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Review

A Scoping Review on Cardio-vascular Beneficial Properties of "Miracle Tree" - *Moringa oleifera* Lam

Vartika Jain[1]*, Bhavika Kunwar[2], S. K. Verma[3]

[1]Assistant Professor, [2]Research Scholar

Department of Botany, Government Meera Girls' College, Udaipur, Rajasthan, India

[3]Professor Emeritus and Director

Department of Medicine, Pacific Medical College and Hospital, Udaipur, Rajasthan, India

*Corresponding author Email: vartikabotany@gmail.com

ABSTRACT

Moringa oleifera Lam. is a member of family Moringaceae and popularly known as Miracle Tree. The plant is reputed for its various medicinal uses in codified and non-codified systems of medicine. Several pharmacological properties such as, antimicrobial, anti-inflammatory, analgesic, antioxidant, anticancer, antidiabetic, antihypertensive, anti-obesity, hepatoprotective, hypolipidemic, cardiotonic and antiulcer have been reported from various parts of the plant in many in vitro, in vivo and clinical studies. However, the current review article focuses on the cardio-vascular beneficial pharmacological activities of the plant as well as phytochemical profile of its different parts. In view of its cardio-therapeutic armor and nutritive account, the plant could be recommended as a dietary supplement for individuals having high risk of developing cardio-vascular diseases.

KEYWORDS: Anti-hypertensive, Hypolipidemic, Niazinin, N,α-L-rhamnopyranosyl vincosamide, Moringin

INTRODUCTION

Cardiovascular diseases include both cardiac and vascular disorders (CVDs). According to World Health Organization (2021), CVDs are one of the major causes behind death all over the globe. Among CVDs, heart attack and stroke accounted for 85% death of 17.9 million global populations. Damage to endothelium is the root cause behind CVDs. Endothelial dysfunction disrupts vascular homeostasis and causes inflammation resulting in vasoconstriction, thrombosis, coagulation problems, leukocyte adhesion, and platelet activation. All these, further provoke for atherosclerosis, the process of building up of cholesterol plaque in the blood vessels, which is one of the leading causes behind development of CVD's[1].

In view of severity of CVD's, scientists have been working out for its prevention and treatment through natural and/or

synthetic substances. Plants, rich in various phytochemicals are the most suitable candidates to search for natural bioactive molecules. Several bioactive substances, such as catechin, diosgenin, sulforaphane, isoflavones, and quercetin aid in cardio-protection and reduce cardiac-related problems[2].

Moringa oleifera Lam. (Family – *Moringaceae*) is a plant with full of nutritive and medicinal value. Its cardio-protective role has also been implicated in several scientific studies[3]. The present review describes nutritive and medicinal uses as well as phytochemistry and cardio-vascular beneficial pharmacological activities of *M. oleifera* tree.

Moringa oleifera Lam.: Botany and Distribution

Moringa oleifera Lam. (Family – *Moringaceae*) is known by the names, Horse Raddish Tree, Drumstick Tree, Miracle tree, *Sahjan, Sainjna, Shobhanjana, Mungna, Achajhada, Shevgi, Midhosaragavo, Nugge, Sohjna, Munga arak* etc. among other names. It is a small to medium size, perennial tree; native to North-West India and cultivated throughout the country. Stem features soft and white wood with thick, deeply fissured and corky bark (Fig. 1). The leaves are tri- and impari-pinnate and the leaflets are ovate, elliptic or blunt pointed at the tip, entire and glabrous (Fig.2). The white flowers are fragrant and grow in panicles (Fig. 3). Greenish pods (Fig. 4) are pendulous with trigonous winged seeds. Pods are called as Drumstick and relished in preparing several cuisines in South India, especially *sambhar* (cooked lentil soup) and pickle. Seeds are also consumed like Peanuts after frying. Its flowers and tender leaves are also edible and used for preparing vegetable and other dishes. Its twigs and leaves are also used for fodder. It grows easily in all types of soil except stiff clay soil and cuttings are best way for its propagation[4,5].

Figure 1: *M.oleifera* plant with dehisced pods

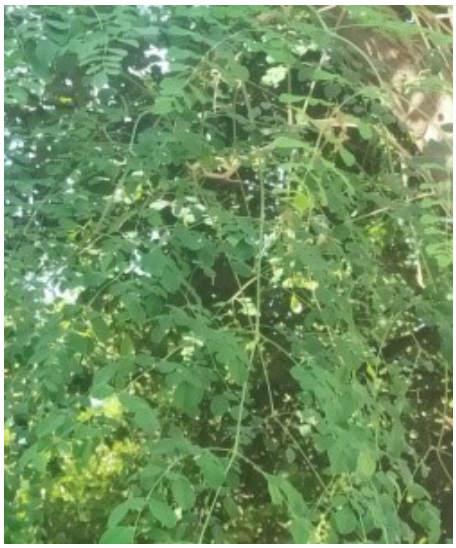

Figure 2: *M.oleifera* Leaves

Figure 3: *M.oleifera* Flowers

Figure 4: *M.oleifera* Pods

Medicinal uses

The plant is reported to be useful for treatment of many human ailments for example, anemia, dyspepsia, arthritis, boils, blood pressure, bone fracture, cancer, centipede bite, conjunctivitis, diabetes, diarrhea, dog bite, calculus, epilepsy, eye infection, hysteria, intestinal worms, coma, flatulence, fever, abdominal spasmodic pain, giddiness, gout, heart ailment, hemorrhoids, injury, influenza, irregular menses, kidney stone, madness, night blindness, nervous debility, paralysis, piles, scabies, scurvy, scorpion bite, sprain, stomach pain, sty, syphilis, throat infection, toothache, typhoid, urine trouble, wound etc. in Ayurveda and Indian Ethnomedicine[6-8].

Nutritive account

M. oleifera is widely used for the treatment of malnutrition especially in young children and mothers due to its high nutritive values. It contains higher amount of essential amino acids including the sulfur-containing amino acids. Leaves of *M. oleifera* contains much more amount of nutrients as compared to their other sources such as vitamin A which is four times of carrots and thirteen times of spinach, vitamin B four times of pork meat, vitamin B_2 fifty times of sarones, vitamin B_3 fifty times of peanut, vitamin C seven times of oranges, vitamin E six times of rapeseed oil, calcium four times of milk, magnesium thirty six times of egg, potassium sixty three times of milk and three times of banana, Iron twenty five times of spinach, protein two times of yoghurt / milk, polyphenol eight times of red wine, amino acid two times of black vinegar and R-amino acid thirty times of brown rice[9-11]. Its leaves are traditionally employed in various cuisines[5] and several innovative recipes have been developed which are tasty as well as good for health[12].

Ferreira *et al.*[13] reported presence of γ and α tocopherols, phenolic compounds, β-carotene, vitamin C and total proteins, including the essential sulfur amino acids, methionine and cysteine in all the parts of *M. oleifera.* Leaves of *M. oleifera* in particular have shown to possess crude protein (27.51%), carbohydrate (43.88%), crude fiber (19.25%), crude fat (2.23%), ash (7.13 %), moisture (76.53%), and a calorific value as 1296.00 kJ/g[14]. Kawo *et al.*[15] evaluated the presence of some major mineral components in the seed powder as Al (144 ppm), Ca (602 ppm), K (732 ppm), Mn (17.5 ppm), P (0.619 mg/kg), Na (86.2 ppm), La (0.73 ppm), Br (0.62 ppm), Sm (0.14 ppm) and Rb (37.5 ppm). Nweze and Nwafor[16] and Ajayi and Fadeyi[17] have demonstrated presence of several minerals in leaves of *M. oleifera.*

Moyo *et al.*[18] demonstrated the nutritional value of *M. oleifera* leaves using proximate and Van Soest methods. Results have shown that the dried leaves had 30.3% crude protein, 19 amino acids, manganese (86.8 mg/kg), iron (490 mg/kg) and selenium (363 mg/kg). Along with these, fatty acids such as, heneicosanoic acid (14.41%), and α-linolenic acid (44.57%), g-linolenic acid (0.20%), palmiteic acid (0.17%), capric acid (0.07%), were present. In comparison to beta-carotene, which had a concentration of 18.5 mg/100 g in the dried leaves, vitamin E had a concentration of 77 mg/100 g. Acid detergent lignin (1.8%), neutral detergent fiber (11.4%), and acid detergent cellulose (4.01%) were the four types of fibers present. Total polyphenols were 2.02%, while condensed tannins were 3.2%.

Ajantha *et al.*[19] described that its leaves possess crude protein (26.01%), moisture (5.36%), ether extract (6.58%), crude fiber (7.08%), total ash (9.41%) and the highest amount of vitamin C (17.31 mg) and vitamin E (113.70 mg). A study has revealed that 100 g its leaves powder contains 45.38 g of carbohydrates, 25.42 g of protein, 2.91 g of fat and 23.33 mg of vitamin C[20]. Sultana[21] reported that fresh leaves of *M. oleifera* had between 187.96 and 278.50 mg of vitamin C per 100 g, and varying amounts of Ca, P and K per 100 g. Eladia and Ampode[22] revealed that pods of *M. oleifera* contains 13.02% crude protein, 36.98% crude fiber, 5.94% ash, and 11.33% moisture. In comparison to fresh leaves, its dry leaves contain more calcium (2185 mg/100g), iron (25.6 mg/100g), magnesium (448 mg/100g), potassium (1236 mg/100g), protein (29.4 g/100g), fiber (12.5 g/100g), carbohydrate (41.2 g/100g) and calories (329 cal/100g). Its seeds are rich in vitamin E (751.67 mg/100g), protein (35.97 g/100g), fat (38.67 g/100g), magnesium (635 mg/100g) and copper (5.2 mg/100g)[3].

Phytochemical armor

Leaves, stem, root, bark, gum, flower, pod and seeds of *M. oleifera* has shown to possess various phytochemicals which have been presented in Table 1. Some of the compounds have also exhibited health-beneficial bioactivities and therefore, the plant is reported to have several pharmacological activities[3].

Table 1: Phytochemicals present in different parts of *M. oleifera* tree

Plant Part	Chemical Compound	References
Leaves	Niazirin, niazirinin, 4-[(4'-O-acetyl-aL-rhamnosyloxy) benzyljisothiocyanate, niaziminin A, niaziminin B	Faizi *et al.*[23]
	4-(alpha-l-rhamnopyranosyloxy)-benzylglucosinolate, quercetin-3-O-glucoside, quercetin-3-O-(6' '-malonyl-glucoside), kaempferol-3-O-glucoside and kaempferol-3-O-(6' '-malonyl-glucoside), 3-caffeoylquinic acid, 5-caffeoylquinic acid	Bennett *et al.*[24]
	α- and γ-tocopherol	Sánchez-Machado *et al.*[25]
	Quercetin and kaempferol	Amaglo *et al.*[26]; Bennett *et al.*[24]; Siddhuraju and Becker[27]
	Hexadecanoic acid, palmitic acid ethyl ester, 2,6- Dimethyl-1, 7-octadiene-3-ol, 4-Hexadecen-6-yne, (z)-(CAS), 2-hexanone, 3- cyclohexyliden-4-ethyl- E2- dodecenyl acetate	Nepolean *et al.*[28]
	Pyrrolemarumine 4″-O-α-L-rhamnopyranoside (marumosides A) and 4′-hydroxyphenylethanamide (marumosides B)	Sahakitpichan *et al.*[29]
	Tannins, alkaloids, phytosterols, triterpenoids, flavonoids, saponins, cardiac glycosides, anthraquinone glycosides, carbohydrates, protein, amino acids, fats & fixed oils	Roopalatha and Nair[30]
	Saponins, condensed tannins, flavonoids, terpenoids, steroids, phenolics, alkaloids, phlobatannins, cardiac glycosides and reducing sugars	Onyekaba *et al.*[31]
	4-(alpha-l-rhamnopyranosyloxy)-benzylglucosinolate (glucomoringin)	Maldini *et al.*[31]
	Carbohydrate, protein, fats, flavonoid, anthraquinone, alkaloids, saponins, steroids, terpenoids, cardiac glycoside, anthocyanin, tannins and carotenoid	Nweze and Nwafor[16]
	Alkaloid, tannins, phlobatannins, phenol, flavonoids, glycoside, saponins, volatile oil, hydrolysable tannin and protein	Imohiosen *et al.*[33]
	N-hexadecanoic acid, tetradecanoic acid, cis-vaccenic acid, octadecanoic acid, palmitoyl chloride, beta-l-rhamnofuranoside, 5-O-acetyl-thio-octyl, gamma-sitosterol, and pregna-7- diene-3-ol-20-one	Bhattacharya *et al.*[34]
	Vitamins, carotenoids, polyphenol, phenolic acids, flavonoids, alkaloids, glucosinolates, isothiocyanates, tannins, saponins and oxalates and phytate	Leone *et al.*[35]

Continued ...

Plant Part	Chemical Compound	References
Leaves	Flavonoids, tannins, saponins, alkaloids, phenol, cyanogenic glucoside and anthraquinones	Ajayi and Fadeyi[17]
	N,α-L-rhamnopyranosyl vincosamide	Cheraghi *et al.*[36] Panda *et al.*[37]
	Saponin, flavonoid, alkaloid and cyanogenic glycoside	Reminus and Cornelius[38]
	Quercetin-3-O-glucoside and kaempferol-3-O-glucoside	Acuram and Chichioco[39]
	Isoquercetin, catechin, tannic acid, gallic acid, quercetin, apigenin, and rutin	Aekthammarat *et al.*[40]
	Glucomoringin, glucosinolates, niazimicin, benzyl isothiocyanate	Fidrianny *et al.*[41]
	Carbonic acid, butyl 2-pentyl ester, 2-isopropoxyethyl propionate, 4H-pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methy,1,3-dioxolan-2-one, 4,5-dimethyl, 1,3-propanediol, 2-ethyl-2- (hydroxymethyl), propionic acid, 2-methyl-, octyl ester, ethanamine, N-ethyl-N-nitroso, 9,12,15-octadecatrienoic acid	Bhalla *et al.*[42]
	Dihydroxyacetone, monomethyl malonate, 4H-Pyran-4-one,2,3-dihydro-3, 5-dihydroxy-6-methyl, 1,3-Propanediol, 2-ethyl-2-(hydroxymethyl), propanoic acid, 2-methyl-, octyl ester, 3-deoxy-d-mannoic lactone, methyl palmitate, sorbitol, inositol, phytol, cyclohexanemethanol, alpha-methyl-4-(1-methylethyl), hexadecanoic acid, n-hexadecanoic acid, 9-octadecenoic acid, methyl ester, 9,12,15-octadecatrienoic acid, octadecanoic acid, 9-octadecenamide	Kandeepan *et al.*[43]
	Flavonoids, terpenoids, cardiac glycosides, saponins, tannins, amino acids and carbohydrates	Kunwar *et al.*[44]
Seed	4-(alpha-L-rhamnosyloxy) benzyl isothiocyanate (A) and 4-(alpha-L-rhamnosyloxy) phenylacetonitrile	Dayrit *et al.*[45]
	O-ethyl-4-(α-l-rhamnosyloxy)benzyl carbamate, 4(α-l-rhamnosyloxy)-benzyl isothiocyanate, niazimicin, niazirin, β-sitosterol, glycerol-1-(9-octadecanoate), 3-O-(6′-O-oleoyl-β-d-glucopyranosyl)-β-sitosterol and β-sitosterol-3-O-β-d-glucopyranoside	Guevara *et al.*[46]
	4-(alpha-l-rhamnopyranosyloxy)- benzylglucosinolate	Bennett *et al.*[24]
	β-sitosterol, campesterol, stigmasterol, Δ^5 and avenasterol, oleic acid, palmitic, stearic, behenic and arachidic acids	Anwar and Rashid[47]

Continued ...

Plant Part	Chemical Compound	References
Seed	Roridin E, veridiflorol, 9-octadecenoic acid	Nepolean *et al.*[28]
	Saponins, tannins, terpenes, alkaloids, flavonoids, carbohydrates, and cardiac glycosides	Ajibade *et al.*[48]
	Carbohydrates, phenols, alkaloids, reducing sugars, proteins, flavonoids and saponins	Unuigbe *et al.*[49]
	Alkaloids, glycerides, flavonoids, steroids, terpenoids, saponins, tannins, eugenol and reducing sugar	Akinyeye *et al.*[50]
	Alkaloids, flavonoids and saponins	Abdulkadir *et al.*[51]
	Alkaloids, tannins, saponins, phenols and flavonoids (kaempferol and quercetin)	Oyebamiji *et al.*[52]
	Pterygospermin, β-sitosterol-3-O-β-D-glucopyranoside, 4-(ɑ -L-rhamnosyloxy) benzyl isothiocyanate	Fidrianny *et al.*[41]
Pods	*O*-[2′-hydroxy-3′-(2″heptenyloxy)]-propyl undecanoate, *O*-ethyl-4-[(α-L-rhamnosyloxy)-benzyl] carbamate, methyl p-hydroxybenzoate and β-sitosterol	Faizi *et al.*[53]
	Alkaloids, flavonoids, saponins and tannins	Abdulkadir *et al.*[51]
Stem	Octacosonoic acid, 4-hydroxymellein, vanillin, β-sitosterone and β-sitosterol	Kesharwani *et al.*[54]
	4-(alpha-l-rhamnopyranosyloxy)-benzylglucosinolate and benzyl glucosinolate	Bennett *et al.*[24]
	Alkaloids, flavonoids, saponins, sterols and tannin	Fahal *et al.*[55]
Root	Moringine and moringinine, 4-hydroxymellein, octacosanoic acid, and β-sitosterol	Kerharo[56], Faizi *et al.*[23]
	Alkaloids, flavonoids and tannins	Abdulkadir *et al.*[51]
	Spirochin and anthonine	Bhattacharya *et al.*[34]
	Benzyl glucosinolate and 4-(α-lrhamnopyranosyloxy)-benzylglucosinolate, aurantiamide acetate, 1, 3-dibenzyl urea, α-phellandrene, deoxy-niazimicine, p-cymene	Kesharwani *et al.*[54]
Bark	Alkaloids, flavonoids, saponins and tannins	Abdulkadir *et al.*[51]
	Flavonoids, carbohydrates, and phenolics	Kurniawan[58]

Continued ...

Plant Part	Chemical Compound	References
Flower	α- and γ-tocopherol	Sánchez-Machado *et al.*[25]
	9-Octadecen–1-ol, (Z)–(CAS) cis-9–Octadecen–1–ol, oleol, satol, ocenol, sipo, decanoic acid, dodecanal	Nepolean *et al.*[28]
	Kaempferol-3- rutinoside	Kesharwani *et al.*[54]
	Tannins, alkaloids, flavonoids, cardiac glycosides	Alhakmani *et al.*[59]
	Sucrose, amino acids, alkaloids, and flavonoids, such as rhamnetin, isoquercitrin, and kaempferitrin	Bhattacharya *et al.*[57]
	Saponin, flavonoid, alkaloid and cyanogenic glycoside	Reminus and Cornelius[38]
	Flavonoids, terpenoids, cardiac glycosides, saponins, tannins, amino acids and carbohydrates	Kunwar *et al.*[44]
Gum Exudates	l-rhamnose, D-glucuronic acid, L-arabinose, D-mannose, D-xylose, and D-galactose	Bhattacharya *et al.*[57]
	O-(-D-β-glucopyranosyluronic acid) (1→6)-O-β-Dgalactopyranosyl(1→6)-D-galactose	Amjad *et al.*[61]
	Leucodelphinidin-3-O-B-D-galactopuranosy (1->4)-O-B-D-glucopyranoside	Khare *et al.*[62]

Pharmacological Profile

M. oleifera is rich in various pharmacological activities for example, antimicrobial, anti-inflammatory, analgesic, anticancer, antihypertensive, antidiabetic, antioxidant, hepatoprotective, hypolipidemic, cardiotonic, antiulcer etc.[3,63,64]. Some of the cardio-vascular beneficial activities (Fig. 5) have been discussed below in detail.

Antioxidant Activity

Bharali *et al.*[65], after giving 125 mg/kg and 250 mg/kg hydro-alcoholic extract of *M. oleifera* pods to female Swiss albino mice, observed a significant increase ($p<0.01$) in the activities of hepatic cytochrome b(5), cytochrome p(450), catalase, glutathione peroxidase and reductase, as well as a significant decrease ($p<0.01$) in the hepatic malondialdehyde levels. *In vitro* antioxidant activity of *M. oleifera* leaf extract in methanol and acetone against accelerated ageing of sunflower oil was assessed by Siddiq *et al.*[66]. Highest antioxidant activity was demonstrated by 80% methanolic extract (3.28±0.04) followed by 100% methanol (3.10±0.16), 80% acetone (2.80±0.14) and 100% acetone (2.68±0.13). Chumark *et al.*[67] investigated in vitro antioxidant potential of leaf extract of *M. oleifera* using DPPH radical scavenging method and IC50 of 78.15 ± 0.92 was found.

The antioxidant capacity of *M. oleifera's* leaf, fruit, and seed aqueous extracts was studied by Singh *et al.*[68] in 2009. The leaf extract performed better than the fruit and seed extracts and standard α-tocopherol in antioxidant activity (85.77%), reducing power, anti-radical power (74.30%), protein oxidation, inhibition of lipid peroxidation, OH-induced deoxyribose degradation and scavenging power of superoxide anion and nitric oxide radicals. Sharma and Singh[69] evaluated antioxidant activity of aqueous and ethanolic extract of leaves and pods of *M. oleifera* against CCl_4 induced hepatocytes injury of albino mice. Pretreatment with *M. oleifera* hydro-alcoholic leaf extract with doses of 500 mg/kg, 750 mg/kg, 1000 mg/kg(p.o.) and aqueous pods extract with doses of 500 mg/kg, 750 mg/kg and 1000 mg/kg(p.o.) improved the SOD, catalase, glutathione, and peroxidase levels significantly and also reduced lipid peroxidation.

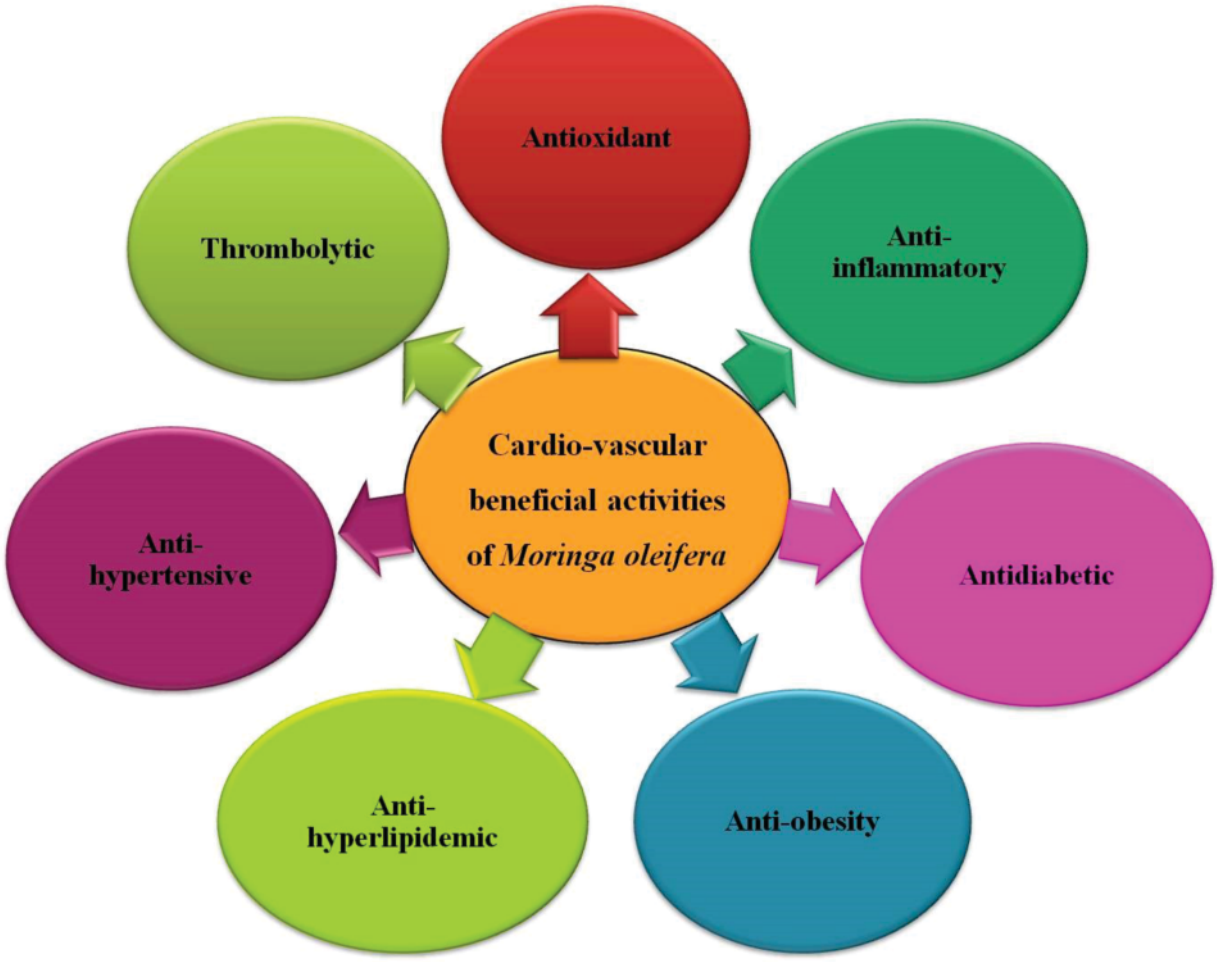

Figure 5: Some cardio-vascular beneficial activities of *M. oleifera*

Shih *et al.*[70] reported *in vitro* antioxidant activity of methanolic extract of leaf, stem and stalk of *M. oleifera*. Methanolic extract showed strong scavenging effect of DPPH radicals (EC_{50} - 200µg/mL) and reducing power. The trend of antioxidative activity of the part of *Moringa* was: leaf > stem > stalk. Kumbhare *et al.*[71] evaluated *in vitro* antioxidant activity of different extracts of stem bark of *M. oleifera* using DPPH and nitric oxide radical scavenging activity. Petroleum ether, chloroform and methanolic extracts of *M. oleifera* were used to evaluate antioxidant activity. Methanolic extract had the highest level of DPPH radical scavenging activity, with an IC_{50} of 54.34 g/mL, followed by chloroform and petroleum ether extract with an IC_{50} of 112.08 and 124.75 µg/mL, respectively.

Antioxidant potential of *M. oleifera* leaves was also observed in postmenopausal women (n=30) after 7g intake for 12 weeks. A significant improvement was exhibited in various parameters such as superoxide dismutase, glutathione peroxidase, ascorbic acid, hemoglobin and malondialdehyde levels along with reduction in blood glucose levels without any side effects[72]. According to Vongsak *et al.*[73], an ethanolic extract of *M. oleifera* leaves has a high ferrous reducing power value (51.50 mmol $FeSO_4$ equivalents/100 g extract) and a strong DPPH-scavenging activity (EC_{50}- 62.94 g/mL).

Charoensin[74] evaluated *in vitro* antioxidant activity from methanol and dichloromethane extract of leaves of *M. oleifera* using of DPPH and 2,2′-azino-bis 3- ethylbenzothiazoline-6-sulfonic acid (ABTS) radical scavenging assays. Methanolic extract has shown higher free radical scavenging activity than the dichloromethane extract with an IC_{50} of 1.60±0.03 mg/ml in DPPH assay and 1.02±0.06 mg/ml in ABTS assay. Tumer *et al.*[75] investigated direct and indirect antioxidant activity in polyphenol and isothiocynate (ITC) rich fractions of *M. oleifera* leaves in hepa1c1c7 cells. The polyphenol fraction of *Moringa* were found to be effective direct antioxidants assayed by oxygen radical absorbance capacity and ITCs fractions were observed as strong indirect antioxidants as assayed through induction of NAD(P)H quinone oxidoreductase 1 activity.

Fitriana *et al.*[76] investigated *in vitro* antioxidant activity of different extracts of leaves of *M. oleifera*. In the DPPH assay, the methanolic extract had the highest free radical scavenging activity, with an IC_{50} value of 49.30 g/mL, followed by ethyl acetate extract (444.10 g/mL), n-hexane extract (715.21 g/mL), and dichloromethane extract (1035.57 g/mL). In ABTS radical scavenging assay, methanolic extract demonstrated IC_{50} of 11.73µg/mL followed by dichloromethane, n-hexane and ethyl acetate extracts with IC50 values of 159.06, 163.79 and 241.33 µg/mL, respectively.

Jahan *et al.*[77] reported *in vitro* antioxidant activity of methanol, acetone and water extract of seed kernel of M. oleifera using different assays. By scavenging DPPH, ABTS, and NO free radicals, aqueous extract of seed kernel has demonstrated significant antioxidant activity, with EC_{50} values of 36.890.154, 13.200.049, and 217.950.327 g/mL, respectively.

Recently, Olaoye *et al.*[78] have reported effect of soil type on the antioxidant level of leaves of *M. oleifera* collected from 21 different locations of Nigeria as evaluated by DPPH and Nitric oxide scavenging activities. Tariq *et al.*[79] have carried out comparative analysis of DPPH radical scavenging activity of seeds of *M. oleifera* collected from Multan and India. Methanolic extract of seed powder from Multan and India exhibited an IC_{50} of 84 and 540 µg/mL respectively.

Anti-diabetic Activity

Ndong *et al.*[80] studied anti-diabetic potential of leaves of *M. oleifera* on glucose tolerance in type 2 diabetic Goto-Kakizaki (GK) and Wistar rats. Blood glucose was significantly ($p<0.05$) reduced at 20, 30, 45 and 60 min in GK rats and at 10, 30 and 45 min in Wistar rats by oral administration of leaf powder of *M. oleifera.* The anti-diabetic effect of leaf powder was more pronounced in GK rats than in Wistar rats. Jaiswal *et al.*[81] assessed anti-diabetic effect of *M. oleifera* leaves on fasting blood glucose (FBG), oral glucose tolerance test (OGTT) and post-prandial glucose (PPG) of normal and streptozotocin (STZ) induced diabetic rats. Following administration of 200 mg/kg aqueous extract of leaves to severely diabetic rats, the greatest decrease of 69.2 and 51.2%, in FBG and PPG levels, was observed, respectively. Kumari[82] has shown decrease in fasting and post-prandial blood glucose levels after consumption of 8g *M. oleifera* leaf tablets for 40 days in 46 individuals. Ghiridhari *et al.*[83] has also reported reduction in HbA1C and post-prandial blood glucose levels after consumption of two leaf tablets daily for 12 weeks in 30 individuals.

Gupta *et al.*[84] examined the *in vivo* anti-diabetic efficacy of a methanolic extract of *M. oleifera* pods in streptozotocin induced diabetic albino rats. Extract of pods in both the concentrations of 150 and 300 mg/kg significantly decreased serum glucose levels in rats. Edoga *et al.*[85] investigated *in vivo* hypoglycemic activity of aqueous extract of leaves of *M. oleifera* in alloxan-induced diabetic rats. Aqueous extract reduced blood glucose levels by 33.29%, 40.69% and 44.06% significantly ($p<0.05$) in doses of 100, 200, 300 mg/kg respectively. A clinical study on 20 male diabetic individuals was performed by Sugunabai *et al.*[86] to evaluate the antidiabetic efficacy of aqueous extract of *M. oleifera.* After 90 days, blood glucose levels and glycosylated haemoglobin were decreased to 22.1% and 20.4% respectively. Al-Malki and Rabey[87] used seed powder of *M. oleifera* in two doses of 50 and 100 mg/kg bw to evaluate antidiabetic activity against STZ induced diabetic adult male albino rats The serum levels of lipid peroxide, IL-6, antioxidant enzyme, immunoglobulins (IgA and IgG), fasting blood sugar, and glycosylated haemoglobin were increased in diabetic rats, and treatment with seed powder showed a restoration of all these parameters.

Hypoglycemic effect of aqueous extract of leaves of *M. oleifera* was assessed by Khan *et al.*[88] in streptozotocin and high-fat diet induced diabetic female Wistar rats. In both the experimental models, fasting blood glucose, lipid profile, and liver marker enzyme levels were significantly ($p<0.05$) recovered. Villarruel-López *et al*.[89] also demonstrated antidiabetic efficacy of leaves of *M. oleifera* against alloxan induced Sprague Dawley diabetic rats. In diabetic Sprague Dawley male rats, Nayak *et al.*[90] examined the in vivo antidiabetic effect of ethanolic extract of *M. oleifera* leaves, and reported that fasting glucose levels significantly decreased from 236 mg/dL to 171 mg/dL.

Recently, anti-hyperglycemic effect of leaf powder of *M. oleifera* (2400 mg/day) was observed in double-blind, placebo-controlled, randomized, clinical study in prediabeteic subjects with favorable changes in glycaemia markers compared to placebo group[91].

Anti-inflammatory Activity

Cáceres *et al*.[92] have shown anti-inflammatory effect of the oral administration of hot water infusions of *M. oleifera* seeds (1000mg/kg) on carrageenan-induced hind paw edema in rats. Aqueous and ethanolic (90%) extracts of *M. oleifera* leaves were examined by Rao *et al.*[93] for in vivo anti-inflammatory efficacy in male albino rats against carrageenin-induced hind paw edema. At a dose of 200 mg/kg of the aqueous and ethanolic extract of leaves, respectively, significant ($p<0.01$) percent reductions of 0.83 ± 0.02 and 1.03 ± 0.02 were seen. Ndiaye *et al*.[94] evaluated efficacy of aqueous extract of *M. oleifera* roots against carrageenin induced inflamed paw in rats. Development of edema was significantly inhibited by 750 mg/kg root extract at 1, 3 and 5 hours as 53.5, 44.6 and 51.1%, respectively. Anti-inflammatory efficacy of ethanolic extract of *M. oleifera* seeds were examined by Mahajan and Mehta[95] against immune mediated inflammatory responses in toluene diisocyanate induced asthmatic Wistar rats.

Using the *in vitro* protein denaturation method, Alhakmani *et*

al.[59] showed that the ethanolic extract of flowers of *M. oleifera* possesses anti-inflammatory properties. At dosages of 100, 200, and 500g/mL, denaturation of egg albumin was significantly inhibited by 58.16±2.32, 88.10±1.80 and 101.50±2.60, respectively. Usman and Barhate[96] evaluated seeds *M. oleifera* for anti-inflammatory properties against carrageenin-induced paw edema in rats. At a dose of 300 mg/kg, ethanol extract demonstrated substantial ($p<0.001$) percent inhibition of 52.7% whereas in same dose, petroleum ether, chloroform, and aqueous extract has decreased the paw edema to the extent of 23%, 24%, and 22% respectively. Using the carrageenin-induced paw edema method and the cotton pellet granuloma method, *in vivo* anti-inflammatory efficacy of ethanolic and aqueous extracts of *M. oleifera* seeds was assessed. Aqueous extract demonstrated percent inhibition of 21.60, 33.33, and 40 at dosages of 250, 500, and 750 mg/kg, while ethanolic extract exhibited 30, 51.62, and 70.65 percent inhibition at doses of 50, 100, and 200 mg/kg, respectively. In the cotton pellet granuloma method, aqueous extract has exhibited 21.37, 32.03, and 62.32 percent inhibition in granulation at dosages of 250, 500, and 750 mg/kg, respectively, whereas ethanolic extract has shown percent inhibition of 18.22, 35.86, and 50.16 in granulation at the dosages of 50, 100, and 200 mg/kg, respectively[97].

Recently, Buabeid *et al.*[98] have shown anti-inflammatory effect of *M. oleifera* leaves in cotton-pellet induced granuloma model in albino rats. It was observed that this effect was comparable ($p>0.05$) to high dose of *M. oleifera* as compared with standard drug. The reason behind the dose-dependent effect of *M. oleifera* leaves was due to downregulation of TNF-α and interleukin-1ß.

Hypolipidemic Activity

In vivo hypocholesterolemic effects of a crude extract from *M. oleifera* leaves were examined by Ghasi *et al.*[99] in Wistar rats fed with a high-fat diet. When combined with a high-fat meal, the administration of the crude leaf extract decreased the increase in blood, liver, and kidney cholesterol levels by 14.35%, 6.40%, and 11.09%, respectively. Mehta *et al.*[100] demonstrated that giving *M. oleifera* (200 mg/kg/day, p.o.) to rabbits for 120 days significantly reduced their serum cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), phospholipids, and atherogenic index while also raising HDL-C levels. In 2008, Ara *et al.*[101] compared the effects of ethanolic extract of leaves of *M. oleifera* with atenolol on the levels of serum triglycerides, blood sugar, and cholesterol in rats, as well as on body weight and heart weight. Atenolol medication and *M. oleifera* leaf extracts decreased lipid levels after intraperitoneal administration for one week.

In vivo hypolipidemic efficacy of *M. oleifera* leaf methanolic extract was examined by Jain *et al.*[102] in albino Wistar rats. For 30 days, methanolic extract was administered orally in dosages of 150, 300, and 600 mg/kg,p.o. Serum cholesterol, triacylglyceride, VLDL-C, LDL-C, and the atherogenic index all significantly decreased, while HDL-C levels increased. Nambiar *et al.*[103] have demonstrated decrease of cholesterol and non-HDL-C along with increase in HDL-C after 4.6 g/day consumption of leaf tablets for 50 days in 17 individuals. Kumari[82] has also shown reduction in cholesterol, triglycerides and LDL and VLDL cholesterol after 40 days consumption of 8g leaf tablets in 46 type 2 diabetic individuals.

Rajanandh *et al.*[104] demonstrated hypolipidemic effect of hydroalchoholic extract of leaves of *M. oleifera* in male Wistar rats. For a period of 28 days, hyperlipidemic rats received the extract orally at two distinct dose levels (100 and 200 mg/kg/bw). The results revealed a significant ($p<0.001$) decrease in elevated levels of total cholesterol, triglycerides, LDL and VLDL cholesterol, body weight, and atherogenic index, as well as a significant ($p<0.001$) increase in HDL cholesterol. After giving methanolic extract of *M. oleifera* leaves to high fat diet-induced hyperlipidemic wistar albino rats for 49 days, Bais *et al.*[105] found a substantial rise in HDL-C and a decrease in blood lipids such as total cholesterol, triglycerides, LDL-C, and VLDL-C. Notably, 26% and 62.1% decrease in atherogenic index was also observed in both the doses of 200 and 400 mg/kg, respectively at the end of the study.

Helmy *et al.*[106] demonstrated hypolipidemic potential of leaf powder and extract of *M. oleifera* using hyperlipidemic adult male albino rats and dry leaf powder were administered with high fat diet in a dose of 0.737% and 1.475% or 200 and 400 mg/kg bw for 60 days. Result exhibited potent decrease in elevated levels of cholesterol, triglycerides, LDL-C and malondialdehyde at a dose of 400 mg/kg bw. Metwally *et al.*[107] have shown antihyperlipidemic effect of ethanolic extract of *M. oleifera* aerial parts in obese Wistar rats. After oral administration of 600 mg/kg BW plant extract, atherogenic index was reduced at the end of 12 weeks.

Madkhali *et al.*[108] have also demonstrated antihyperlipidemic property of methanolic extract of leaves of *M. oleifera* in animal study. Reduction in total cholesterol, triglycerides, LDL-C, and VLDL-C as well as increase in HDL-C was observed after 3 weeks administration of methanolic extract in a dose of 400 mg/kg BW in rats. Another important observation was endothelium-mediated vasodilatation and repairing of collagen elastic ratio and damage caused to aorta. This shows the cardio-vascular beneficial potential of *M. oleifera* leaves. Recently, Mabrouki *et al.*[109] have also shown hypolipidemic potential of methanolic extract of *M. oleifera* leaves in doses of 200 and 400 mg. At the end of 12 weeks, cholesterol, triglycerides, LDL-C, were reduced and HDL-C was improved in obese rats. Moreover, cardiac enzymes CK-MB, AST, and ALT were improved and lipid peroxidase level was decreased. Besides, cardiac catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were improved.

Thrombolytic Activity

Recently, *in vitro* thrombolytic activity of methanolic extracts of leaves and flowers of *M. oleifera* in a concentration of 1 mg/ml has been demonstrated by Kunwar *et al.*[44]. Extract of leaves exhibited 41.40% thrombolytic activity whereas methanolic extract of flowers has shown 20.52% clot lysis. The activity was significant in comparison with both positive control streptokinase and negative control distilled water. This further emphasizes the importance of conducting long term studies to establish the cardio-vascular protective potential of *M. oleifera.*

Antiobesity Activity

Metwally *et al.*[107] investigated molecular mechanism for anti-obesity activity from ethanolic extract of aerial parts of *M. oleifera* in female wistar rats. The extract was orally administered to obese female rats at a dose of 600mg/kg bw daily for 12 weeks. The present study revealed that extract of *M. oleifera* down-regulated the mRNA expression of leptin and resistin as well as up-regulated adiponectin gene expression in obese rats. Besides this, reduction in body weight, insulin resistance and improvement of coronary artery index was also observed.

Anti-hyptertensive Activity

Gilani *et al.*[110] isolated niazinin A, niazinin B, niazimicin and niaziminin A + B from ethanolic extract of leaves of *M. oleifera* and intravenous administration of these compounds (1–10 mg/kg) produced hypotensive and bradycardiac activity in anaesthetized rats. From the ethanolic extract of leaves of *M. oleifera* six new compounds, three synthetically known glycosides having thiocarbamate, carbamate or nitrile groups and fully acetylated glycosides were isolated by Faizi *et al.*[111]. Thiocarbamated glycosides have shown hypotensive and hypoglycemic potential.

A statistical significant reduction in arterial blood pressure was observed in monocrotaline-induced pulmonary hypertensive rats after acute treatment of leaf extract of *M. oleifera* at a concentration of 4.5 mg/kg bw[112]. Sana *et al.*[113] showed that intravenous administration of petroleum ether and dichloromethane extracts of *M. oleifera* roots at a concentration of 30 mg/kg lower mean arterial pressure in normotensive rats. Both the extracts are expected to release nitric oxide or EDRF in smooth muscle cells as dichloromethane extract stimulated pathways other than cholinergic whereas muscarinic receptor pathways were stimulated by petroleum ether extract. This indicated release of EDRF in conditions of normal blood pressure.

Fombang *et al.*[114] reported anti-hypertensive activity of leaf powder of *M. oleifera* in 30 obese hypertensive individuals. After daily administration of 30 g leaf powder, a significant reduction in systolic and diastolic blood pressure was observed at the end of two months along with decrease in BMI. This also demonstrated diuretic action of its leaves by enhancing frequency of urine by 27.2%. Notably, daily consumption of 4 g leaf powder of *M. oleifera* for four weeks reduced five mmHg systolic and diastolic blood pressure in type-2 diabetic individuals[115].

Systemic and ocular hypotensive effect of leaves of *M. oleifera* was also observed in a clinical study on 30 adults with normal blood pressure. Oral administration of its aqueous extracts in three different doses 28.5, 57, and 85.7 mg/kg reduced the blood pressure and intraocular pressure significantly at 30, 60, and 90 min. However, baseline values were returned after 150 min. This effect was attributed to high potassium and calcium content preventing the excess sodium absorption leading to reduction in blood pressure[116]. Sailesh *et al.*[117] have shown significant reduction in systolic and diastolic blood pressure after one month administration of 150 ml leaf juice of *M. oleifera* twice daily to 20 patients having stage 1 hypertension.

Oral administration of aqueous extract (30 and 60 mg/kg/day) of *M. oleifera* leaves for 3 weeks in Nω-nitro-L-arginine-methyl ester (L-NAME) induced hypertensive rats, blood pressure and heart rate were decreased. Acetylcholine-induced impairment of mesenteric arterial relaxation was also significantly reduced. The endothelium of the mesenteric artery beds in rats that received a 0.001-3 mg bolus injection of the extract exhibited a dose-dependent vasorelaxation. Moreover, decrease in vascular O_2- production and malondialdehyde level in plasma and thoracic aorta was observed along with increase in SOD and CAT enzymes. This indicates the effectiveness of *M. oleifera* against oxidative stress-related hypertension in L-NAME rats because L-NAME acts as an inhibitor of nitric oxide synthase[118].

Acuram and Chichioco[39] have shown significant decrease in systolic blood pressure of L-NAME induced hypertensive mice after four weeks oral administration of methanolic and ethyl acetate extracts of *M. oleifera* leaves in doses of 0.01 and 0.3g/kg/day. They also demonstrated the ACE inhibition mechanism behind the reduction in blood pressure by isolating two bioactive molecules, namely, quercetin-3-O-glucoside and kaempferol-3-O-glucoside whose *in vitro* ACE inhibition activity was more than the positive control Captopril.

Later Aekthammarat *et al.*[40] intravenously administered 30 mg/kg aqueous extract of *M. oleifera* leaves to L-NAME) induced hypertensive rats. The longer-lasting blood pressure lowering effects were observed which may have been caused by NOS-sGC dependent signalling activating eNOS. A vasorelaxating effect in endothelium was observed due to increase in availability of nitric oxide. Chan Sun *et al.*[119] demonstrated reduction in postprandial blood pressure of healthy individuals after seven days administration of 120 g cooked leaves of *M. oleifera.* Free radical scavenging activity of nitrile, thiocarbamate, and isothiocyanate was suggested to be responsible for hypotensive activity.

Kumolosasi *et al.*[120] have demonstrated reduction in systolic and diastolic blood pressure after administration of ethanol and aqueous extracts (1000 mg/kg) of leaves, twig, pods, roots and seeds to spontaneously hypertensive rats at the end of 14 days. Besides, significant diuretic activity of ethanolic leaf extract was observed. Aqueous and ethanolic extract of leaves and ethanolic extract of pods have shown more than 50 % angiotensin converting enzyme (ACE) inhibitory activity and suggested that the plant could be suggested as dietary supplement to pre-hypertensive individuals.

Cardioprotective Activity

In vivo cardioprotective efficacy against isoproterenol-induced myocardial infarction was found by Nandave *et al.*[121] in Wistar albino rats. The biochemical enzymes, superoxide dismutase, glutathione peroxidase, catalase, lactate dehydrogenase, and creatine kinase-MB were significantly and favorably modulated by the continuous administration of *M. oleifera.*

Oral administration of 750 mg seed powder of *M. oleifera* for 20 weeks to spontaneously hypertensive rats (SHR) did not affect blood pressure but reduced nocturnal heart rate and improved cardiac diastolic function. The calcium-regulated mechanism and other signalling pathways linked to pressure-overload-induced left ventricular hypertrophy were suggested to be the potential targets for the treatment with seed powder. Moreover, reduced vascular stresses were observed in aortas of SHR treated with seed powder, which were correlated with an increase in SOD2, a decrease in the level of free 8-isoprostane in the blood, and vascular expressions of p22phox and p47phox. iNOS and NF-B protein expressions were found to be lower after the treatment, leading to lower levels of circulating nitrites and C-reactive proteins. Moreover, treated SHR group exhibited greater artery resistance to the functional test for endothelium-dependent carbachol-induced relaxation. This study indicates that *M. oleifera* seed powder possesses vascular antioxidant, anti-inflammatory, and endothelial protective potential against cardiovascular problems indicated by oxidative stress and inflammation[122].

Seed powder of *M. oleifera* has also shown to induce endothelial relaxation by down-regulating arginase-1 and enhancing Akt signalling and activating endothelial NO synthase in aged rats. The powder was given in a dose of 750 mg/kg daily for four weeks[123].

Cardio-protective effect of an alkaloid, N,α-L-rhamnopyranosyl vincosamide (VR), isolated from leaves of *M. oleifera* has been demonstrated by Panda *et al.*[37.] Oral administration of VR (40 mg/kg BW) inhibited elevation of ST segment and decreased the number of necrotic cells in cardiac muscle at the end of seven days in rat models induced with cardiotoxicity by ISO. VR also attenuated various elevated biomarkers such as cTnT, CK-MB, LDH, and SGPT. This bioactive molecule also exhibited antioxidant activity by increasing levels of SOD, CAT, GPx, and GSH enzymes *in vitro* and *in vivo*. Cheraghi *et al*.[36] also demonstrated the free radical scavenging activities of VR which increased GSH and SOD enzyme levels and decreased mRNA level of cardiac hypertrophy markers ANP, BNP, and β-MHC mRNA in doxorubicin–induced cardiotoxic rat heart after two weeks intraperitoneal administration.

Aqueous extracts of *M. oleifera* leaves in concentration of 20% and 40% significantly reduced triglycerides and AST, ALP and CAT enzymes of cardiac tissues of Wistar albino rats in which toxicity was induced by simultaneous administration of 30 mg/kg bw potassium bromate. This indicates cardio-protective potential of *M. oleifera* leaves[124].

Oral administration of butanolic fraction of leaves of *M. oleifera* (100 mg/kg/day) increased SOD, CAT, GPx, and total GSH levels and reduced MDA levels at the end of 28 days in ISO-induced cardiotoxic rat models. This effect was credited with presence of bioactive compounds such as ellagic acid, quercetin, rutin, and kaempferol. Myocardial damage was also reduced as demonstrated by amelioration in increase of CK-MB, LDH, and cTnT biomarkers as well as reduction in inflammation, necrosis and infarction[125].

Hugar *et al.*[126] have demonstrated cardio-protective effect of *M. oleifera* seeds in Wistar albino rats. Myocardial infarction (MI) was induced in rats using isoproterenol and methanolic extract of its seeds were administered for 32 days. Elevated serum myocardial enzymes (LDH, CPK, AST, ALT and CK-MB) and lipid parameters were reduced in a dose-dependent manner by *M. oleifera* seed extract.

Four weeks administration of ethanolic extract of *M. oleifera* leaves in a concentration of 680 mg/day increased GSH and GPx levels in benzene-induced leukemia rat models and doxorubicin induced cardio-toxic rat models. It's interesting to note that administering *M. oleifera* along with doxorubicin had a greater ameliorative impact than administering it alone and significantly decreased ɤ-H2AX and ET-1 expressions in heart tissue as a marker of cardiac toxicity as well as decreased apoptotic markers p53 and caspase 3 and markers of inflammation, namely, TNF-α, NF-κB, and MCP-1[127].

Oral administration of *M. oleifera* seed powder to wild-type C57/BL6 male mice which were induced with MI reduced the mortality and improved cardiac dysfunctions. After 28 days of MI induction, size of infarction was also reduced by seed powder. This positive effect in MI induced mice was attributed to antioxidant and apoptosis inhibitory activity of its seed powder[128].

Safety and Toxicity

Several toxicity studies of various extracts of *M. oleifera* have been carried out in animal studies and the plant has been proved safer in low doses. No acute, sub-acute and chronic toxicity

was observed with administration of leaves and bark extracts of *M.oleifera*[129]. However, in high doses of leaves and seeds extract of *M. oleifera,* changes in blood and organ damage parameters was observed[130,131].

Interestingly, a single dose of 50 g leaf powder or 40 days daily consumption of 8g leaf powder did not show any adverse effects in human beings[132]. Detailed studies related to safety issues associated with consumption of different parts of *M. oleifera* are warranted.

CONCLUSION

The Miracle Tree, *Moringa oleifera* is in fact, a plant with amazing amounts of minerals and vitamins such as calcium, potassium and vitamin C & E. The phytochemical armor is full with polyphenols and flavonoids among others. Besides, it has shown cardio-vascular risk factor modifying activities such as reduction in blood lipids, blood pressure, blood sugar, obesity, inflammation as well as improvement in thrombolysis and antioxidant levels in many *in vitro*, animal and clinical studies. Interestingly, it has also exhibited improvement in conditions of endothelial dysfunction and cardio-toxicity. However, safety profile and large scale, clinical studies on population of various ethnicities should be carried out in order to recommend it as a cardio-protective herb.

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