% after 90 days ($P < 0.01$), indicating that *M. oleifera* medication can induce with time better glucose tolerance. However, it should be noted that treatment allocation to patients appear to have not been randomized as baseline values for the two parameters were higher in the experimental group than in the control group, 7.8 ± 0.5 vs. $7.4 \pm 0.6\%$ for HbA$_{1c}$, 210 ± 49 vs. 179 ± 36 mg/dL for PPPG.

THERAPEUTIC POTENTIAL OF *M. OLEIFERA* IN DYSLIPIDEMIA
LIPID HOMEOSTASIS
Lipids constitute a major class of hydrophobic constituents of the body. Their main forms are cholesterol, phospholipids (PL), and triglycerides (TG). Lipids are involved in a variety of biological processes, including membrane formation, intracellular and intercellular signaling, as well as energy storage and production. The body derives its lipids from *de novo* cellular biosynthesis and from nutrition. Cellular biosynthesis of lipids is regulated at the transcriptional level by sterol-regulated element-binding proteins (SREBPs) 1 and 2. SREBP-1 promotes the biosynthesis fatty acids and TG, SREBP-2 that of cholesterol (Horton, 2002).

Intestinal and plasma lipids are transported by lipoproteins particles. Apolipoproteins (Apo) constitute the protein components of these particles. Lipoproteins vary in density and, depending on their relative contents in TG, cholesterol, and PL, are identified as chylomicrons, very low-density lipoprotein (VLDL), LDL, intermediate density lipoprotein (IDL), and high-density lipoprotein (HDL). Lipids are transported by chylomicrons in the intestinal lymphatic system; and, in the bloodstream, by chylomicron remnants, VLDL, LDL, IDL, and HDL (Abeles et al., 1992; Havel and Kane, 2001).

The liver plays a pivotal role in lipid metabolism. It extracts cholesterol from intestinal chylomicrons and excretes it back into the intestines with bile acids. It biosynthesizes TG and cholesterol and packages them as VLDL, that it secretes into the bloodstream. Through the LDL receptor (LDLR), it clears up plasma LDL as well as IDL from VLDL or HDL catabolism. HDL mediates the reverse transport of cholesterol from extra-hepatic tissues to the liver (Havel and Kane, 2001). Liver LDLR levels and its capacity to clear blood LDL are down-regulated by proprotein convertase

subtilisin/kexin-type 9 (PCSK9), a plasma protein secreted by this organ (Horton et al., 2009).

DYSLIPIDEMIA

Dyslipidemia is a disorder characterized by alterations in the levels and composition of plasma lipids. According to Adult Treatment Panel III (2001), plasma levels ≥200 mg/dL for TC, ≥130 mg/dL for LDL-C, <40 mg/dL for HDL-C, and ≥150 mg/dL for TG are dyslipidemic. Dyslipidemia may result from inborn defects of lipoprotein production or metabolism; but in most cases, it is secondary to an unhealthy lifestyle (e.g., excessive cigarette smoking or alcohol consumption), other health disorders (e.g., obesity, diabetes, infection, obstructive liver disease), or medication (e.g., β blockers, steroids).

Besides hypertension, chronic dyslipidemia is a major cause of atherosclerosis, a vascular disease affecting blood circulation in the coronary, central, and peripheral arteries. The pathology is initiated by irritation of the arterial endothelium by high level of circulating LDL-C, which leads to overexpression of adhesion and chemoattraction molecules (e.g., vascular cell adhesion molecule-1, intercellular adhesion molecule, P and E selectins, monocyte chemoattractant protein-1) to injured sites, and the recruitment and capture of circulating monocytes to these sites. These immune cells penetrate into the sub endothelium and differentiate into tissue macrophages, which take up oxidized LDL (oxLDL) via scavenger receptors (e.g., CD36, scavenger receptor-A), becoming the lipid-laden foam cells characteristic of atheromatous plaques. In response to growth factors, resident vascular smooth muscle cells (VSMC) proliferate and form a fibrous cap overlying the plaques. The oxidative process that leads to oxLDL production also contributes to atherogenesis, as this modified lipoprotein and its by-products (oxysterols and oxPL) act as monocyte chemoattractants and VSMC mitogens. Clinical complications of this process include a narrowing of the arterial lumen, plaque rupture, and formation of circulating thrombi. These complications could lead to coronary artery disease (CAD), myocardial infarction, thrombo-embolic stroke, and peripheral artery disease (Steinberg, 2002; Libby et al., 2011).

Over the years, there has been a vigorous debate over the predictive value of plasma LDL-C level as a marker of CVD risk in humans. An emerging view is that the level of non-HDL lipoproteins, also captured in the TC/HDL-C or HDL-C/non-HDL-C ratio, may constitute a better marker, and its reduction a more cogent measure of the efficacy of anti-dyslipidemia therapies (Sniderman et al., 2010; Manickam et al., 2011).

EVIDENCE OF ANTI-DYSLIPIDEMIC PROPERTY OF *M. OLEIFERA*

Five studies were identified in the scientific literature: three were conducted with experimental animals (Ghasi et al., 2000; Chumark et al., 2008; Jain et al., 2010), two with human subjects (Kumari, 2010; Nambiar et al., 2010). They are summarized in **Table 2**.

Animal studies

Chumark et al. (2008) examined the therapeutic potential of *M. oleifera* leaves on dyslipidemia induced in rabbits on a high-cholesterol (5%) diet (HCD) for 12 weeks. By the end of the regimen, relative to rabbits on a normal diet, HCD-fed rabbits experienced several-fold (×) increases in the plasma levels of total cholesterol (TC, 55×), HDL-C (17×), LDL-C (131×), and TG (4×). The diet also caused extensive plaque formation in carotid arteries. When these HCD rabbits were concomitantly fed a *M. oleifera* aqueous leaf extract, at the daily dose of 100 mg/kg-bw for the duration of the protocol, these increases were reduced: for TC and lipoprotein-cholesterol by about 50%, for TG by 75%, and for carotic plaque formation by 97%. This protective effect was comparable to that of the anti-cholesterol drug simvastatin, given p.o., at a daily dose of 5 mg/kg-bw. Similar results were also obtained with HCD rabbits fed an aqueous extract of *M. oleifera* fruits (Mehta et al., 2003).

Table 2 | *Moringa oleifera* experimental therapy for chronic hyperlipidemia.

A. ANIMAL MODELS					
Species	**Inducer**	**Plant part (extract)**	**Protocol[a]**	**Corrective outcomes**	**Reference**
Rabbit	HCD	Leaf (water)	5 mg/kg-bw; p.o., daily; 12 weeks	↓TC; ↓LDL; ↓HDL; ↓TG; ↓carotid plaque formation	Chumark et al. (2008)
Rat	HFD	Leaf (water)	1 g/kg-bw; p.o., daily; 30 days	↓TC	Ghasi et al. (2000)
Rat	HFD	Leaf (methanol)	150–600 mg/kg-bw; p.o., daily; 30 days	↓TC; ↓LDL; ↑HDL; ↓VLDL; ↓TG; ↑fecal cholesterol; ↓atherogenic index	Jain et al. (2010)

B. HUMAN HYPERLIPIDEMICS (TC > 180 mg/dL or TG > 140 mg/dL)					
Exper. N	**Contr. N**	**Plant part (formulation)**	**Protocol**	**Corrective outcomes (in the experimental group)**	**Reference**
17	18	Leaf (tablet)	4.6 g/day; p.o., daily; 50 days	↓TC; ↑HDL-C; ↓non-HDL-C	Nambiar et al. (2010)
46	9	Leaf (tablet)	8 g/day; p.o., daily; 40 days	↓TC; ↓LDL-C; ↓VLDL-C	Kumari (2010)

Exper. N, number of subjects in the experimental (treated) group; Contr. N, number of subjects in the control (untreated) group. The other abbreviations are explained in the text.

[a]*The protocol brief description is given in three lines: line 1, dose; line 2, mode of administration and frequency; line 2, duration of treatment before assessment.*

The anti-dyslipidemic effects of *M. oleifera* leaves were also examined in rats fed a high-fat diet (HFD). In one study (Ghasi et al., 2000), Wistar rats were fed, for 30 days, a HFD containing 16% (w/w) fat, with or without an aqueous extract of *M. oleifera* leaves at a daily dose of 1 g/kg-bw. In untreated rats, the diet caused a 30% increase in plasma TC. In treated rats, the increase was reduced to 14%. In another study (Jain et al., 2010), albino rats were fed, for 30 days, a HFD containing 26% fat, with or without a methanolic extracts of *M. oleifera* leaves at daily doses of 150, 300, or 600 mg/kg-bw. In untreated rats, the diet increased plasma TC ($2.4\times$), LDL-C ($7.7\times$), VLDL-C ($1.7\times$), and TG ($1.6\times$). At the highest dose, *M. oleifera* treatment reduced these increases to $1.5\times$, $2.2\times$, $1.3\times$, and $1.3\times$, respectively ($P < 0.01$). Interestingly, serum HDL-C was unchanged by HFD diet alone; it was increased $2.4\times$ in rats fed leaf extract-supplemented HFD, significantly reducing the TC/HDL-C ratio.

Human studies

Nambiar et al. (2010) examined the potential anti-dyslipidemic effect of *M. oleifera* in 35 hyperlipidemic subjects (TC > 180 mg/dL or TG > 140 mg/dL), 26 men and 9 women. The control and experimental groups consisted of 18 subjects and 17 subjects, respectively. Anthropometric values (age, height, weight, body mass index, waist/hip ratio) within gender were similar between the two groups, as was their daily nutrient intake. The experimental group consumed a daily total of 4.6 g of dehydrated *M. oleifera* leaves, as four 550-mg tablets twice daily, for 50 days. Plasma lipid profiles were determined before and after the regimen. Compared to the control group, the experimental group experienced a 1.6% fall in plasma TC ($P < 0.05$) and a 6.3% increase of HDL-C, with non-significant trends toward lower LDL-C, VLDL-C, and TG. However, relative to baseline, final non-HDL-C and TC/HDL-C values decreased by 3.7 and 6.6%, respectively ($P < 0.001$), indicating that the treatment induced a lesser atherogenic lipid profile.

In the study of T2DM patients reported by Kumari (2010), the corrective effect of *M. oleifera* dietary leaves on dyslipidemia was also examined. Compared to the control group, the experimental group receiving 8 g of *M. oleifera* leaf powder daily for 40 days experienced a significant fall in the plasma levels of TC (-14%), LDL-C (-29%), VLDL-C (-15%), and TG (-14%; $P < 0.05$ to <0.01). HDL-C increased by 9% (non-significant), but the HDL-C/non-HDL-C ratio increased by 37% ($P < 0.01$).

PHARMACOLOGY OF *M. OLEIFERA* LEAVES
BROAD-SPECTRUM PHYSIOLOGICAL PROPERTIES

Because of the chemical complexity of the *M. oleifera* medicinal formulations used in the studies reviewed above, their apparent therapeutic effects could be due to the combined actions of various bioactive components found in the plant, including trace metal ions, vitamins, alkaloids, carotenoids, polyphenols, fats, carbohydrates, and proteins (Coppin, 2008; Amaglo et al., 2010). Some compounds may collectively affect broad aspects of physiology, such as nutriment absorption and processing, redox state, or immunity.

Anti-nutrient properties

Moringa oleifera leaves contain phytosterols such as β-sitosterol (Jain et al., 2010). These compounds can reduce intestinal uptake of dietary cholesterol (Lin et al., 2010). They could partly account for the decrease of plasma cholesterol and the increase of fecal cholesterol observed in rodents treated with *M. oleifera* leaves (Mehta et al., 2003; Jain et al., 2010). *M. oleifera* leaf powder also contain about 12% (w/w) fibers (Joshi and Mehta, 2010). Dietary fibers reduce gastric emptying (Bortolotti et al., 2008). They may partly explain the greater stomach content, the improved OGTT response in treated GK diabetic rats (Ndong et al., 2007b), as well as the progressive improvement of PPPG levels in treated T2DM patients (Ghiridhari et al., 2011).

Antioxidant properties

The viability and functionality of a cell partly depends on a favorable redox state, i.e., on its ability to prevent excessive oxidation of its macromolecules, including DNA, proteins, and lipids (Ryter et al., 2007; Limon-Pacheco and Gonsebatt, 2009). ROS and free radicals are the major mediators of the oxidative process. Cellular inability to reduce ROS leads to oxidative stress. All cells are variably capable of endogenous self-protection against this stress through the actions of enzymes such as catalase, superoxide dismutase, and glutathione peroxidase, as well as through reducing molecules such as glutathione. Nutritional antioxidants such as vitamins A, C, and E provide additional protection from the stress (Limon-Pacheco and Gonsebatt, 2009).
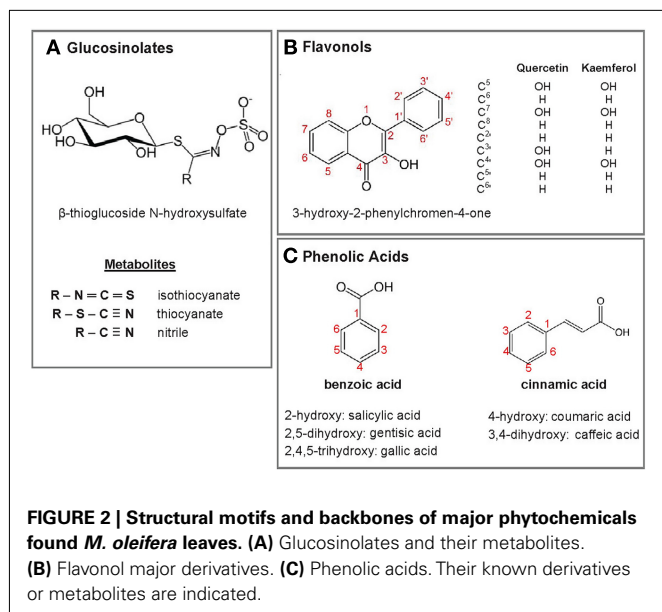
Oxidative stress is widely accepted as a major contributing factor in the pathogenesis of CVD and diabetes (Dhalla et al., 2000; Kaneto et al., 2007; Rodrigo et al., 2011). A recurring explanation for the therapeutic actions of *M. oleifera* medication is the relatively high antioxidant activity of its leaves, flowers, and seeds (Chumark et al., 2008; Sreelatha and Padma, 2009; Verma et al., 2009; Atawodi et al., 2010). Among the major classes of phytochemicals found in the plant, flavonoids appear to carry most of this activity.

Anti-inflammatory properties

Inflammation with its wide array of cytokines secreted by immune cells is an integral part of the pathophysiology of obesity, hypertension, atherosclerosis, and diabetes (Rana et al., 2007). Extracts from *M. oleifera* leaves have been shown to modulate humoral and cellular immunity in rats and mice (Gupta et al., 2010; Sudha et al., 2010). They have exhibited strong anti-inflammatory properties in rodent models of chemically induced inflammation of the paw (Sulaiman et al., 2008; Mahajan and Mehta, 2009). These properties have been more extensively studied with fruit and seed extracts (Cheenpracha et al., 2010; Mahajan and Mehta, 2010; Muangnoi et al., 2011). They may also contribute to the observed anti-atherogenic and anti-diabetic effects of *M. oleifera* therapy.

BIOACTIVE PHYTOCHEMICALS

An informative historical account of research in the phytochemistry of *M. oleifera* prior to 1995 can be found in Saleem's doctoral thesis available on line (Saleem, 1995). Since then, the research has been expanded and refined, not only on the chemical structures of plant molecules, but also on their nutritional and medicinal

FIGURE 2 | Structural motifs and backbones of major phytochemicals found *M. oleifera* leaves. (A) Glucosinolates and their metabolites. **(B)** Flavonol major derivatives. **(C)** Phenolic acids. Their known derivatives or metabolites are indicated.

FIGURE 3 | Some bioactive phytochemicals found *M. oleifera* leaves. Their structures were obtained from the online in the PubChem database at www.pubmed.ncbi.nlm.nih.org/.

properties. Of major medicinal interest are three structural classes of phytochemicals: glucosinolates, flavonoids, and phenolic acids (Saleem, 1995; Bennett et al., 2003; Lako et al., 2007; Manguro and Lemmen, 2007; Coppin, 2008; Amaglo et al., 2010; Kasolo et al., 2010). Their content in *M. oleifera* leaves varies somewhat with the geographic and climatic conditions under which the plant was grown, as well as with the processing methods for the collected leaves (Bennett et al., 2003; Coppin, 2008; Mukunzi et al., 2011).

Glucosinolates are characterized by β-thioglucoside *N*-hydroxysulfate motif (**Figure 2A**). In *M. oleifera* leaves, most phytochemicals of this class carry a benzyl-glycoside group linked to the single carbon of the motif. The most abundant of them is 4-*O*-(α-L-rhamnopyranosyl-oxy)-benzylglucosinolate, otherwise known as glucomoringin (Amaglo et al., 2010). Enzymatic hydrolysis of the glucosinolate motif of members of this class leads to the formation of corresponding isothiocyanates, thiocyanates, or nitriles. Several of these by-products have been shown to possess antihypertensive properties (Faizi et al., 1992, 1994, 1998).

Flavonoids and phenolic acids are collectively referred to phenolic compounds. The structural skeleton of flavonoids is made of two aromatic rings joined by a three-carbon link; that of the sub-class of flavonols is 3-hydroxy-2-phenylchromen-4-one (**Figure 2B**). Quercetin and kaempferol, in their as 3′-*O*-glycoside forms, are the predominant flavonols in *M. oleifera* leaves. The sugar moieties include, among others, rhamnoglycosyl (rutinosides), glucosyl (glucosides), 6′ malonyglucosyl, and 2′-galloylrutinoside groups (Bennett et al., 2003; Manguro and Lemmen, 2007; Amaglo et al., 2010). Biologically, flavonoids are best known for their antioxidant properties, but their metabolic pathways of activity remain to be fully elucidated (Rice-Evans, 2001). Phenolic acids have benzoic acid and cinnamic acid as backbones, with one or several hydroxyl groups (**Figure 2C**). Chlorogenic acid, which is an ester of dihydrocinnamic acid (caffeic acid) and quinic acid, is a major phenolic acid in *M. oleifera* leaves (Bennett et al., 2003; Amaglo et al., 2010).
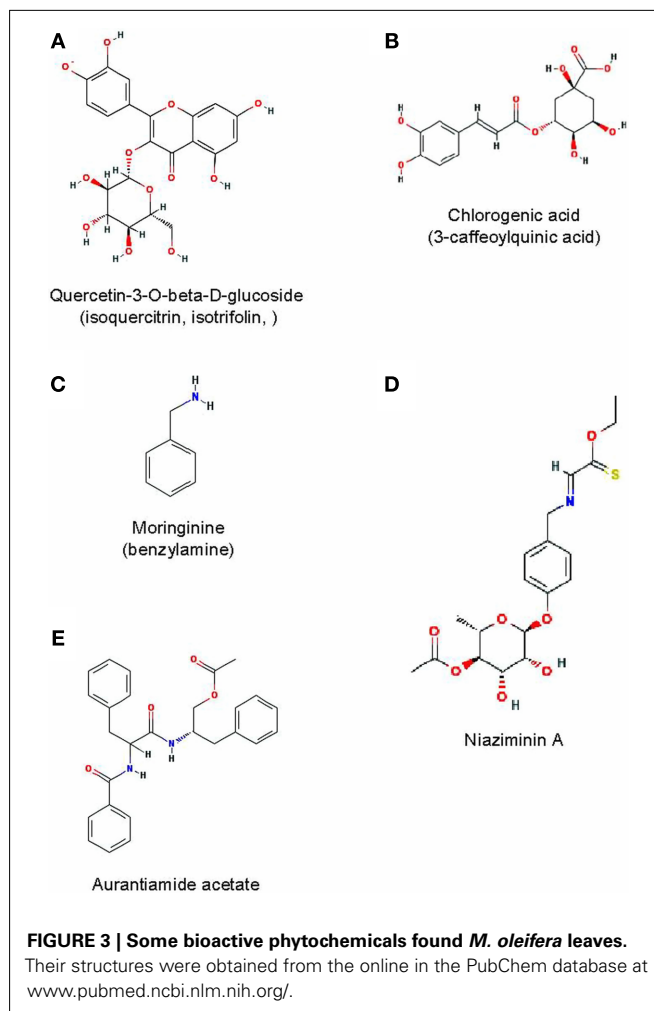
Four of the best-characterized phytochemicals for their therapeutic efficacy in hyperglycemia, dyslipidemia, or related physiological conditions are shown in **Figure 3**.

Quercetin

The flavonol quercetin is found at concentrations as high as 100 mg/100 g of dried *M. oleifera* leaves (Lako et al., 2007), predominantly as quercetin-3-*O*-β-D-glucoside also known as isoquercitrin or isotrifolin (Bennett et al., 2003; Atawodi et al., 2010; **Figure 3A**). Quercetin is a potent antioxidant (Zhang et al., 2011) with multiple therapeutic properties (Bischoff, 2008). It can reduce hyperlipidemia and atherosclerosis in HCD or HFD rabbits (Juzwiak et al., 2005; Kamada et al., 2005). It has shown antidyslipidemic, hypotensive, and anti-diabetic effects in the obese Zucker rat model of metabolic syndrome (Rivera et al., 2008). It can protect insulin-producing pancreatic β cells from STZ-induced oxidative stress and apoptosis in rats (Coskun et al., 2005). Its hypotensive effect has been confirmed in a randomized, double-blind placebo-controlled, human study (Edwards et al., 2007).

Chlorogenic acid

Chlorogenic acid (**Figure 3B**) can beneficially affect glucose metabolism. It has been shown to inhibit glucose-6-phosphate

translocase in rat liver, reducing hepatic gluconeogenesis and glycogenolysis (Hemmerle et al., 1997; Karthikesan et al., 2010a). It was found to lower PPBG in obese Zucker rats (Rodriguez de Sotillo and Hadley, 2002). In OGTT experiments performed on rats or humans, it reduced the glycemic response in both species (van Dijk et al., 2009; Tunnicliffe et al., 2011); in rodents, it also reduced the glucose AUC (Tunnicliffe et al., 2011). Its anti-dyslipidemic properties are more evident as its dietary supplementation has been shown to significantly reduce plasma TC and TG in obese Zucker rats or HFD mice (Rodriguez de Sotillo and Hadley, 2002; Cho et al., 2010) and to reverse STZ-induced dyslipidemia in diabetic rats (Karthikesan et al., 2010b).

Moringinine

The alkaloid moringinine was initially purified from *M. oleifera* root bark (Ghosh et al., 1935) and later chemically identified as benzylamine (Chakravarti, 1955; **Figure 3C**). It is also present in leaves. This substance was suspected to mediate the hypoglycemic effect of the plant. An early study showed that Wistar rats provided with drinking water containing 2.9 g/L of benzylamine for 7 weeks exhibited a reduced hyperglycemic response in an intraperitoneal glucose tolerance test (IPGTT), suggesting improved glucose tolerance (Bour et al., 2005). More recently, the effect was further explored using HFD-fed, insulin-resistant C57BL/6 mice taking an estimated daily dose 386 mg/kg-bw in drinking water for 17 weeks. Compared to untreated controls, these mice gained less weight, had reduced FPG and plasma TC, and were more glucose tolerant (Iffiu-Soltesz et al., 2010).

Niaziminin

Niaziminin (**Figure 3D**) is a mustard oil glycoside initially isolated (along with other glycosides such as niazinin and niazimicin) from ethanolic extracts of *M. oleifera* leaves, based on their hypotensive properties on Wistar rats. At 1 mg and 3 mg/kg-bw, these compounds caused a 16–22 and a 40–65% fall of mean arterial blood pressure (MABP), respectively (Faizi et al., 1992). Other active isothiocyanate glycosides and thiocarbamates were isolated from the plant using the same bioassay (Faizi et al., 1994, 1998; Saleem, 1995).

Aurantiamide acetate

This compound was isolated from *M. oleifera* roots and structurally identified as *N*-benzoylphenylalanyl phenylalinol acetate (**Figure 3E**). At 25 μM, this unusual dipeptide derivative inhibited by nearly 90% the secretion TNFα and IL-2 from lipopolysaccharide-stimulated peripheral blood lymphocytes in culture. It had no effect on IL-6 secretion (Sashidhara et al., 2009). This inhibitory activity may contribute to the anti-inflammatory properties of the plant.

TOXICOLOGY OF *M. OLEIFERA* THERAPY LEAVES

In the studies reviewed in this report, no acute or sub-acute toxicity was reported following treatment with *M. oleifera* leaves at the dosage used. The toxicology of this phytotherapy was specifically addressed in two studies. Using rats, Adedapo et al. (2009) examined the safety of an aqueous extract of *M. oleifera* taken orally at 400, 800, 1600, and 2000 mg/kg-bw ($n = 6$ rats/dose). The treatment was either acute (single dose followed by a 48-h observation

period), or sub-acute (daily doses, except the highest, for 21 days followed by hematological profiling). Acute treatment caused no death at 400 or 800 mg/kg-bw; it caused 1/6 and 2/6 deaths at 1600 and 2000 mg/kg-bw, respectively. At these high doses, surviving rats exhibited transient dullness for up to 5 h. Sub-acute treatment with 400 mg/kg-bw caused a modest (10%), but significant ($P < 0.05$) increase in packed cell volume (PCV) and white-blood cell (WBC) count; with 800 mg/kg-bw, it lowered the PCV, but increased the WBC; with 1600 mg/kg-bw, it lowered both parameters. The WBC changes affected lymphocytes, neutrophils, and monocytes, but not eosinophils. Blood levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were also examined as surrogate indicators of hepatic function. The results were inconsistent: treatment with 400 and 1600 mg/kg-bw increased AST and ALT levels by 40–50%; with 800 mg/kg-bw, it lowered it by about 50%. A 70% increase in ALP levels was observed only after treatment with 1600 mg/kg-bw. Histological examination of tissue sections stained with hematoxylin and eosin revealed no alteration in testis or kidney; a diffuse tissue degeneration was noted in liver. Interestingly, a dose-dependent reduction of body weight gain was noted at the term of the sub-acute treatment with *M. oleifera* extract: whereas untreated rats gained 53% more weight, those treated with 400, 800, 1600 mg/kg-bw of extract gained only 37, 27, and 18%, more, respectively. It is unclear whether this effect is symptomatic of an underlying pathology or indicative of a potential anti-obesity property of the plant. Considering the alterations induced by the sub-acute treatment to be mild, the investigators concluded that nutritional and therapeutic consumption of *M. oleifera* leaves at doses below 2 g/kg-bw is safe.

Other investigators have examined the effects of hexane extracts of *M. oleifera* leaves on the reproductive organs of male mice after an oral gavage at 17, 170, and 1700 mg/kg-bw/day for 21 days. They observed a dose-dependent significant increase in testis and epididymis weights, in seminiferous tubule diameter and in epididymal epithelium thickness, but no change in the plasma levels of gonadotropins. They concluded that these changes reflected enhanced spermatogenesis (Cajuday and Pocsidio, 2010).

Several studies using experimental rodent models have shown that *M. oleifera* leaf extracts can protect the liver from chemically induced damage (Pari and Kumar, 2002; Ndong et al., 2007a; Fakurazi et al., 2008; Buraimoh, 2011).

CONCLUSION AND PERSPECTIVES

Collectively, the studies described in this review provide compelling, albeit very preliminary, experimental evidence of a therapeutic potential of *M. oleifera* leaves in chronic hyperglycemia and dyslipidemia. No report contradicting this evidence was found in the scientific literature. A common weakness of all the human studies reviewed herein was the fact that none was randomized and double-blind, raising the possibilities of bias in the allocation of patients to control and experimental groups.

In spite of converging results, a comparative analysis of these studies is made difficult by variations in agro-climatic conditions of plant growth and harvesting, in leaf processing methods, in final galenic formulations, and in therapeutic protocols. The phytochemical composition of *M. oleifera* parts have been shown to

vary significantly among regions and seasons (Iqbal and Bhanger, 2006; Juliani et al., 2009). Leaf extraction solvents determine the nature and the relative concentrations of bioactive or medicinal ingredients found in final galenic formulations (Siddhuraju and Becker, 2003).

Evaluation of the phytotherapy was often restricted to a narrow set of parameters of disease. For examples, most studies of the anti-diabetic effects were limited to measures of FPG and PPPG levels. Fasting and post-OGTT insulin levels were almost never examined to verify whether the treatment improved the ability of the endocrine pancreas to produce and secrete this hormone in response to elevated blood glucose. Insulin clamp studies would have clarified whether the treatment increased tissue sensitivity to the hormone. Since the medication was administered p.o., measures of plasma levels of incretins and other enterohormones would have given insights on how GIT physiology is affected by the treatment.

In the same vein, it is unclear whether the hypocholesterolemic effect of the therapy was associated with repressed *de novo* cholesterol biosynthesis (a statin-like effect), increased hepatic cholesterol clearance (statin-like or anti-PCSK9-like effects) or increased intestinal excretion. It might be interesting to find the physiological basis of the cardioprotective increase of the TC/non-HDL-C ratio following treatment. A more extensive analysis on circulating biochemical markers of inflammation would be justified, as the balance of pro and anti-inflammatory cytokines could influence the course of both diabetes and atherosclerosis.

Besides a rationalized investigation of the therapeutic effect of *M. oleifera* leaves, it is possible to conduct an unbiased search for the affected physiological pathways. This could be achieved by globally comparing tissues or fluids of untreated and treated animals or humans, using the powerful techniques of systems biology, the so-called "omics" (transcriptomics, proteomics, and metabolomics), combined with the equally powerful algorithms of modern bioinformatics (Zhang et al., 2010).

Further exploration of the potentials and the eventual use of *M. oleifera* therapy in humans will require that reference standards be set for its cultivation, the collection of its parts, as well as for their final conditioning under good agricultural and collection practices (GACP). Such guidelines, specifically directed toward medicinal plants have been defined by the WHO (2003). Furthermore, when the pharmacological basis of the therapeutic effects on a particular pathology is rationally well circumscribed, standardized assays should be required to evaluate all galenic lots for the relevant properties. For example, on the basis of current knowledge, it would indicated that the content in fibers, phytosterols as well in antioxidant and anti-inflammatory activities be evaluated and documented in *M. oleifera* galenic formulations destined to the treatment of atherosclerosis or diabetes. The shelf life of these properties under specified storage conditions should also be established.

In conclusion, based on the available experimental evidence, *M. oleifera* leaf powder holds some therapeutic potential for chronic hyperglycemia and hyperlipidemia. However, before it is advocated in any formulation for the treatment of these metabolic disorders in humans, state-of-the art clinical studies must be conducted to establish the consistency of its medicinal efficacy and the safest modalities of its administration.

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