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Chapter 6

Safety and Efficacy of *Moringa oleifera* Lamarck (1785) — Therapeutic and Toxicological Properties

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1. Introduction

About 80% of the worldwide population use herbal products for their basic health care (primary care), such as extracts, teas and their active principles [1]. Despite the interest in molecular modeling, combinatorial chemistry and other chemical synthesis techniques by institutions and pharmaceutical industries, the natural products, particularly medicinal plants, persist as an important source of new therapeutic agents against infectious (fungal or bacterial) and cardiovascular diseases, insects, cancer, immunomodulation and on nervous system diseases [2-7].

According to the World Health Organization, medicinal plant is any plant that contains, in one or more of its organs, substances that can be employed for therapeutic purposes or used as precursors of substances utilized for such purposes [1]. The phytotherapic, in turn, is a drug obtained exclusively based on active vegetables raw material and is characterized by knowledge of its effectiveness and risks of their consumption as well as the

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reproducibility and consistency of its quality [8]. Therefore, the production of vegetal drugs obeys specific laws in a way to maintain attributes and properties from manufacturing to importation and marketing, whatever use (oral and topical) or manner of preparation (infusions, decoctions and macerations) [9].

The most hazardous concept is that which declares that medicinal plants are nontoxic and without risks to human health since they are natural and have been tested worldwide through centuries. Adverse events, including 101 deaths associated with dietary supplements were reported to the FDA (Food and Drug Administration), but these adverse effects were not well reported whereas there is no an efficient monitoring system in the United States like that for allopathic medicines [10]. Researches conducted in the United Kingdom suggest an incidence around 7% attributed to plants and phytotherapics. Studies conducted in Taiwan and Hong Kong hospitals showed an admission rate caused by plants ranging from 0.2 to 0.5% [11,12]. In Brazil, there were 1037 reports of human poisoning with plants in 2009 (1.29% of total), with 61.9% of poisonings occurred in patients with 1-9 years old. About 0.31% deaths were directly linked to herbal poisoning [13]. The quality of the commercialized medicinal plants, the population inexperience, the origin of the plant, period and methods of collection, storage, drying, packaging, contamination by fungi and other microorganisms and the quantity ingested are factors that obscure the diagnosis and complicate the treatment in cases of poisoning by toxic plants [14,15].

The folk usage of the different parts of *Moringa oleifera* reproduces the general and indiscriminate use of plants in order to treat or (even) cure diseases without regard to their toxic potential. Thus, this chapter aims to review the pharmacological and toxicological potential of *M. oleifera* and their purposes for use and consumption.

2. Taxonomy, distribution and general use and consumption

Moringa oleifera Lamarck, 1785 (synonymy *Moringa pterygosperma* Gaertn.) is the most widespread species belonging to the Moringaceae family (Papaverales Order, Figure 1A), which possess additional 13 species of trees and shrubs originally spread in several Asian countries, such as India, Pakistan, Bangladesh, Afghanistan and Sri Lanka [16,17]. However, *M. oleifera* has been cultivated and introduced in several parts of tropical regions in the world such as Malaysia, Philippines, Singapore, Thailand, Mexico, Peru, the Caribbean Islands, Paraguay and Brazil [16,18].

With several popular names such as “morunga”, “árbol de rábano”, “árbol de los espárragos”, horseradish tree, drumstick tree, never die tree, “sajna”, Ben oil tree, “lírio-branco” and “quiabo de quina” [16-19]. *M. oleifera* is a deciduous and allogamous plant which grows even in poor soils (pH 5-9) and arid climates, being slightly affected by drought (250-300 mm/year). Its fruits present 12 seeds (in average); they are dry, simple and brown (when mature), possessing a dehiscent loculicide capsule with a triangular aspect (Figure 1B). Its embryo is oleaginous, has a pair of cotyledons and a cryptocotyledonary hypogeal germination that

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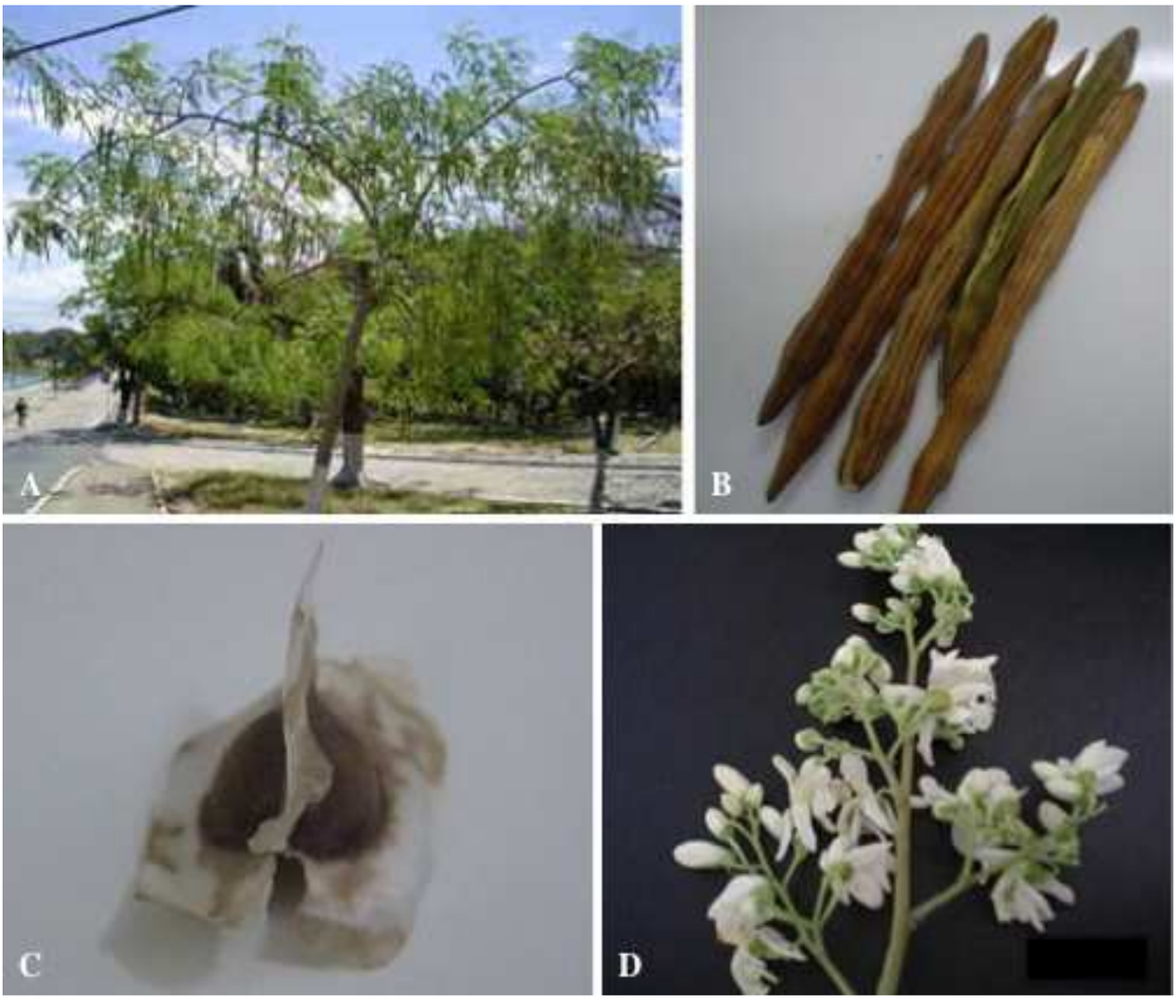

Figure 1. Parts of *Moringa oleifera* Lam. A-Plant; B-Pods; C-Seed; D-Inflorescence. Source: Personal archives.

begins between 5-8 days after seeding [20,21]. Root development presents positive geotropism; the central root is thick, long and with secondary ramifications [21].

Its seeds are anemochoric, bitegumetend, exalbuminous and winged (Figure 1C), making seed dispersal more effective [21]. They can be introduced directly in a definitive way or in seedbeds, though their dissemination can also be made by poles, without previous exceptional requirements, growing quickly up to 4m in the first year and 15 m in height in development later stages. Under favorable conditions, a plant might produce 50-70 kg of fruits/year [18,20,21].

Historically, ancient Romans, Greeks and Egyptians utilized all parts of the plant for human consumption as well as Asian communities have been made now [3, 16]. This primeval use in the East World has been attributed to its Asian origin and a massive popular use of the flora in the Asiatic continent [22]. The flowers (Figure 1D) are rich in $Ca^{2+}$and $K^{+}$and leaves are widely used as food complement, with appreciable amounts of vitamins [(A, 7-fold higher than in oranges), B and C], $Fe^{2+}$and proteins [23-25]. Leaves put in soups are used by Philippines'

women to improve the breast milk production and possess 4-fold the calcium in milk [16,26]. The roots, presenting alkaloids (0.2% of total), are scarcely consumed [16, 27]. However, when powdered, are appreciated as a spicy flavor similar to that showed by horseradish, explaining why the plant is commonly called "Horseradish Tree".

The seed oil is used in industry to manufacture cosmetics, lubricate machines and clocks, such as cooking oil, fuel for lamps and it is highly appreciated in perfume industries due to its ability in retaining fragrances [16] and high stability to oxidative rancidity [28]. Cooked fresh pods are very consumed in Haiti due to its taste comparable to asparagus or green beans; when dried and crushed, they show suitable characteristics to substitute traditional beds of laboratory animals (pine, for example), exhibiting a high absorptive capacity, low concentration of antinutritional compounds and endurance to autoclaving [29]. Stems are extensively used in paper factories and construction of furniture and fences [24].

The approximate composition of *M. oleifera* seeds shows levels of proteins (377.5 ± 1.9 g/kg dry matter) higher than those found in important legumes for human nutrition (149-220 g/kg) [30-32]. In fact, cytochemistry analysis performed in [33] detected a large amount of cotyledonary protein bodies. The oil content (363.2 ± 2.6 g / kg) is greater than that of soybean varieties [32]. The main saturated fatty acids found in this oil are behenic, palmitic, stearic and arachidic, also containing appreciable quantities of unsaturated fatty acids, especially oleic (65-80%) [28,31], which are desirable in terms of applications and nutritional stability for cooking and frying. Vegetable oils with a high percentage of oleic acid has received much attention since the association of diets rich in saturated and unsaturated *trans* fatty acids and increased risk of cardiovascular diseases due to high cholesterol levels have been documented [34].

M. oleifera (leaves, in particular) have also shown a great potential for animal feeding but this approach is underexplored. A complete drying process takes 72 h and yields 1kg of flour from 10 kg of fresh material. Dried powdered leaves have shown promising results to feed fishes [35], chickens [36] and sheep [37,38].

Additionally, studies demonstrate that the high content of proteins has ideal levels of essential amino acids and good availability for intestinal absorption and rumen degradability of nitrogen comparable to soybean meal [30,39,40], indicating a great potential of the leaves as a food supplement for ruminants, though little is known about changes that these proteins may cause in the final composition of the milk or how they may affect the animal growth. Recently, leaves and twigs' flour prepared by drying and grinding was given in substitution to the standard feedstuff of grass (*Pennisetum purpureum*) during six days to lactating cows. Presenting an apparent digestibility index similar to the standard diet, no changes were found in milk composition. On the other hand, cows fed with concentrated soybean meal produced more milk (13.2 kg/day), revealing better energy content in comparison with those that consume moringa meal (12.3 kg/day) [41]. In this event, the hypothesis that meal would influence organoleptic characteristics of milk are not corroborated, since the color, taste and smell remained unchanged, an encouraging finding for farmers who usually face problems with beef cattle undernutrition due to limitations in quality and/or quantity of the feed available.

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In a study of 45 days exposure, sheep were fed with 4-6 g/day of MO delipidated seeds. It was found a significant increase in body weight gain with 4g/day of supplementation, corroborated by a higher nitrogen retention and efficiency in the microbial nitrogen production. These animals also showed elevated levels of plasmatic glucose [38], suggesting a relationship between sugar absorption rate and metabolizable energy intake. This result indicates that intake of 4g/day improved diet energy value due to, at least in part, the alterations in gastro-intestinal tract microbial population which led to upper fermentative efficiency than those cows fed only with soybean meal. In another report, rats that consumed the aqueous extract of seeds during 30 days showed increased serum albumin and retention of body nitrogen (67.53 ± 2.49 g/100 g) compared to the control group that consumed only tap water (59.55 ± 3.02 g/100g) [32]. The albumin capacity in acting as a reservoir of amino acids may explain the improvement in body nitrogen, since those amino acids not incorporated into a high molecular weight protein are rapidly eliminated by the urinary system [42].

It is known that the seed meal has high levels of essential amino acids, except to lysine, threonine and valine amino acids which are present at low amounts and are important for children nutrition between 2-5 years-old. Elevated contents of methionine and cysteine residues are close to that realized in human and cow's milk and hen eggs. This abundance in essential amino acids stimulates its use as an excellent food supplement for vegetables that are normally poor in sulfur amino acids. Concerning mice requirements in growth phase, the lysine is the first limiting amino acid in the seeds, followed by isoleucine and leucine [30,43]. When added as a supplement to a child's diet, just 25 g of the leaf powder supplies all the calcium and vitamin A daily needs, about half the protein and potassium, and about three-quarters of the iron daily needs [44]. With advances in molecular techniques to manipulate genes, the seeds serve as ideal model for improving the protein quality of foods.

3. Coagulating properties

There are troubles of water distribution for human consumption in many parts over the world. To treat this water before distribution, inorganic and synthetic compounds have been used for sedimentation, filtration and disinfection. Aluminum [aluminum sulphate, $Al_2(SO4)_3$] and iron [ferric sulfate, $Fe_2(SO_4)_3$] salts, positively charged, lead to the flocculation of negative particles in water via neutralization [45]. Notwithstanding this extensive usage, these salts and synthetic polymers have high costs and low distribution, making their use in developing countries and impecunious sites an interfering economic factor that affects the quality of drinking water [45,46]. Although alum and iron salts are the most widely used chemical coagulants for community drinking water treatment, other coagulants have been and are being used to coagulate household water at point of use, including alum potash, crushed almonds or beans and seeds of *Moringa oleifera* [47]. Some reports describe organic coagulants consisting in polysaccharides, proteins and especially starches, among which are highlighted the cassava flour, arrowroot and potato starch [48], which emphasize the natural coagulants' value as safer and ecologically more acceptable.

Moringa oleifera seeds have been employed as an alternative source to clean water, replacing synthetic coagulants [17], which are often expensive and associated with diseases, such as cancer and Alzheimer [49,50]. Moringa seeds are also used to clean, by flocculation, vegetable oils and irrigation, tap and waste waters, removing algae, volatile organic compounds and heavy metals from the liquid under treatment [46,51-53]. In Brazilian Northeast, they are crushed and put in containers (such as pots, 30-200 mg of seeds/liter of water) to storage water temporarily [19].

Advantages in exploiting the seeds include coagulation efficiency comparable to aluminum salts, complete degradation, pH maintenance, water conductivity, concentration of anions and cations [46,54], and its ability to dramatically decrease bacteria content in 99.9% [55,56]. Stored seeds up to 18 months kept the turbidity reduction in similar percentages. On the other hand, seeds with 24 months displayed a significant reduction in flocculation efficiency. Flocculating effects are greater at pH 6.5 while low temperature (< 15 °C) drops the efficiency of this process [57]. Cationic peptides of low molecular mass (6-16 kDa) are considered the main responsible for sedimentation of the suspended material in water, juices and drinks [56,58,59]. On the other hand, a non-protein active component with 3kDa isolated from seeds was able to flocculate a kaolin suspension [60].

In reference [61] have shown that a seed recombinant protein (isoelectric point of 12.6) expressed in *Escherichia coli* was capable to flocculate rhizobacteria and clay, suggesting that microorganisms undergo sedimentation similar to the colloids. Recently, in [62] also showed the clarifier competence of tablets produced with moringa seeds, which were able to remove oil from water utilized in petroleum extraction with efficiency percentages ranging from 76% (coagulant extracted in aqueous medium) to 96% (coagulant extracted in saline). The principal inconvenience of seeds in water purification is the augmentation in organic matter during treatment [46]. Thus, the water treated with seeds should not be stored for a period longer than 24 h, since the richness in nutrients promotes quick growth of microorganisms.

4. Pharmacological properties

Many medicinal properties of *M. oleifera* have been constantly supported by scientific works and reflect the folk knowledge of its therapeutic qualities (Table 1).

4.1. Antioxidant, antiulcer, hypocholesterolemic and hypotensive

Medicinal plants are good sources of cytoprotective compounds [2]. A single dose (150 mg/kg body weight) of methanolic extract of *M. oleifera* leaves protected bone marrow against chromosomal alterations (aberrations, metaphasic chromosome breaks and micronucleus formation) in mice exposed to gamma irradiation, allowing regeneration of hematopoietic stem cells and increasing survival of the animals [63]. This anticlastogenic effect was also seen in animals treated for 14 consecutive days with a diet enriched with increasing percentage of pods (cooked and pre-frozen), decreasing the number of micronucleated peripheral erythrocytes induced by mitomycin C exposure [64].

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Pharmacological Activity	Part of plant	Reference
Abortifacient	Leaves, roots	[113], [114]
Against *Plasmodium falciparum* and *Schistosoma mansoni* cercariae	Seeds	[105], [106]
Analgesic	Roots	[27], [84]
Antiatherosclerotic	Leaves	[69]
Anticlastogenic	Leaves, pods	[63], [64]
Anti-constipant	Flowers	[109]
Anticonvulsant	Leaves, roots	[27], [103], [104]
Antiespasmodic	Leaves, seeds	[80]
Antihelminthic	Seeds	[53]
Anti-inflammatory	Seeds, leaves, roots	[80], [81], [82], [83]
Antioxidant	Leaves, seeds	[24], [25], [26], [63], [67], [68], [70]
Antipyretic	Leaves	[18]
Antitumor	Seeds, stem, leaves	[68], [72], [87], [88]
Antiulcerogenic	Leaves, seeds	[65], [66]
Bactericidal	Leaves, stem, pods	[17], [93], [97], [94], [95], [96]
Bradycardic/Hipotensive	Seeds	[77], [78], [79]
Diuretic	Seeds	[80]
Fungicide	Leaves, seeds	[91], [92], [93]
Hepatoprotective	Seeds, leaves	[109], [121]
Hypocholesterolemic	Leaves, seeds, stem	[73], [74], [75], [76]
Immunomodulatory	Seeds	[32], [74], [98], [107]
Larvicidal	Seeds	[32], [100]
Pupicidal	Seeds	[98]
Purgative	Leaves	[18]
Repellent	Seeds	[98]

Table 1. Pharmacological properties of *Moringa oleifera* Lamarck, 1785 (Moringaceae).

The leaf methanolic extract (100 and 150mg/kg) inhibits significantly the formation of gastric lesions caused by acetylsalicylic acid (55 and 78.3%), serotonin (86.5 and 92.4%), indomethacin (86 and 88 8%) and acetic acid (66.2 and 73.4%), respectively, and improves the healing rate of gastric ulcers induced by acetic acid [65]. In a similar way, water extract of *M. oleifera* leaves caused an enhancement of enterochromaffin cell (EC) density with increased 5-hydroxytryptamine (5-HT) content as well as mucosa thickness, showing maximum stomach protection at a dose of 300 mg/kg against lesions induced by aspirin as evidenced by increased mean ulcer index. Treatment with this extract after 14 consecutive days also reduced the severity of ulcer formation [66]. 5-HT is a key regulator neurotransmitter of smooth muscles of cardiovascular as well as gastrointestinal tract, being found in high concentration in EC cells [42]. So, the healing of gastric damage proposed is likely related to the 5-HT releasing from EC cells, which augments mucus secretion via cyclooxygenase pathway, inducing prostaglandin (PG) synthesis, especially PGE_2 and PGI_2, and leading to cytoprotection.

Antioxidant compounds from *M. oleifera* have also been frequently pointed as responsible by the antiatherosclerotic, antigenotoxic, anti-ulcerogenic, hypocholesterolemic and anti-inflammatory properties in the plant. Indeed, leaves, stem bark, flowers and/or seeds have significant quantities of antioxidant molecules such as α-, β-and γ-tocopherols, stigmasterol, campesterol [28,67], quercetin, kaempferol, vitamin A and C and polyphenols [25,68-70]. In India and Philippines, fresh leaves are used to preserve foods, suggesting that they are suitable source of antioxidants [26]. β-sitosterol, a vegetal sterol similar to cholesterol existing in hybrid varieties of *M. oleifera*, seems to be a compound capable of lowering plasma LDL-C (low density lipoprotein cholesterol) [71,72].

The authors of the reference [73] demonstrated that treated rabbits with ground cooked seeds (200 mg/kg/day) showed reduction in plasma levels of total cholesterol (TC), phospholipids, triglycerides (TG), LDL-C and VLDL-C (very low density lipoprotein cholesterol) as well as decreasing in lipid content in kidney, liver, heart and aorta. In this way, [74] and [75] working with similar doses (400 and 300-600 mg/kg, respectively) showed substantial increase in HDL-C (high density lipoprotein cholesterol), the latter also demonstrating dropping in blood levels of TC, TG, LDL-C and VLDL-C. This HDL-C increasing is a desirable event in an ideal hypocholesterolemic agent, since it indicates a possible role in reducing the atherosclerosis incidence. Related findings were seen in [69] and [76], who also divulged the great therapeutic potential and prevention of cardiovascular diseases showed by the water extract of leaves, reducing serum TC and TG and declining formation of atheroma plaques with efficacy equivalent to simvastatin.

The research [69] suggest a direct relationship between phenolic compounds present in leaves and hypolipidemic action, demonstrating that the water extract inhibited oxidative modifications in LDL-C molecule and probably suppressed initiation and propagation of lipid peroxidation and cellular damage induced by free radicals at levels similar to vitamin E [42, 68]. Since vitamin C might scavenge free radicals and regenerate, indirectly, vitamin E [42], this synergism between vitamins A and C have attracted interest as agents to delay and/or blockade atherosclerosis by LDL-C oxidation reducing as a way to keep the intracellular redox state and avoid damage to endothelial cells. Then, it is possible that the atherogenic index decreasing

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could represent an anti-inflammatory action of antioxidants present in *M. oleifera* leaves, seeds and stem bark, since atherosclerosis is a chronic inflammatory and degenerative process that affects blood vessels.

Correlated with cardioprotective effects, extracts from leaves, stem bark and pods and nitrile compounds, mustard glycosides and thiocarbamates isolated [4-(α-L-rhamnosyloxy)-benzyl isothiocyanate (Figure 2A), niazirinin, niazinins (A and B) and niaziminin] has negative inotropic and chronotropic effects on heart musculature causing bradycardia and hypotension (1-20mg/kg), suggesting that amide or-N=C-moieties and/or sulfur atoms could be critical for the cardiodepressant action [77-79]. Smooth muscle relaxation studied in isolated ileum and uterus certainly corroborates the popular use of the plant in gastrointestinal disorders and explains its antispasmodic activity [80]. Since pre-treatment with atropine did not abolish the hypotensive effects of *M. oleifera* compounds, it is probably that these effects are not mediated by stimulation of M_2 muscarinic receptors and they could trigger independent non-acetylcholine pathway(s).

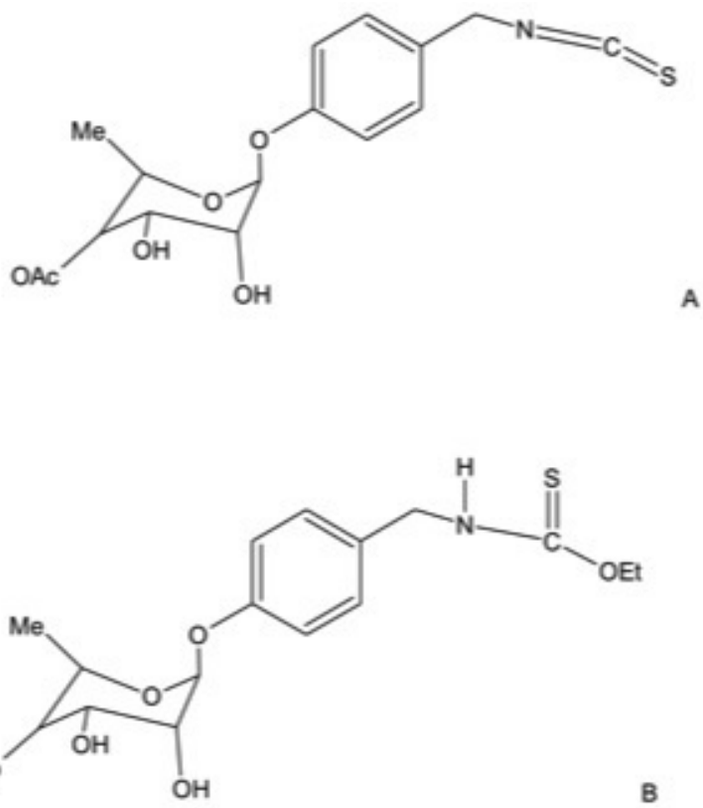

Figure 2. Structures of the compounds 4-(α-L-rhamnosyloxy)-benzyl isothiocyanate (A) and Niazimicin (B).

4.2. Anti-inflammatory and antitumor

The aqueous (1000 mg/kg), ethanolic, hexane and butanolic (3000 mg/kg) extracts of *M. oleifera* seeds reduced edema development in percentages ranging from 34 to 85% [80,81]. The

root methanolic extract, with oral IC_{50} value of 660 mg/kg body weight, also showed anti-inflammatory activity in classical models (paw edema induced by carrageenin and air bag), reducing fluid exudation in a dose dependent way, acute and chronic inflammation and accumulation of cells [82,83]. Compounds (aurantiamide acetate and 1,3-dibenzyl urea) isolated from alcoholic extract of roots decreased serum levels of tumor necrosis factor alpha (TNF-α) and interleukin-2 (IL-2), while 1,3-dibenzyl urea showed analgesic activity [84]. It is known that increased expression of pro-inflammatory cytokines are involved in a variety of autoimmune diseases such as psoriasis, arthritis, systemic lupus erythematosus and Graves' disease [85,86]. Then, compounds as aurantiamide acetate and 1,3-dibenzyl urea that reduce and/or inhibit cytokine production emerge as promising molecules to treat rheumatic diseases, preventing hyaline cartilage destruction and deformity of joints and avoiding the formation and establishment of a debilitating inflammatory process [85].

Inflammation, polycyclic aromatic hydrocarbons such as benzo[a]pyrene and 7,12-dimethyl-benzanthracene (DMBA), alcohol, bacteria (*Helicobacer pylori* and *E. coli*) and viruses are involved in promoting carcinogenesis (Weinberg 2008). The text [72] showed that the ethanolic extract of seeds and the isolated molecules niazimicin (IC_{50} of 35.3 mg/mL, Figure 2B), 4-(α-L-rhamnosyloxy)-benzyl isothiocyanate (32.7 mg/mL), 3-*O*-(6-*O*-oleoyl-β-D-glucopyranosyl)-β-sitosterol (70.4 mg/mL) and β-sitosterol-3-*O*-β-D-glucopyranoside (27.9 mg/mL) inhibited *in vitro* leukemia induction by Epstein-Barr virus (EBV) and reduced the viability of Raji malignant cells. Other studies also exhibit cytotoxic activity of leaves on lymphocytic and myelocytic leukemia lines [87,88].

In carcinogenesis studies, niazimicin-treated animals showed delay in skin carcinoma formation induced by DMBA (initiator) and TPA (12-O-tetradecanoylphorbol-13-acetate, promoter) and they also revealed reducing in the number of papillomas, displaying greater activity than β-carotene and glycyrrhetic acid against cancer promoters [72]. The antimutagenic activity evidenced by micronucleus formation attenuation [63,64] may be a factor involved in deferring carcinoma progression. Hence, antioxidants like β-carotene and glycyrrhetic acid might be very effective in combating cancer. Moreover, since the methanolic extract of leaves caused emerging of apoptotic bodies, chromatin condensation, cell shrinking, DNA fragmentation and induce the generation of reactive oxygen species (ROS) in epidermoid carcinoma KB cells, it is believed that *M. oleifera* antiproliferative activity is related to apoptosis intrinsic pathway(s), probably because of the cytochrome *c* release from mitochondria following ROS production [89,90].

4.3. Antimicrobial

Seeds and leaves (and extracts) show activity against different species of fungi (*Trichophyton rubrum, Trichophyton metagrophytes, Microscoporum canis, Epidermophytoon floccosumn, Aspergillus flavus, Rhizopus stolonifer, Fusarium solani, Rhizopus solani and Mucor* sp.) [91-93], some of which being strictly anthropophilic dermatophytes. Correspondingly, these extracts have bactericidal and/or bacteriostatic action against *Staphylococcus aureus, Vibrio cholerae, V. parahaemolyticus, Enterococcus faecalis, Salmonella enteritidis, Aeromonas caviae, Pasturella multo-*

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cida, Bacillus subtilis, E. coli, Pseudomonas aeruginosa, Enterobacter cloace, Proteus vulgaris e Micrococcus kristinae [93-96].

Initially, it was difficult to accurately identify the responsible component(s) for the antimicrobial properties, since majority of studies was performed with seed and leaf crude extracts. Tannins and polyphenols found in *Moringa* species have shown antibacterial activity. However, some authors attributed this effect to the compounds 4-(α-L-rhamnosyloxy)-benzyl isothiocyanate, moriginin and 4-(α-L-rhamnosyloxy)-phenylacetonitrile synthesized by the plant [17,97]. Molecules isolated from root barks [deoxy-niazimicin (N-benzyl, S-etyl tioformate) and pterigospermin] also showed bactericide and fungicide action [24].

Outcomes have demonstrated that these extracts are more effective in low and moderate temperatures (4-37°C), whereas temperatures greater than 70°C lead to loss of antibacterial and antifungal activities, suggesting that specific bioactive compounds would be proteins capable of binding to negatively charged surfaces [32,93]. This finding partially explains the seed water purification efficiency to drop bacteria suspension after 1-2 h of treatment, whose ability has been accredited to basic flocculent proteins [55,61]. Besides, positive monovalent and divalent ions (Na^+, K^+, Ca^{2+}, Mg^{2+}) diminished the antifungal and bactericidal activities of plant proteins due to plasma membrane structure stabilization [93].

4.4. Larvicidal

The search for novel products that improve the epidemiological control of vector-borne diseases is relevant, whereas the selective pressure of conventional and synthetic insecticides has amplified mosquitoes resistance for different classes of insecticides (e.g. DDT and other chlorinated hydrocarbons) and present undesirable effects on non-targets organisms, requesting innovative substances that are specific, biodegradable and safer environmentally as mosquito control agents [32,98]. In this event, products derived from plants have promising outcomes since they have been traditionally used by communities against insects [6].

Aqueous extract of moringa seeds exhibited larvicidal action against *Aedes aegypti* on different stages of larval cycle (LC_{50} of 1.260μg/mL for larvae in III instar). After 24 h exposure (5.2 mg/mL), this extract caused remarkable mortality (99.2%), though this activity had gone after heating the extract at 80°C/10 min [32]. Leaf extracts [hexane (52 and 61% mortality), ethyl acetate (78 and 68%) and methanol (100 and 100%), respectively)] were quite active on *Culex gelidus* and *C. quinquefasciatus* in IV instar [99]. Similarly and more recently, [98] showed that methanolic extracts from seeds are also effective on different phases of the *Anopheles stephensi* malarial vector, presenting larvicidal [LC_{50} values ranging from 57.79 (I instar larvae) to 78.93 ppm (IV instar), pupicidal (67.77 ppm) and repellent activities.

At work [100] has associated this larvicidal potential with flocculating proteins such as lectins found in the seeds, which delay and/or impede the larvae development of the *A. aegypti* mosquito and other insects, especially extending larval early stages (L1 and L2). Lectin treated-larvae in IV instar presented morphological changes as enlarged intestinal lumen and hypertrophy or loss of the luminal epithelium. The peritrophic matrix dividing the gut lumen contents from intestinal epithelial layer contains glycosaminoglycans enclosed in a chitinnous

matrix susceptible to enzymatic action. Thus, it is feasible that chitin-lectin complexes interfere with the peritrophic matrix integrity, leading to the death of larvae [101]. It is likely that bioactive organic chemicals as phenols, terpenoids, glycosides and alkaloids found in *M. oleifera* may jointly or independently contribute to cause oviposition deterrent and skin repellent [70,98,102].

Thus, low toxicity of "morunga" extracts, competence of dispersion and plant maintenance, resistance to inhospitable environments, low cost and simple technology are some factors that convert *M. oleifera* an alternative to unpolluted drinking water and add it in programs to control disease-transmitting mosquitoes, especially in rural areas and developing countries, where access to drinking water is problematical and its accumulation in artificial containers commonly found in and around human residences create an ideal site to lay eggs and breed larvae.

4.5. Action on Central Nervous System (CNS)

Aqueous (100-450 mg/k, oral) and methanolic (350-700 mg/kg, intraperitoneal) root extracts reduced locomotor activity of rats and the number of seizures induced by penicillin and strychnine [27, 103]. Aqueous extract also amplified rates of 5-HT and reduced levels of dopamine in the brain cortex, cerebellum and caudate nucleus and noradrenaline measure in the cerebral cortex [103]. Methanol extract produced CNS depression, decreases the mortality of strychnine-and leptazol-treated animals, increased the sleeping time, caused analgesia and potentiated morphine analgesic effects [27]. This sleepiness extension and anticonvulsant and analgesic activities can be justified by the 5-HT brain rising.

More recently, discoveries also showed that ethanol extract from *M. oleifera* leaves (250-2000 mg/kg) caused decreasing in rearing, grooming, head dips and locomotion of mice, enhanced learning and memory, increased anxiogenic effect and reduced convulsions induced by pentylenetetrazol, though it has no effect on picrotoxin and strychnine induced convulsion. In this event, it is possible that these activities are mediated through the enhancement of central inhibitory mechanism involving release γ-amino butyric acid (GABA) [104]. These findings partially justified the traditional use of *M. oleifera* parts for the treatment of epilepsy.

Other pharmacological activities of *M. oleifera* include the seed biological action upon *Plasmodium falciparum* [105], *Schistosoma mansoni* cercariae [106] and helminth eggs [53], diuretic activity [80] and spleen and thymus enlargement [32,74]; the leaves are purgative, antipyretic [18], immunomodulatory [107] and inhibit conversion of thyroxine (T_4) in triiodothyronine (T_3), with high likelihood to be employed in the treatment of hyperthyroidism [108]; the flowers are aphrodisiac [68], hepatoprotective [109] and antidiabetic [110]; the roots, carminative and anti-constipant [99] and stem barks possess antitumor activity and prevent splenomegaly [68]. This notable pharmacological potential suggests that the beneficial effect of the plant may be associated with individual or combined action of its constituents, such as phenols, aromatic isothiocyanates, flavonoids and sterols [39,102].

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5. Toxicological aspects

Plants have a variety of indispensable macro and micronutrients to feed heterotrophic organisms, including ruminants and monogastric animals such as sheeps, rats, mice and humans. However, side effects and aversions to vegetal substances as alkaloids, tannins, cyanogenic glycosides, terpenes, lectins and glucosinolates are habitual [111]. Thus, animals can identify tastes from sweet (carbohydrate, for example, an indication of calories) to the unpleasant taste of toxins. Among these, some present bitter flavor (alkaloids, saponins and cyanogenic glycosides), astringent (tannins) or offensive odors (terpenes). Dislikes can be wild (temporary) or strong (permanent) depending on the toxin dosages and how they affect the gut and central nervous system. These aversions hardly develop if toxins act gradually (days to weeks). Furthermore, toxins can activate the emetic center, causing nausea and vomiting [112]. Tropical seeds usually have high content of antinutritional factors, specially tannins and lectins [111].

5.1. Leaves, flowers and roots

M. oleifera leaves possess minor quantities of tannin (12 g/kg dry material), phytic acid (21 g/kg) and absence of trypsin, amylase inhibitors, lectins and glucosinolates, an aspect which encourages their consumption. Pods and stem have negligible amounts of tannin, but saponins and alkaloids are found in significant quantities in leaves and stem, respectively, though they should be considered non-toxic to ruminants [39].

Water extract of roots inhibit development of uterus and blastocyst implantation [113], indicating an abortifacient effect that interferes in estrogen and progesterone levels, modifying the normal physiology of the genital tract during the fertile period. Relatedly, Indian women frequently use leaf extracts as natural oral contraceptives [114].

Extracts from roots and flowers (200 mg/kg/day) were able to maintain transaminase (aspartate aminotransferase, AST; alanine aminotransferase, ALT) and bilirubin levels, protect against hepatotoxicity induced by acetaminophen toxic metabolites produced by P_{450} monooxygenase enzymes and presented slight acute toxicity, since it was found LD_{50} values of 1023 and 1078 mg/kg for root and 1047 and 1092 mg/kg for flowers extracts (ethanolic and aqueous extracts, respectively) [109] (Table 2).

However, root methanolic extracts (intraperitoneally and weekly doses greater than 46 mg/kg/day) produced hepatotoxicity and nephrotoxicity associated with hematological and plasma changes, particularly, AST, ALT, cholesterol, bilirubin, urea, proteins and causing leukocytosis and clotting time increasing [115]. Histological examinations in guinea pigs also propose toxicity of root methanolic extract (3.5, 4.6 and 7.0 mg/kg), whereas balloon degeneration and micro and macrovesicular steatosis (in liver) and interstitial inflammation, tubular damage and amorphous eosinophilic materials (in kidneys) were seen, demonstrating reversible signals of histo-architectural distortions [116].

Reference [117] reported that acute and sub-cronic exposure to higher doses of aqueous leaf extracts (400 to 6400 mg/kg) revealed to be relatively safe for human and rodents, since any

Part of plant	Extract	LD_{50} value (mg/kg body weight)	Route of administration	Reference
Seeds	Aqueous	446.5	intraperitoneal	[32]
Leaves	Aqueous	1585	oral	[119]
		> 2000		[117], [118], [119],
	Ethanolic	> 6400	oral	[104]
	Methanolic	7420	intraperitoneal	[63]
Flowers	Aqueous	1092	intraperitoneal	[108]
	Ethanolic	1047	intraperitoneal	[108]
Root	Aqueous	1078	intraperitoneal	[108]
	Ethanolic	1023	intraperitoneal	[108]
	Methanolic	223.6	intraperitoneal	[116]
Stem	Ethanolic	> 5000	oral	[75]

Table 2. Lethal dose 50% (LD_{50}) of *Moringa oleifera* extracts upon laboratory mammals.

mortality was detected when administered orally. These results are in according to [118], who documented that moringa leaf extracts are non-lethal at 2000 mg/kg and [104], whose publication demonstrated that ethanol extract from moringa leaves were not toxic to mice and revealed a LD_{50} higher than 6.4 g/kg in oral acute toxicity studies. Nevertheless, i.p. injection presented 20% and 80% mortality in Wistar albino mice at doses of 1000 and 2000 mg/kg, with LD_{50} of 1585 mg/kg and acute administration at 3000mg/kg reduces urea and albumin levels, indicating liver and renal dysfunction [119] probably initiated by toxicants such as isothiocinates and glycosides during biotransformation and corroborating those outcomes described by [115] and [118], whose mice presented biochemical alterations suggestive of renal damage. An opposing discovery to all previous researches divulged, for the first time, showed that *M. oleifera* has genotoxic potential at higher doses (3000 mg/kg), increasing significantly the number of polychromatic micronucleated erythrocytes derived from bone marrow of rodents (20.2 ± 4.0 cells/1000 cells) when compared to control (0.9% saline) [119].

5.2. Seeds

The best advantage of using *M. oleifera* seeds for water clarification is its low toxicity. The aqueous extract of seeds (400 mg/kg/day) caused no biochemical, histological and hematological alterations, while it increased albumin and HDL-C serum and reduced AST and ALT levels

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[74]. *Ad libitum* intake of aqueous extract as the unique source of water in doses of 1300-1670mg/kg/day for a month was also harmless and no change suggestive of toxicity was observed [32].

In [120] verified that seeds orally administered for 5 days at 500 mg/kg/day protected against toxic arsenic effects and recovery physiological measures to normal values (hemoglobin, erythrocytes and levels of δ-aminolevulinic acid dehydratase and glutathione S-transferase), probably due to the arsenic tissue removal. Previously, [121] showed that oral administration of hydroalcoholic extract of *M. oleifera* fresh pods increased hepatic levels of cytochrome b_5, cytochrome P_{450}, glutathione peroxidase, catalase, reductase and S-transferase enzymes involved in reactions of Phases I and II responsible by detoxification of exogenous substances such as carcinogens and plant poisonous. These findings were corroborated by [122], who showed that seed hydroethanolic extract (1g/kg) avoided the development of hepatic fibrosis induced by carbon tetrachloride and reduced histopathological and biochemical characters of inflammatory necrosis on hepatocytes (cellular infiltration, fatty degeneration and levels of AST, ALT, myeloperoxidase, collagens and biomarkers of oxidative stress). These findings highlighted the chemopreventive properties that have been attributed to antioxidant compounds in the seeds [68,72,121].

Despite investigations have indicated absence of toxicity following oral consumption of the seed aqueous extract, reproducing the intake of treated water with clarifying agent [32,74,123], nutritional assessments reported that those growing rats fed during 10 days with a diet whose total protein content (10%) was replaced by seed flour and whose doses were 24-fold higher than the highest dose tested by [123], suffered from severe growth disorders, loss of appetite and weight, hyperplasia of the small and large intestine, liver, pancreas, kidneys, heart, stomach and atrophy of key organs like spleen and thymus, though protein digestibility is similar to the foodstuff presenting egg white [30]. The antinutritional compounds prevailing in mature seeds, mainly glucosinolates (65.5 mmol/g), phytic acid (41 g/kg) and lectins [30,39, 124,125] should be responsible for these effects. Phytates, when found in percentages between 1-6% and ingested for extended periods, they may reduce the bioavailability of minerals ($Ca^{2+}$and Zn^{2+}), starch and proteins in monogastric animals. Glucosinolates disturb growth and reproduction.

Lectins, in turn, are proteins or glycoproteins with reversible binding sites to carbohydrates [111]. They interact with the intestinal mucosa and interfere with digestion and absorption of nutrients, reduce activity of amylase, establish stable complexes with trypsin/chymotrypsin [126], cause pancreatic hypertrophy [127] and decrease growth rate [30]. In fact, studies have emphasized the *M. oleifera* haemagglutinating activity and associated it with lectins detected in the seeds [30,100,128].

Additionally, weight gain reduction in sheep supplemented with 6 g/dia of *M. oleifera* delipidated seeds compared with animals feed with 4 g/day may be explicated by the abundant presence of cationic proteins with antimicrobial activity [38] and/or because of bitter taste [39]. Therefore, antibacterial activity of seeds should inhibit the animal growth, altering its intestinal flora and rates of fermentation efficiency.

The bitter taste in the seeds, important to provide its typical aroma, is alleviated by treatment [39], suggesting that its taste would not be a limiting factor for using them, since even cow's milk whose dairy cattle was treated with moringa meal did not reveal changes in quality [41]. Furthermore, it is known that most adverse effects are eliminated by suitable methods as washing, storage, drying and/or heating. For example, lectin biological properties are lost after protein denaturation by temperature and pH. Nevertheless, these techniques are expensive and prolonged cooking of seeds result in nutritional value reduction and loss of micronutrients, specifically vitamins and minerals. The text [129] showed that roasted seeds promote formation of mutagenic compounds [4-(alpha-L-rhamnosyloxy)phenylacetonitrile, 4 hydroxyphenylacetontrile and 4-hydroxyphenyl-acetamide). On the other hand, it was observed that moringa seed flour has post-treated proteins with good digestibility and absorption [39,41].

Environmental assessments with seed water extract using the microcrustaceans *Artemia salina* and *Daphnia magna* showed LC_{50} values of 177.8 and 188.7 μg/mL, respectively [32,74]. The research [130], working with the *Scenedesmus obliquus* green algae, another aquatic organism, found LC_{50} of 207.5 and 287.5 mg/mL (methanolic and aqueous seed extracts, respectively). In addition, acute toxicity tests in mammals (*Mus musculus*) revealed a LD_{50} of 446.5 mg/kg body weight [32]. Thus, both studies with marine organisms as well as those performed in mice indicate low toxicity of moringa seed extracts [131,132].

In summary, results obtained by [30,32,74,104,116,117,119,123,133,] confirm that toxicity of *M. oleifera* depends on concentration, part of the plant used, and manner of preparation and routes of administration. Then, though the consumption of different parts of specie for various purposes has been widely accepted, it is important to note that intake without any pre-treatment should be done carefully, since the specific adverse(s) factor(s) remains unclear whereas the presence of other unknown toxicants is uncertain. Additionally, little has been done to define, optimize and standardize conditions for their use and a few government programs encourage or disseminate such treatment for household water or determine its acceptability, sustainability, costs and effectiveness.

6. Conclusion

Relatively safe for human, *M. oleifera* is a worthy pharmacological and nutritional alternative, especially taking into account that technology requirements for leaves and seeds' flour production is cheap and simple, which benefits small farmers and the general population by providing an abundant food supply and bioactive substances.

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