Pharmacological properties of *Moringa oleifera* Lamarck related to cardiovascular diseases: A review of the literature

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ABSTRACT

Diseases of the heart and blood vessels, known as cardiovascular diseases (CVDs), are one of the leading causes of death worldwide [11]. CVDs encompass a set of conditions that affect both the heart and blood vessels and include coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart anomalies, deep vein thrombosis and pulmonary embolism. Moringa oleifera belongs to the Moringaceae family, popularly known as white lily, white acacia or quince okra, it has high levels of beta-carotene and polyphenols and is used to prevent diseases such as atherosclerosis, in addition to being used to strengthen the Cardiovascular system. This integrative literature review aimed to seek and present current evidence about the pharmacological potential of Moringa oleifera lamarck on cardiovascular diseases, explaining the main pharmacological findings. 5,284 articles were found where, through the inclusion criteria, only 10 fit within the study. The referenced studies were carried out with the aim of describing the therapeutic potential of Moringa oleifera lamarck (MO) on cardiovascular diseases. Due to its therapeutic potential, the interest of dietary supplementation with Moringa oleifera seeds for middle-aged or elderly people is suggested, aiming to limit aging-related endothelial dysfunction and prevent the development of cardiovascular diseases, being particularly relevant in countries that may have limited access to pharmacological treatments, as a non-drug means for healthy aging. According to studies, Moringa oleifera seed has a beneficial role against functional and structural cardiac remodeling induced by hypertension, antioxidant and anti-inflammatory effects, beneficial action on endothelial function and other cardiac complications.

Keywords: Diaseses, Moringa oleifera, Pharmacological Activity.

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INTRODUCTION

Diseases of the heart and blood vessels, known as cardiovascular diseases (CVDs), are one of the leading causes of death worldwide [11]. CVDs encompass a set of conditions that affect both the heart and blood vessels and include coronary heart disease, cerebrovascular disease, peripheral artery disease, rheumatic heart disease, congenital heart anomalies, deep vein thrombosis, and pulmonary embolism [25].

In the Americas, cardiovascular diseases (CVD) account for 29% of all deaths, making it the leading cause of death in the region. In addition, CVD is also the leading cause of disability. High blood pressure is the most significant reversible risk factor for the development of these diseases and deaths; more than half of CVD cases and 17% of deaths overall in the Americas can be attributed to high blood pressure. About 8% of health expenditures in the region are related to hypertension, which demonstrates a sensible use of resources, since controlling high blood pressure reduces both mortality rates and cases of disability, in addition to presenting a very positive and cost-effective cost-benefit ratio in most situations [8, 10].

Arterial hypertension (AH) is a chronic non-communicable condition (NCD) that is characterized by high blood pressure levels [21, 22]. In this case, the benefits of treatment, whether drug or not, outweigh the possible risks [15, 18]. This condition is marked by persistent elevation of blood pressure, i.e., when systolic blood pressure (SBP) is equal to or greater than 140 mmHg and/or diastolic blood pressure (DBP) is equal to or greater than 90 mmHg [31].

The use of natural remedies in alternative medicine has sparked interest in the treatment of cardiovascular diseases based on traditional methods [44, 45]. In this sense, phytotherapy is characterized by the use of medicinal plants in different pharmaceutical forms and presentations, without the use of isolated active substances, but rather an herbal complex that can act individually, additionally, or in synergy to promote the recovery of health [6, 42].

In developing countries, almost 80% of the inhabitants still rely on herbal extracts as a source of medicines [14]. According to Hönh et al (2018) [18], several parts of a plant (leaves, pods, flowers, bark, and seeds) are used in the preparation of herbal medicines because they have medicinal properties. The species *Moringa oleifera* lamarck belongs to the Moringacea family, is popularly known as white lily, white wattle or okra, is a plant native to India and found in several regions of the Middle East and in tropical and subtropical areas and in Brazil [30]. It is a small tree with rapid growth, reaching up to 12 m in height [38].

The bioactive compounds present in this plant have been linked to a range of health benefits, including strengthening the immune system, modulating blood glucose levels, and potentially lowering cholesterol. Preliminary studies also suggest anti-inflammatory, antioxidant, and even anticancer effects in certain contexts [46].

Moringa also has great value in agriculture. Its leaves are highly appreciated as a source of organic fertilizer, contributing to the improvement of soil fertility. In addition, *Moringa* trees are famous for their deep roots, which play an important role in stabilizing the soil by preventing erosion. The seeds of the plant have also been used to purify water, removing impurities and making it suitable for human consumption [18].

Due to its high levels of beta-carotene and polyphenols, *Moringa oleifera* is widely used to prevent diseases, such as atherosclerosis, which can be combated due to its antioxidant effect [25, 28]. In addition, it contributes to strengthening the cardiovascular system [29, 30]. Studies also indicate that M. oleifera plays a role in lowering blood cholesterol levels, as noted by Mabrouki et al. in 2015 [27].

In traditional Chinese medicine, in tropical Africa, America and Asia, *Moringa* is used to treat systemic arterial hypertension, thus showing considerable potential to prevent cardiovascular disease [26, 37]. The natural chemical compounds, such as thiocarbamate, glycosides, isothiocyanate, methyl p-hydroxybenzoate, and β-sitosterol found in the aqueous and alcoholic extracts of the seeds and pods, have been shown to have a significant effect on lowering blood pressure. The reduction in blood pressure was mainly attributed to these components present in the extract [5].

The increase in the consumption of *Moringa* oleiferae due to its pharmacological benefits and potential The present integrative literature review aimed to search for and present current evidence about the pharmacological potential of this species on cardiovascular diseases.

MATERIALS AND METHODS

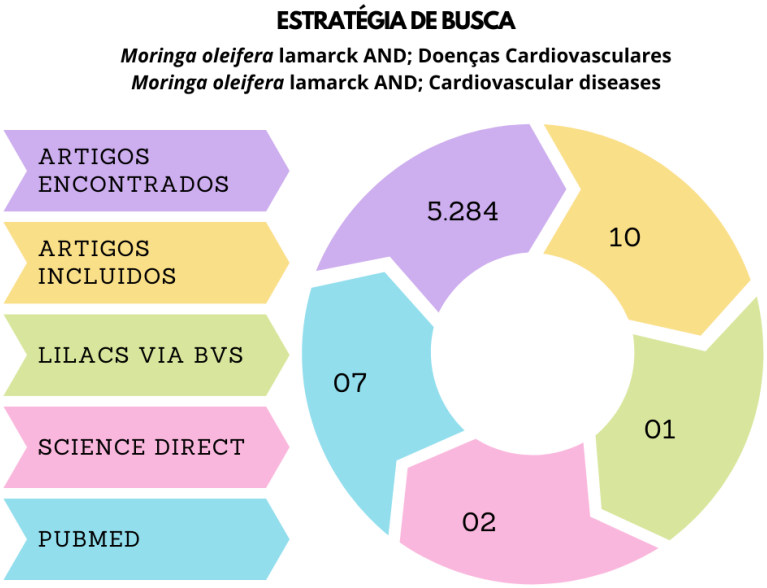
This is an integrative literature review with a qualitative and descriptive approach, as a way to enable the synthesis and analysis of scientific knowledge. The integrative review seeks to report in an organized way the results that are acquired on the theme that is desired, configuring the order of the findings in an organized and comprehensive way, even if it is comprehensive [19]. Before the development of the study, the hypothesis and objective of the integrative review were established; the criteria for inclusion and exclusion of articles were determined; The information collected from the selected articles was characterized and the results were analyzed and discussed.

To obtain the data for this study, the following databases were used: Virtual Health Library (VHL), Latin American and Caribbean Health Sciences Literature (LILACS), ScienceDirect, National Library of Medicine Service of the United States for free access to Medline (PubMED), and Scientific Electronic Library Online (Scielo) using the following descriptors in health science (DeCS/MeSH) *Moringa oleifera (Moringa oleifera*) Intention-to-Treat Analysis, and Heart Diseases were selected from articles written in Portuguese, English, and Spanish *Figure 1*. To combine the

descriptors, the Boolean operator "AND" was used, thus allowing combinations between the expressions.

The inclusion criteria used were original articles in English and/or in Portuguese and their respective descriptors in English, which presented works according to the proposed theme, between the period 2016 and August 2023 and as exclusion criteria, studies that did not contemplate the proposed theme, duplicates in the databases, articles from systematic or integrative reviews and articles not available in full were excluded from the study. The selected articles were presented in *Table 1* so that there could be data separation and better analysis. The results were organized according to the author's name, year of publication, name of the journal in which it was published, type of study, objectives, methodology, sample/groups, and outcomes, aiming at the reader's understanding.

Figure 1: Flowchart for the search and selection of studies



Source: The author's, 2023.

RESULTS AND DISCUSSION

According to the World Health Organization (WHO), the medicinal plant is defined as: "any and all plants that have, in one or more organs, substances that can be used for therapeutic purposes or that are precursors of semi-synthetic drugs" [44]. As recently as 2011, the World Health Organization estimated that by 2025, approximately 1.6 billion adults will suffer from hypertension and cardiovascular complications [43, 45].

Cardiovascular diseases are the leading cause of morbidity and mortality worldwide. Among cardiovascular diseases, hypertension is the main risk factor that contributes to the development of many diseases [11, 12].

In this context, the use of medicinal plants and their derivatives for the treatment of cardiovascular diseases are well accepted by traditional medicine around the world. The leaves, seeds, bark, roots, sap, and flowers of *Moringa oleifera* are widely used in traditional medicine, and the leaves and pods of immature seeds are used as food products in human nutrition [38, 35, 43].

The articles that were selected to compose this review were described in *(Table 01),* in summary, 5,284 articles were found, where through the inclusion criteria only 10 fit within the study. The referenced studies were carried out with the aim of describing the therapeutic potential of *Moringa oleifera* Lamarck on cardiovascular diseases.

Table 1 - Summary of selected articles involving a study demonstrating the pharmacological effects of Moringa oleifera Lamarck on the cardiovascular system.

AUTHOR	MAGAZINE/DOI	OBJECTIVE	DOSES/TREATMENT TIME	PART USED / ACTIVE INGREDIENT	PHARMACOLOGICAL EFFECT
[34] Randriambo *et al.*, 2016	AmericanJournalofHypertension DOI: 10.1093/ajh/hpw001	To investigate the cardiac effects of oral administration of *Moringa oleifera* seed powder (MOI) in spontaneous hypertensive rats (SHR).	750 mg/kg/day; 16 weeks	Seeds	Reduction of left ventricular fibrosis of MO-treated HRS. Upregulation of PPAR-α and δ signaling.
[9] Cheraghi *et al.*, 2017	Journal of Microencapsulation DOI: 0.1080/02652048.2017.1311955	To verify the cardioprotective effect of N,α-L-rhamnopyranosilvincosamide (VR), isolated from *Moringaoleifera* leaves in rats.	200 kg/kg/dia 12 weeks	N,α-L-rhamnopyranosylvincosamide – leaf alkali	Reduced levels of glutathione peroxidase and superoxide dismutase increased after administration of VR, this extract also reduced the initially increased level of malondialdehyde enzymes in cardiac tissue.
[32] Randriamboet al., 2017	*Oxidative Medicine andCellularLongevity* DOI: 10.1155/2017/4129459	To evaluate the in vivo pharmacological efficacy of a diet containing MOI seeds to reduce oxidative and nitrosative stress and vascular inflammation in SHR.	750mg/day/rate; SHR MOI group) for 20 weeks	Seeds	Enhancement of the antioxidant and anti-inflammatory effect of orally administered MOI seeds and their beneficial action on endothelial function in a rat model of hypertension.
[12Dixit] *et al.*, 2018	Diabetes Obes. Metab • DOI: 10.1111/Sun.13443	To reassess the efficacy of LI85008F weight loss in healthy overweight adults through a 16-week	900 mg/day (human study). 16 weeks of treatment.	Leaves (aqueous extract).	Decreased body weight, BMI, total body fat, waist and hip circumference, and LDL. Increased HDL

		randomized, double-blind, placebo-controlled clinical trial.			
3Aekthammarath, Pannangpetch & Tangsucharit, 2019	*Phytomedicine* DOI.org/10.1016/j.phymed.2018.10.023	Investigating the aqueous extract of *Moringa oleifera* leaves (MOE) could alleviate N-ω-nitro-L-arginine-methyl ester (L-NAME)-induced high blood pressure via modulation of vascular function and antioxidant properties.	EOM (30 and 60 mg/kg/day), EOM bolus injection (0.001–3 mg), 3 weeks of treatment	Leaves (aqueous extract)	Reduction of BP, HR, vascular production of O2− and MDA level in plasma and thoracic aorta. Increased SOD and dose-dependent vasorelaxation in the endothelium of mesenteric arterial beds
[33] Randriambo *et al.*, 2019	*Oxidative Medicine andCellularLongevity* Doi.org/10.1155/2019/2567198	To investigate the beneficial effects of MOI seeds against aging-related vascular dysfunction in middle-aged Wistar rats (MAWR) by analyzing endothelial function in conductance (aorta) and resistance (mesenteric).	750kg/day/4 weeks	Seeds	Increased Akt Signaling and NO endothelial synthase. Decrease in Arginase-1. Endothelial relaxation.
[23] Kundimi *et al.*, 2020	Lipid Health Disorders DOI: 10.1186/s12944-020-01376-7.	To investigate the thermogenic potential of LI85008F in obese Sprague Dawley rats induced by high-fat diet	100 and 250 mg/kg/day/28 days	Ethanolic extract of leaves	Increased Resting Energy Expenditure (REE), fatty oxidation Decrease in total body fat mass, WAT fat mass and cell size, liver weight, liver triglycerides, and serum leptin level
[7] Chan Sun et al., 2020	J Am Coll Nutr DOI: 10.1080/07315724.2019.1608602.	Monitor the Effect of Eating Cooked *Moringa Oleifera* Leaves on Healthy Participants' Blood Pressure (BP)	120g of *M. oleifera* leaves cooked for a week in 41 Humans	Cooked leaves	Decrease in postprandial blood pressure after 2 hours.
[2] Aekthammarat *et al.*, 2020	Journal Biomedicine & Pharmacotherapy	To evaluate the antihypertensive mechanisms	Doses: 1, 3, 10 and 30 mg/kg extract.	Leaves (aqueous extract)	EOM reduces arterial BP by inducing relaxation of the small resistance artery,

	DOI: 10.1016/j.biopha.2020.110605	of EOM. We investigated the role of endothelium-derived NO in BP reduction and vasorelaxant activities endothelium-dependent in responses to EOM using in *vivo* and ex vivo approaches	30 min after administration of L-NAME		primarily *through* activation of the eNOS-NO-sGC pathway.
[27] Mabroukiet al., 2020	*Biomed. Res. Int.* DOI: 10.1155/2020/6583603.	To evaluate the effect of methanolic extract of *Moringa oleifera* leaves (MEML) on high-fat diet-induced obesity (HFD-) and cardiac damage in rats	200 and 400 mg/kg BW; 12 weeks of treatment	Leaves (methanolic extract)	Decrease in BW, TC, TG, LDL, CK-MB, AST, ALT and lipid peroxidation levels, Increased Activity of HDL, SOD, CAT and GPx

Caption: MOE: Morina Oleifera Lamarck; BP: Blood Pressure; GER: Resting energy expenditure; WAT: White adipose tissue; Akt: Serine-threonine kinase; RV: α-L-rhamnopyranosilvincosamide; NO: Nitric Oxide; HR: Heart Rate; e-NOS: Endothelial Nitric Oxide Synthase; MDA: malondialdehyde; BMI: body mass index; *CAT*: Catalase enzymes; *SOD*: Superoxide dismutase; GPx: glutathione peroxidase; LDL: low-density lipoprotein; HDL: high-density lipoproteins; CK-MB: creatine kinase-MB; AST: aspartate transaminae; AST: Aspartate Aminotransferase; TC: Total Cholesterol.

A study conducted by Mabrouki *et al*, (2020) [27] evaluated the therapeutic potential of methanolic extract of *Moringa oleifera* leaves (MEML) in the treatment of obesity, as well as its protective effect on cardiac disorders induced by a high-fat diet. In their research, to determine whether obesity is a primary factor contributing to oxidative stress in heart tissue, lipid peroxidation, a marker of oxidative damage, was observed.

M. oleifera is rich in protein, vitamin A, minerals, essential amino acids, antioxidants, and flavonoids, as well as isothiocyanates [41, 46], and M. oleifera leaves are rich in beta-carotene, vitamin C, vitamin E, and polyphenols and are a good source of natural antioxidant [36, 40]. Lipid peroxidation expressed by thiobarbituric acid reactive substances (TBARS) was significantly increased in the HFD (*High-fat diet*) group of rats compared to the control group. However, the administration of MEML resulted in a significant reduction of TBARS to near-normal values, also improving, in a dose-dependent manner, the levels of antioxidant enzymes [47].

Kundimi et al, (2020) [23] combined 60% OM to turmeric rhizome extract *at doses of* 100 and 250 mg/kg body weight for 28 days in rats which significantly reduced body weight, inguinal white adipose tissue fat cell size and epididymal white adipose tissue (WAT), however there was no significant difference in decreasing brown adipose tissue fat (BAT). Although the authors did not

explain the darkening of WAT or the modulation of BAT to increase energy metabolism, there was also an increase in the expression of uncoupling protein 1 (UCP1) and the negative expression of key adipogenic marker proteins (perilipin, aP-2α, C/EBPα, CD36 and PPARγ.

Administration of a magnetic hydrogel nanocompound of α-L-rhamnopyranosyl vincosamide (VR) isolated from MO leaves (VR-MHN) also showed a reduction in the size of isoproterenol-induced myocardial infraction in rats due to the cardioprotective potential of VR-MHN due to its antioxidant properties, protecting the heart from the actions of free radicals [9].

Assays revealed that antioxidant activity of *both Moringa oleifera* extract (MOE) and ascorbic acid were increased in a concentration-dependent manner in hypertensive animals induced by L-NAME. After treatment with MOE (30 and 60 mg/kg/day) for 3 weeks, it was found to have significantly suppressed the production of vascular hydrogen peroxide and reduced MDA levels in the plasma and aorta of L-NAME hypertensive rats, verifying that MOE has the ability to attenuate high blood pressure, in addition to reducing adrenaline-mediated vasoconstriction in the artery of L-NAME hypertensive rats. Treatment with MOE also reduces systemic and vascular oxidative stress in hypertensive rats [1, 3]

The NADPH oxidase (NOX) family of enzymes is one of the main sources of reactive oxygen species - ROS in the cardiovascular system, the treatment of spontaneously hypertensive rats (SHR) with (750mg/kg/day) for 20 weeks with feed made from *Moringa oleifera seeds* has been shown to be efficient in reducing the expression of NADPH oxidase and regulated the expression of SOD2 [34]. Oxidative stress is known to be causally involved in endothelium dysfunction associated with hypertension [32].

In agreement with the antioxidant effect of OM, a reduction in nitrosative stress was observed in aortas of SHR rats treated with OM, associated with a reduction in the expression and/or activation of the transcription factor (NFκB p65) and the inducible NO-synthetase enzyme (iNOS), thus revealing an anti-inflammatory action of Moringa oleifera extract *[33].*

One study demonstrated that *Moringa oleifera extract* (MOE) caused vasodilation in mesenteric beds isolated from hypertensive rats by inhibition of the enzyme NO-synthetase with L-NAME, in the endothelium-dependent effect appears to involve the stimulation of hyperpolarizing factors. On the other hand, the independent action of the endothelium seems to be mediated by the blockade of the entry of extracellular Ca2+, as well as by the blocking of the release of intracellular Ca2+ via Ca2+-sensitive channels to IP3 [39]. Therefore, MOE has potential as a natural vasodilator to treat hypertension and other vasoconstriction-related conditions [1].

Mabrouki et al (2020) [26] reported in their study that rats treated with a high-fat diet - *High-fat diet* (HFD), suffered cardiac damage, evidenced by disorganized myocardial fibers associated with interstitial edema, inflammatory cells, and myocardial fibrosis. However, the histopathological

abnormalities were not of the same severity in the animals treated with methanolic extract of *Moringa Oleifera* (MEML). In the same study, Mabrouki et al (2020) [20] concluded that histological evidence indicated that doses of the methanolic extract of *M. oleifera* (200 and 400 mg/kg) played an effective role in treating obesity and reducing cardiometabolic abnormalities.

According to Koike *et al.* (2020) [20] in their study verified the beneficial role of *Moringa oleifera* seed against hypertension-induced cardiac functional and structural remodeling and scientifically support the empirical use of this plant to treat cardiac complications due to blood pressure overload. Chan Sun *et al* (2020) [7] conducted a prospective placebo-controlled clinical study on 41 healthy individuals, the participant group ingested 120 g of *Moringa oleifera* (OM), while the control group ingested only water, it was observed that systolic and diastolic BP decreased after 2 hours of its ingestion by the control group, this study did not perform photochemical analysis of OM leaves However, the possible reduction in blood pressure can be attributed to the free radical scavenging activity of nitrile, thiocarbamate and isothiocyanate.

Dixit et al (2018) [13] verified the effect of OM on 66 healthy overweight adults. Daily intake of a 900 mg dose for 16 weeks also significantly reduced body weight, BMI, total body fat, waist and hip circumferences, as well as decreased LDL and increased HDL levels.

Randriambo a vonjy et al, (2016) [36] evaluated the protective effects of *Moringa oleifera* seeds in spontaneously hypertensive rats. The seeds were inserted into the diets of the rats under treatment and resulted in a reduction in nocturnal heart rate when the animals were awake and active, with no change in daytime heart rate, and this effect was significant after 10 days of treatment. In addition, the left ventricular (LV) internal diastolic diameter was significantly reduced in spontaneously hypertensive (SHR) rats, however treatment with *Moringa oleifera* restored this parameter, evidencing its cardioprotective effect, reducing cardiac remodeling and fibrosis.

The same study shows that treatment with *M. oleifera* affected signaling pathways involved in LV pressure overload-induced hypertrophy, in particular the mechanisms related to calcium ion dynamics. The potential target of treatment with *M. oleifera* may be calcineurin, whose activity progressively increased with age in the heart of SHR and its inhibition reduces the development of hypertrophy [36].

Randriambo a vonjy et al. (2017) [34] in another study demonstrated that *M. oleifera* reduces oxidative stress in SHR aortas, through the evaluation of *in situ production* and topographic distribution of superoxide radical ($O2^{\cdot-}$) in aortic sections of the animals tested. The aortas of SHR showed a marked increase in EtBr (ethidium bromide) fluorescence which reflects in a high oxidative tension in the vascular wall, in contrast, aortic sections of SHR rats treated with *M. oleifera* were comparable to those of the control, evidencing its vascular and systemic antioxidant effect.

In a study with Moringa oleifera *leaf extract* in rats, Aekthammaratet al. (2020) [1, 4] demonstrated an increase in nitric oxide (NO) production, resulting in relaxation of the aorta and mesenteric arteries with participation of the eNOS-NO-sGC pathway, however, not involving the cyclooxygenase (COX) enzyme. Another study demonstrated that Moringa oleifera *extract* (MOE) reduced blood pressure by inducing relaxation of the small resistance artery, by involving the eNOS-NO-sGC pathway [2, 16].

CONCLUSION

With the present study, it can be concluded that *Moringa oleifera* Lamarck has prominent therapeutic activity that is mainly attributed to the considerable amounts of health-promoting nutrients and phenolic compounds present in this plant. Consuming moringa can be beneficial in a number of ways. Its leaves are rich in nutrients such as vitamins, minerals, and antioxidants, promoting overall health, strengthening the immune system, and reducing inflammation. It can also help regulate blood sugar levels, improve skin health, and contribute to the fight and prevention of cardiovascular disease. *Moringa oleifera* has a beneficial role against the functional and structural cardiac remodeling induced by hypertension, beneficial action on endothelial function and other cardiac complications.

Therefore, due to its therapeutic potential, the studies selected here to compose this review may suggest the interest of dietary supplementation with *Moringa oleifera* seeds for middle-aged or elderly people in order to limit aging-related endothelial dysfunction and prevent the development of cardiovascular diseases, being particularly relevant in countries that may have limited access to pharmacological treatments. As a non-medicated means for healthy aging in addition, its cultivation is relatively easy and can be a sustainable source of food and resources for communities. It is indisputable that there is a need for more specific research in order to explore possible drugs or nutraceuticals from this plant for the treatment of various conditions, especially cardiovascular disorders.

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