



A systematic review of pharmacological activities and safety of *Moringa oleifera*

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ABSTRACT

In the last few decades, *Moringa oleifera*, a multipurpose medicinal plant (MMP) has received increased research attention and commercial interest for its nutritional, therapeutic and pharmacological properties. Rigorous approaches including biological assays, animal and clinical trials are required towards safe usage as herbal therapy. We conducted a systematic review of the known pharmacological activities, toxicity, and safety of *M. oleifera*, usually used locally in the treatment and prevention of myriads of illnesses. Five major bibliographic databases (SCOPUS, Web of Science, Science Direct, PubMed, and Mendeley) were searched for studies reported on pharmacological activities, toxicity, and safety assessment of *M. oleifera* in the last 29 years (1990 – 2019). Studies on animals and humans involving aqueous leaf extracts and different preparations from *M. oleifera* seed and bark were also considered. All articles retained, and data collected were evaluated based on the period of the article, country where such studies were conducted and the document type. Our search results identified and analyzed 165 articles while 63 studies were eventually retained. Diverse pharmacological activities including neuroprotective, antimicrobial, antiasthmatic, anti-malaria, cardioprotective, antidiabetic, antiobesity, hepatoprotective and cytotoxic effects, amongst others, were recorded. Toxicity studies in animal models and few human studies showed that *M. oleifera* is safe with no adverse effect reported. The importance of the plant is highlighted in the search for new bioactive compounds to explore its therapeutic potentials towards drug discovery and development in the pharmaceutical and allied industries.

Implication for health policy/practice/research/medical education:

This review provides a detailed insight into the pharmacological activities and safety of *Moringa oleifera* and shows that *M. oleifera* can be used as a reliable source for preparation of new drugs.

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Introduction

Multi-purpose medicinal plants (MMPs) have continued to elicit research interest and commercial attention globally as natural resources considered rich in nutritional and pharmacological properties to treat and cure several diseases (1,2). Several medicinal products as multi-therapeutic agents have been derived from such herbs and plants and considered safe for consumption (3,4). Reports indicated that less than 30% of sub-Saharan Africa's (SSA) population has access to modern health care and pharmaceuticals (5). The other 480 million people in the region rely on traditional medicines, mainly from MMPs (5,6). The medicinal importance and efficacy of the

MMPs have been variously associated with the presence of antioxidants and polyphenolic compounds (1,7,8). In recent years, scientific and commercial efforts are being intensified to advance the sustainable utilization of natural antioxidants from plants in the food and nutrition industry as well as preventive health care (9-12). Over a decade ago, the global market worth of medicinal herbs was estimated to the tune of US\$65 billion and with increased usage of up to US\$5 trillion by 2025 (5). Thus, the relevance of MMPs as a reliable source of nutritive food, medicine and pharmacology will continue to elicit research interest and commercial attention to producing effective pharmaceuticals to combat diseases and

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infections, particularly in the SSA. Ethnopharmacology has proven to be an influential and reliable tool in the search for indigenous plant species with medicinal and pharmacological properties that can be screened for pharmaceuticals toward successful drug discovery and development (13-15). The adoption of herbal medicine is generally hampered by inadequate knowledge of chemical constituents, pharmacokinetics and pharmacodynamics (16). Other limiting factors include poor quality control, scientific and clinical evidence of their efficacy and effectiveness (17,18). In many African traditional herbal remedies, lack of standardization is one of the major constraints to their safety and adoption (19).

In this systematic review, we present *M. oleifera* as one of the valuable MMPs globally recognized as a food and medicinal plant providing natural supplements for healthy living (1,20,21). It is a plant with numerous local utilizations with huge pharmaceutical potentials that can be exploited for human health benefits (22,23). The multipurpose medicinal activities and ethnopharmacological use pattern of *M. oleifera* have been reported from many cultures around the world to treat and cure many illnesses like high fever, diabetes, hypertension, sickle cell anemia and cancer, among others (24-26). Several authors have also reported various bioactivity and pharmacological mechanisms of *M. oleifera* parts including leaf, root, seed, and barks (1,27-30). The hypocholesterolemic activity has been demonstrated in Wistar rats and rabbits (31,32). A detailed review of hyperglycemia and dyslipidemia activities of the plant has also been published by Mbikay (33). Similarly, various parts are widely used in the treatment of neurodegenerative illnesses (23,25,34,35). Precisely, an avalanche of evidence on pharmacological activities has been highlighted in the literature and commercial products attributing such rich activities to the abundant presence of bioactive molecules including antioxidants, flavonoids, quercetin, Moringine among others (36-39).

Globally, there is increased scientific research, commercialization, utilization and demand for *M. oleifera* based pharmaceuticals and supplements to challenge various illnesses and support healthier living. A review of existing literature also indicates commensurate studies on animal models to support and confirm the pharmacological properties and safety of *M. oleifera*. However, safety reports on human studies with no adverse effects are few (40). Herbal extracts and products are limited in use and adoption probably due to the uncertainty surrounding their toxicity level and safety (41). In addition, several reports have shown that toxicity studies are necessary to validate the safety limits of many herbal preparations (42,43). From our observation and market surveys, Moringa-based products and supplements are becoming increasingly available in the open market, as well as online portals without commensurate toxicity assessment tests to

establish their safe consumption. Also, different degrees of toxicity have been reported on various seed extracts of *M. oleifera* and thus requiring more scientific reviews and experimental trials (42,44). Hence, this systematic review is aimed to update existing information on the overall value of the pharmacological activities, toxicity and safety potentials of *M. oleifera* as an MMP.

Methods

Search strategy

We conducted a systematic review on pharmacological, toxicity and safety of *M. oleifera* over a period of 29 years (1990 to 2019). Five major databases including PubMed, ScienceDirect, Web of Science, Scopus and Mendeley were engaged in the course of searching for relevant information and data. The search terms were “*M. oleifera*” and (“pharmacological activities”, “safety”) without narrowing or limiting search items. Table 1 shows the search terms and combinations. For our search strategy, the systematic procedure reported by Page and Moher (45) was adopted.

Study selection

Article and study selection was based on originality of research works, keywords and search terms in the title, abstracts and studies involving pharmacological, toxicological and safety assessment of extracts of *M. oleifera*. Inclusion criteria were papers that evaluated the medicinal and pharmacological properties of *M. oleifera* parts (leaves, seeds, and barks) in the treatment of several ailments. We excluded review articles, abstracts, case reports and conference proceedings with no link with our inclusion criteria. The articles were reviewed for titles and abstracts by two reviewers (JOP, OSA) while duplicated articles were eliminated.

Data extraction

One author (JOP) extracted data using standardized forms. Publications with available abstracts were reviewed.

Table 1. Search terms used for databases

S/N	Searches*
1	<i>Moringa oleifera</i>
2	Pharmacological properties
3	Pharmacological activities
4	2 or 3
5	1 and 4
6	Safety
7	Toxicity
8	6 or 7
9	5 and 8

*Searches on PubMed, Scopus, Science Direct, and Mendeley, Web of Science, followed the same pattern.

Searched terms and documents were analyzed based on period/year of publication, country/territory, document type (review papers, research papers, books, etc) and subject areas using Excel 2013. The collected information included different types of extracts, pharmacological compounds, and activities, model experiments (animals: rats, mice, clinical trials), the dosage of extracts or drugs and the outcomes. Results were measured in terms of pharmacological and toxicity activities as well as the safety of *M. oleifera* extracts and other preparations. Publications with abstracts on human and animal studies with the main outcome as mentioned above were included. All data were analyzed and presented in the form of a flowchart, charts, tables, and figures.

Quality assessment

We carefully assessed the pharmacological activities, toxicity and safety of *M. oleifera* with clear case definitions. Studies with ambiguous investigations and outcomes were excluded. The procedure of Siqueira-Lima et al (46) was adopted to assess the quality of clinical trials involving a living organism. The studies selected involving random treatment distribution, outcome measurements, and blinded outcome evaluation were analyzed using Excel 2013.

Toxicity and safety studies

Toxicity and safety studies involving animal models and human clinical trials were considered based on histopathology tests, relative organ weights, and toxicity biomarkers.

Results

After careful searches of databases, we identified and selected 165 articles that clearly matched our selection criteria out of a total of 618 articles searched. The breakdown of the database searches was as follows: 35 articles out of 52 from Scopus, 55 articles out of 456 from ScienceDirect, 50 articles out of 85 from PubMed while 13 from Web of Science and 12 from Mendeley directly related to the purpose of this review were selected. From the 165 articles selected, 50 articles duplicated in two or more databases were excluded leaving us with 115 articles. After preliminary selection of articles based on inclusion benchmarks, a total of 63 published articles were carefully chosen while others were excluded. The data in Figure 1 shows the flowchart of our search strategy. Most of the studies on pharmacological activities, toxicity, and safety on *M. oleifera* were carried out by experts from Indian, Nigeria, South Africa, Italy, Bangladesh, Egypt, Cameroun, Malaysia, Iran among others. Source of articles identified and selected for this review, articles per database searched, year and number of publications as well as geographical location and number of publications were illustrated in Figure 2.

Pharmacological activities of *Moringa oleifera*

Articles resulting from the search provided information which revealed a high degree of diversity in the pharmacological activities of *M. oleifera* linked to various extracts, fractions, and compounds isolated from *M. oleifera*. Neuroprotective, antimicrobial and antiasthmatic, anti-malaria, cardioprotective, antidiabetic and antiobesity, as well as cytotoxic activities amongst

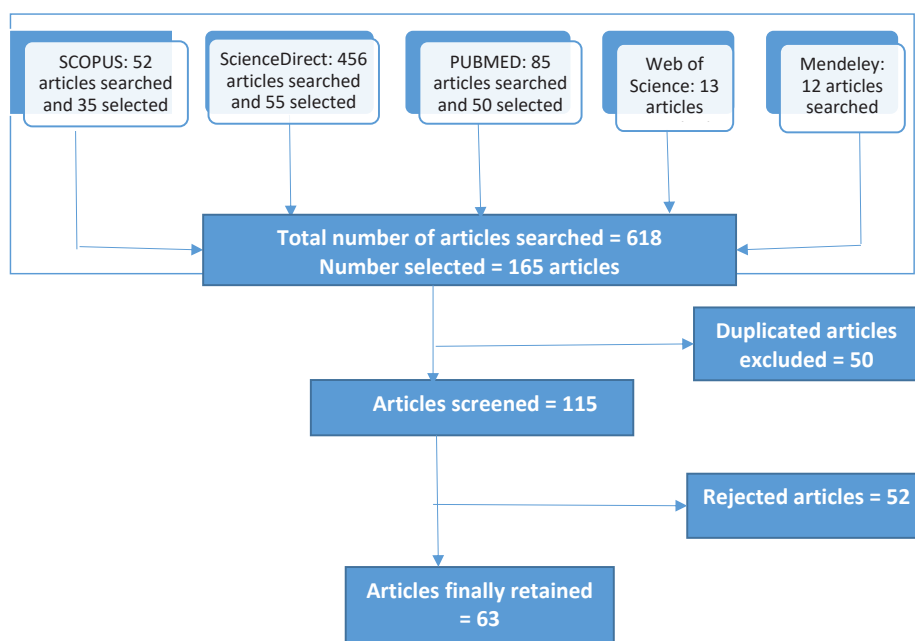


Figure 1. Flowchart of the search strategy and articles included in this review.

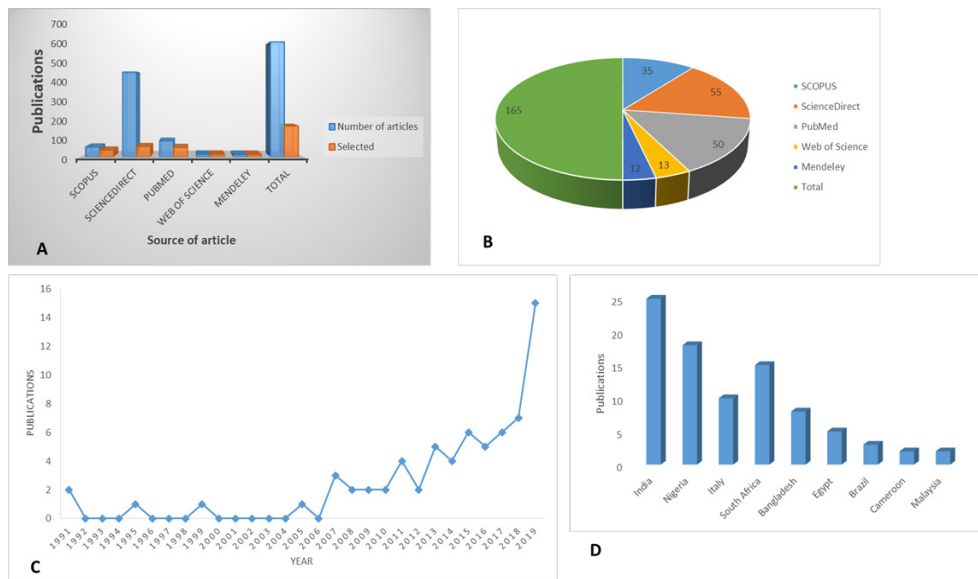


Figure 2. Source of the articles identified and selected for the systematic review according to (A) articles from the different databases, (B) selected articles per database search, (C) year and the number of publications and (D) geographical location and number of publications.

others were recorded (Figure 3). Moringa isothiocyanate was variously mentioned and associated with the pharmacological activities of *M. oleifera*. Information in Table 2 shows the pharmacological properties included in this review, authorship, countries of studies, specific investigation and outcomes.

Toxicity and safety of *Moringa oleifera*

Studies on the toxicity and safety of *M. oleifera* included in this review are shown in Table 3. Generally, studies on the toxic effects and safety have reported of *M. oleifera* to be safe in various models on mice, rats, rabbits, *in vitro* assays and some clinical trials (42,58-60). In retrospect, very few toxicity and safety evaluations were encountered in investigations involving humans or clinical trials.

Sixteen studies were evaluated on quality assessment of pharmacological studies of *M. oleifera* using experimental animals. Among the articles retained, above 75% of studies reported and mentioned the random distribution of animals during experimental procedures. Ten studies clearly mentioned sample size while six did not (Figure 4). From the articles retained, doses tested on the experimental subjects showed no adverse effects.

Discussion

Database searches and global relevance of *M. oleifera*

The outcomes of this systematic review confirm that *M. oleifera* is an important plant species with a plethora of pharmacological and therapeutic activities. Our data indicate that Indian researchers were the highest

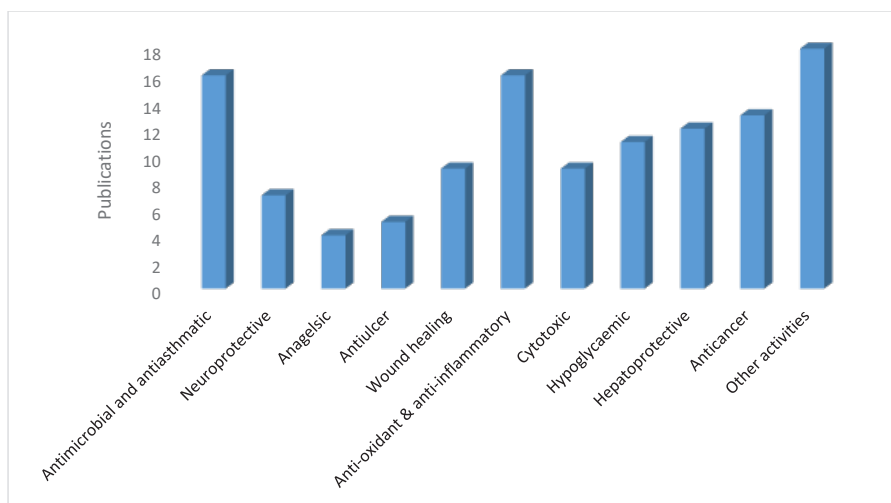


Figure 3. Major pharmacological properties described for *Moringa oleifera*.

Table 2. Specific pharmacological properties of *Moringa oleifera* included in this review

S/N	Author	Country	Specific investigation	Findings	Pharmacological properties
1	Moura et al (47)	Brazil	Evaluated the antimicrobial perspective of water-soluble moringa seed lectin on bacteria: <i>Serratia marcescens</i> and <i>Bacillus</i> sp. Inhibitory effect against <i>S. marcescens</i> and <i>Bacillus</i> sp. Biofilm formation studied	The water-soluble <i>M. oleifera</i> Lectin suppressed the formation of biofilm by the bacteria (<i>S. marcescens</i>), also inhibited bacterial growth. The lectin also suppressed the growth of <i>Bacillus</i> sp. at the reported concentration.	Antimicrobial: (antibacterial and antibiofilm)
2.	Jaja-Chimedza et al (48)	USA	Comparative studies on the anti-inflammatory activities of isothiocyanate-enriched MSE, CTE and CEM	Moringa isothiocyanate-1 of MSE significantly reduced carrageenan-induced paw edema in Sprague-Dawley rats at a rate comparable to aspirin, whereas CTE had no significant effect. It significantly inhibited the gene expression of lipopolysaccharide- iNOS, IL-1 β and IL-6 and NO production, whereas, at all the concentrations tested, CEM had no significant activity.	Anti-inflammatory and anti-oxidant
3.	Omodanisi et al (49)	South Africa	Male Wistar rats were induced with STZ and consequently exposed to methanolic leaf extract of <i>M. oleifera</i> to evaluate its anti-oxidant, inflammatory and hypoglycemic activities.	A significant reduction in plasma glucose level reported in Moringa treated diabetic rats. The hypolipidemic activity was demonstrated in diabetic rats. Antioxidant activity was reported to be high. <i>Moringa</i> leaf extract showed a depressing impact on biomarkers-TNF- α and IL-6. Diabetic nephropathy was significantly reduced.	
4	Cheraghi et al (50)	Iran	Cardioprotective property of <i>M. oleifera</i> leaves using isolated N, α -L-rhamnopyranose VR compound was evaluated in rats induced with doxorubicin cardiac toxicity	VR reduced MDA levels in heart tissues. Consequent upon administration, reduced SOD and GSH levels were increased. VR administration inhibited the appearance of markers of heart failure.	Cardioprotective
5.	Giacoppo et al (51)	Italy	The study evaluated the antiproliferative properties of <i>M. oleifera</i> leaves using isolated isothiocyanate (moringin) complexes on human neuroblastoma cells.	The growth of SH-SY5Y cancer cells was suppressed. MAC treated cells displayed a dosage reliant downregulation of phosphatidylinositol 3-kinase (P13K)/ Akt (protein kinase B)/ mammalian target of rapamycin pathway. MAC treatment also induced apoptotic cell death pathway in the tumor cells.	Anticancer
6.	Tiloke et al (52)	South Africa	Investigated the anticancer activities of leaf extract of <i>M. oleifera</i> on human esophageal Cancer Cell lines	Leaf extract significantly increased DNA fragmentation and lipid peroxidation in the cancer cells. Induction of apoptosis was also observed.	
7.	Jaafaru et al (53)	Malaysia	Examined the anticancer effect of Moringa-complex compound: GMG-ITC-RSE on human prostate cancer cells (PC-3).	Anti-proliferative effects on PC-3 cells were reported while the safety of the Glucomoringin-isothiocyanate rich soluble extracts was confirmed.	
8.	Muhammad et al (54)	Malaysia	Wound healing abilities of bioactive <i>M. oleifera</i> aqueous fraction on STZ and NAD - induced diabetic Wister rats were evaluated.	Antibacterial susceptibility testing revealed that <i>Moringa oleifera</i> aqueous fraction repressed bacteria growth on chronic wounds of diabetes (<i>S. aureus</i> , <i>P. aeruginosa</i> , and <i>E. coli</i>). The bioactive fraction of <i>Moringa</i> enhanced wound healing in diabetic rats by downregulating proinflammatory cytokines and promoting angiogenesis.	Wound healing
9.	Hannan et al (55)	Republic of Korea	<i>In vitro</i> neuroprotective potential of <i>M. oleifera</i> ethanolic leaf extract evaluated.	Leaf extract dose-dependently increased number, length, and branching of neuritis. <i>Moringa</i> leaf extract protected neurons against naturally occurring cell injury by significantly increasing neuronal viability, enhanced neuronal differentiation and synaptogenesis.	Neuroprotective
10.	Devaraj and Krishna (56)	India	Evaluation of the antiulcerative activity of polyherbal concoction containing <i>M. oleifera</i> , <i>Raphanus sativus</i> , <i>Amaranthus tricolor</i> leaf extract in experimental model of gastric ulcer in male Albino Wister rats	Polyherbal concoction exhibited significant antiulcer activity. Herbal formulation was reported to be efficacious in preventing stomach sores caused by reperfusion and ischemia, ethanol and indomethacin.	Antiulcer
11.	Manaheji et al (57)	Iran	Arthritis-induced rats on CFA were subjected to methanolic leaf and root extracts of <i>M. oleifera</i> to evaluate the analgesic properties	The extracts considerably reduced symptoms of pain, heat and particularly the allodynia and thermal hyperalgesia in tested rats with CFA-induced arthritis	Analgesic

GMG-ITC-RSE - Glucomoringin-isothiocyanate rich soluble extract, MSE- *M. oleifera* seed extract, CTE- curcuminoid-enriched turmeric extract, CEM- curcumin-enriched material, VR- vincosamide, CFA - complete Freund's adjuvant; NAD, nicotinamide; STZ, Streptozotocin; iNOS, inducible nitric oxide synthase; NO, nitric oxide; IL, interleukin; TNF, tumor necrosis factor; MDA, malondialdehyde; SOD, superoxide dismutase; GSH, glutathione peroxidase.

Table 3. Toxicity and safety studies of *Moringa oleifera* included in this review

S/N	Author	Country	Model experiment	Specific investigation	Findings
1.	Adedapo et al (61)	Nigeria	Rats	Oral toxicity and safety of <i>M. oleifera</i> leaf extracts were investigated in rats at different standards and higher doses administered for 21 days.	No adverse effect on studied organ and organism. The extracts were reported to be safe for consumption in tested organisms.
2.	Asare et al (20)	Ghana	Rats and human	The study evaluated the toxicity and safety of an aqueous leaf extract of <i>M. oleifera</i> in different rats and human blood cells. The rats were fed with high doses of the extracts at 1000 and 3000 mg/kg of and observed for two weeks. Outer blood mononuclear cells in humans were also subjected to graded doses of the extract.	No toxicity was recorded at low and standard doses but at a very high dose of 3000 mg/kg b.wt, the extracts were genotoxic. The dose of 3000 mg/kg was too high which exceeded the recommended doses. Thus, at recommended/standard doses, no traces of genotoxicity were found both in rat's human cells examined.
3.	Jaafaru et al (60)	Malaysia	Rats and human	Toxicity and antiproliferative actions of <i>M. oleifera</i> glucomoringin-isothiocyanate on cellular multiplication and apoptosis in human prostate cancer cells (PC-3) was investigated	The glucomoringin-isothiocyanate was found to be non-toxic, induced apoptosis and inhibited human cancer cell proliferation.
4	Kim et al (42)	USA	Rats	Toxicity evaluation to determine the safety of Moringa isothiocyanate-1 -enriched hydro-alcoholic MSE was investigated in rats. Toxicity was determined in various internal organs and cells: gastrointestinal and stomach lesion and discoloration among others.	No mortality was recorded at normal, mid-high and mid-low dose groups. However, mortality was observed in group fed with very high doses of the extracts.
5	Villarruel-Lopez et al (62)	Mexico	Sprague Dawley rats	Toxicity and genotoxicity of leaf powder of <i>M. oleifera</i> administered at different doses were evaluated in rats using LD50 and micronuclei assay. Different organs were observed by the hematoxylin-eosin technique.	Tested doses were not lethal on experimental rats. Genotoxicity parameter were not statistically significant.
6	Chin et al (59)	Malaysia	Rats	Harmful/toxic studies of <i>M. oleifera</i> extract on the dermal wound on healthy rats were carried out and symptoms of toxicity evaluated. STZ/HFD-induced diabetic rat excised with abrasion wounds and observed for wound healing for a period of 21 days.	No signs of dermal toxicities observed on <i>M. oleifera</i> film formations. The <i>in vivo</i> dermal toxicity and safety test showed that all film dressings were non-toxic.
7	Awodele et al (58).	Nigeria	Mice	The toxic effect of <i>M. oleifera</i> aqueous leaf extracts on mice was evaluated using oral administration of 6400 mg/kg extracts and intraperitoneal dose of 1500 mg/kg. In another trial, the mice were orally administered different doses for 60 days.	No toxicity level recorded on examined organs and cells. The study concluded that leaf extracts of <i>M. oleifera</i> were safe in the experimental animals used.
8	Oyagbemi et al (63).	Nigeria	Wista Rats	The study investigated the toxicity of <i>M. oleifera</i> methanolic extracts at differing dosages in 30 Wistar rats for 2 months.	No adverse effect reported
9	Agrawal and Mehta (64)		Clinical trial (Human)	Antiasthmatic effect of <i>M. oleifera</i> seed kernels on bronchial asthma of 20 asthmatic patients was investigated. Toxicity was also evaluated on the patients	No adverse effect reported and that <i>M. oleifera</i> seed kernels were safe.

MSE, *Moringa* seeds extract.

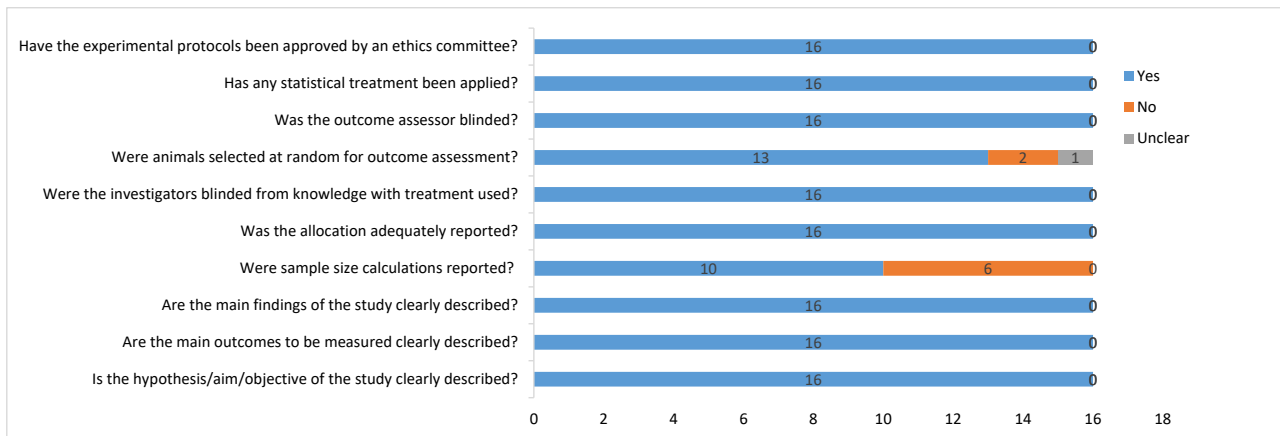


Figure 4. Methodological quality of preclinical pharmacological studies. Articles considered for each criterion adopted are represented on the chart.

investigators on *M. oleifera* utilization and exploitation followed by those from Nigeria. There was also a steady rise in publications from 1991 and to a peak in 2018/2019. The high number of articles returned from searches, those retained and the spread of articles that cut across Africa, Asia, the Middle East, Europe, and America is an indication of global research interest on *M. oleifera*. This is unprecedented and comprehensive in recent times. The articles were inclusive and detailed enough to understand the mechanisms of the pharmacological activities, toxicity, and safety of *M. oleifera* as a herbal source. Scientific investigations over the last 29 years on *M. oleifera* have been impressive and substantiated many of the traditional folklore claims on the plant. These can be further explored for drug development and nutritional enhancement using genetic-based approaches and smart-technologies. The positive correlation between the intake of *M. oleifera*-enriched foods and reduction in the risk of having certain types of non-communicable diseases also confirm the rich pharmacological properties of the plant (65, 66). Overall, the bioactive components in *M. oleifera* have been well researched, isolated and documented to promote good health and living (66). This review summarizes the pharmacological activities and safety of *M. oleifera* as a reliable source of new drugs in the near future.

Pharmacological activities of *M. oleifera*

Anti-oxidant and free radical scavenging activities/properties

A high number of articles retained for the pharmacological activities reported the anti-oxidant and free radical scavenging activities of *M. oleifera*. Anti-oxidants are usually reducing agents like ascorbic acid, thiols, and polyphenols that reduce signs of aging, the risk of heart attacks and stroke (44,67). Articles reviewed indicate that *M. oleifera* is rich in antioxidants and phenolics with the ability to stabilize free radicals produced in cells to tolerate electrons. Recently, the antioxidant activities

of isothiocyanate-enriched *M. oleifera* seed extract were recommended as good botanical leads to mitigate inflammatory-mediated chronic disorders (48). Adedapo et al (44) also validated the antioxidant capabilities of *M. oleifera* leaf extracts with the potentials to relieve pains without toxic reactions. Several other studies have outlined the analgesic, anti-oxidant and free radical scavenging capabilities of *M. oleifera* as a multi-purpose medicinal plant (44, 68, 69). The *in vitro* and *ex vivo* antioxidant, hypolipidaemia and antiatherosclerotic capabilities of *M. oleifera* leave extract have been demonstrated in rats as an active therapeutic agent against cardiovascular diseases (70,71). Adepoju-Bello et al (72) investigated the *in vitro* antioxidant properties of *M. oleifera* using 1,1-diphenyl-2-picrylhydrazil (DPPH) scavenging assay. The outcomes confirmed that, among the different doses used, 50% of *M. oleifera* ethanolic extract at a dose of 300 mg/kg was superior with very high antioxidant capabilities, restored weight and pronounced hypoglycaemic effect in Wistar rats (72).

Anti-inflammatory and analgesic activities

Over 75% of the articles retained highlighted the anti-inflammatory and pain relieving activities of *M. oleifera* which also have been associated with the plant's high antioxidants content. We noticed increased investigation on the anti-inflammatory, antitumor and anticancer abilities of *M. oleifera*. Inflammation is a multifarious biological reaction of vascular cells to detrimental stimuli, for instance, pathogenic infections, injured cells or irritations (44,73). It is a protecting effort/mechanism by which organisms tend to get rid of harmful impetuses and initiate the healing process (44). Pain, heat, redness, swelling, and loss of functions are some of the usual symptoms of acute inflammation (74). Adedapo et al (75) validated the antioxidant, anti-inflammatory and antinociceptive capabilities of the methanolic extract of *M. oleifera* foliage. The analgesic effects of *M. oleifera*

methanolic leaf and root extracts on induced arthritis in rats also established that the extracts considerably reduced all the mechanical symptoms of pain and inflammation among the studied rats (57). A depressing outcome on the inflammatory biomarkers-tumor necrosis factor (TNF- α) and IL-6 diabetic nephropathy in streptozotocin-induced diabetic male Wistar rats were also observed (76). Thus, the analgesic and anti-inflammatory capabilities of *M. oleifera* parts are not in doubt and could be carefully explored as a cheap and effective drug source to relieve pain and treat inflammation-related disorders.

Anti-microbial and antiasthmatic activities

Plant-based sources of cheaper, effective and reliable antibiotics to combat many human and agricultural infectious diseases are gaining scientific attention around the world. Findings from this review showed that *M. oleifera* is one of those plant species with proven pieces of evidence of abundant antioxidants and antimicrobial capabilities (77). Caceres et al (39) investigated the leaves, seeds, barks, and roots of *M. oleifera* against many microorganisms and established the anti-microbial effects of the studied *M. oleifera* parts. The presence of 4-(alpha-L-rhamnosyloxy) benzyl isothiocyanate (1) and 4-(4'-O-acetyl-alpha-L-rhamnosyloxy)-benzyl isothiocyanate have been implicated in the antimicrobial capabilities of the plant (39,78,79). For instance, in the studies of Padla et al (78), the bioactive complexes (isothiocyanate 1 & 2) screened for antimicrobial capabilities against certain microbes were implicated to inhibit the growth of gram-positive bacteria and other microbes. Elgamily et al (80) explored the alcoholic extracts of *M. oleifera* parts for dental antibacterial and antifungal abilities with resultant inhibition against *Staphylococcus aureus* and *S. mutans*. In all the articles retained, isothiocyanate complexes were highlighted to be responsible for its antimicrobial activities. *M. oleifera* leaf extracts were also found to be potent against infectious diseases caused by multidrug-resistant gram-negative bacteria (81). The investigation of Moura et al (47) clearly established the antimicrobial capabilities of the seed lectins from *M. oleifera* found to suppress the formation of biofilm by *S. marcescens* and inhibited bacterial growth. The lectin also suppressed the growth of *Bacillus sp.* With respect to the antiasthmatic activity of the species, a clinical evaluation of seed kernels on twenty asthmatic patients indicated its efficacy and safety to treat asthma in human clinical trials (64). According to the study, alkaloid moringine relaxes bronchioles which closely bear a resemblance to ephedrine in action and valuable to treat asthma and other related ailments. Based on the noticeable reduction in asthma symptoms and improved breathing functions of the patients, *M. oleifera* is a very potent herbal source that can be used in asthma prevention and treatment. Infectious diseases are the main cause of death in teenagers (39,81). It is common

in developing nations with high mortality being recorded every year (81). Consequently, bacteria are increasingly becoming resistant to antibiotics as a result of a change in response to the use of antibiotics, overuse, and misuse (81-83). Antibiotics resistance is currently a leading threat in the health sector. The WHO at a recent press conference organized to commemorate the 2018 world antibiotics and diabetes awareness week in Nigeria cautioned the public against the misuse of antibiotics and urged healthy feeding as well as physical exercise to combat diabetes (Read more at <https://www.vanguardngr.com/2018/11/who-cautions-against-misuse-of-antibiotics>).

Cytotoxicity, neuroprotective and anti-cancer activities

The various dietary and behavioural risks causing cancer include indulgence in tobacco and alcohol use, inadequate consumption of fruits and vegetables, lack of physical activities and obesity. Conventional chemotherapy is often characterized by known and unknown side-effects. Consequently, plant-based alternative drugs and remedies are vigorously being explored as possible therapeutic agents. Findings from this review show that *M. oleifera* contains rich bioactive compounds which can be harnessed in the treatment and management of chronic diseases including cancer, HIV/AIDS amongst others (84). The antitumor actions of *M. oleifera* have been connected to the two-well characterized phytochemicals moringinine and quercetin which reverses tumorigenesis (85,86). The recent study of Jaafaru et al (60) provided more insight into the neuroprotection activities of *M. oleifera* isothiocyanate against hydrogen peroxide-induced oxidative stress. The isolated compounds, 4-(α -L-rhamnopyranosyloxy) benzyl ITC (moringin) complexed with alpha-cyclodextrin (moringin + α -CD; MAC), were shown to possess antiproliferative capabilities on SH-SY5Y human neuroblastoma cells (53,60). The nontoxic *M. oleifera* complexes induced apoptosis and inhibited the metastasis of cancer cells in man (60). In similar studies, isothiocyanate from *M. oleifera* seeds was demonstrated to mitigate hydrogen peroxide-induced cytotoxicity and maintained human neuronal cell morphology (53). Previous studies have also shown the antioxidants and anticancer capabilities of *M. oleifera* crude and aqueous extract with the ability to induce reactive oxygen species (ROS) (87,88). In addition, the antiproliferative activities on two cancer cells HepG2 (liver carcinoma cell line) and MCF7 (breast cancer cell line) confirmed *M. oleifera* as a probable source of cancer therapy (52,89,90). In another study, the beneficial effect of root extract of *M. oleifera* was evaluated against beryllium-induced oxidative stress in rats (91). The study confirmed that *M. oleifera* with piperine therapy was potent, while the mixture of *M. oleifera* and curcumin was more active and showed better therapeutic outcomes. The potential anticancer efficacy of the plant using the leaf ethanolic extracts has also

been demonstrated in human cancer cells such as breast cancer cell type MDA-MB-231, HCT-8 (colorectal) cells and A549 lung cancer cells (89, 92). Phytonanoparticles of *M. oleifera* and its potential antiproliferative agents against cancer are consistent with the safety reports and clinical responses on *M. oleifera* utilization to treat and cure cancer, neuroblastoma and other related diseases (64,93,94). Suppression of tumor growth and induction of apoptosis on Ehrlich's solid tumor implanted mice also indicated a reliable anti-tumor/anti-cancer capabilities of *M. oleifera* leaf extracts (95). With the preponderance of scientific reports on the cytotoxicity, neuroprotective and anticancer capabilities of *M. oleifera* parts, it is hoped that pharmaceutical companies around the globe will step in and develop Moringa-based drugs to cure cancer and other degenerative diseases.

Anti-diabetic and anti-obesity activities

People around the world have exploited herbal medicine to solve their health challenges and ultimately for a healthier living (96). Diabetes, being a protracted metabolic malady of the endocrine system, is characterized by abnormalities in carbohydrates, protein, and fat metabolism (97,98). The incidence of diabetes is increasing at an alarming rate with the attendant high cost of management/treatment and its related complications (96,99-101). In 2012 alone, diabetes caused 1.5 million deaths with an increased projection estimated in recent years (99,101). Stroke, heart attack, overweight, kidney failure, obesity, leg amputation, vision loss, and nerve damage are some of the complications of diabetes. Obesity in Africa is also on the increase, being associated with various medical conditions that may lead to death. An imbalance in the intestinal flora is one of the main factors related to obesity and metabolic disorders. The human gut microbiome undertakes a variety of metabolic functions such as the breakdown of complex organic substances into easily digestible sources of energy. *M. oleifera* possesses antidiabetic, hypo- and hyperglycemia effects (1,102). Consequently, the antidiabetic therapeutic effect of *M. oleifera* has been attributed to its polyphenols content to reduce blood glucose and lipids concentration after ingestion (96). According to the investigation of Abd Eldaim et al (103), *M. oleifera* leaves aqueous extract significantly ameliorated hepatotoxicity and reduced hyperglycemia in alloxan-induced diabetic rats. In another study designed to demonstrate the efficacy of *M. oleifera* ethanolic extract in rats induced with high-fat diet obesity, body weight was significantly reduced in rats treated with the extracts (104). Potential hypoglycemic activity of phenolic glycosides from *M. oleifera* seed also showed significant therapeutic properties in reducing blood pressure, blood sugar and enhancing the immune system in humans (105). *M. oleifera* leaves extract was thus confirmed to exhibit hypolipidemic and antiobesity potentials with the capacity to protect the body against

negative effects of high fat diet-induced obesity.

Numerous non-diabetic and diabetic animal studies have demonstrated the antidiabetic effect of *M. oleifera* leaf extracts to reduce plasma glucose levels and increase glucose tolerance (29,106,107). A significant decrease in the level of plasma glucose was reported in rats having diabetes using *M. oleifera* leaves extract (76). The study of Jaiswal et al (107) also established the antidiabetic effect of constant consumption of the leaves of *M. oleifera* as a therapeutic means to protect diabetic patients against oxidative damage. The leaf preparation of the plant was also shown to significantly ameliorate streptozotocin-induced diabetes milletus in adult rats with the outcome of a reduction in biomarkers of diabetes (108). Alejandra Sanchez-Munoz et al (109) recently demonstrated the effect of *M. oleifera* extract on supercomplex formation, ATPase activity, ROS production, glutathione (GSH) level, lipid peroxidation, and protein carboxylation. Their findings indicated that hyperglycemia modifies oxygen consumption, supercomplexes formation, and increases ROS levels of STZ-diabetic rats while *M. oleifera* treated rats were protected against some alterations. Recently, Leone et al (110) demonstrated the potential hypoglycemic capabilities of the powdered form of the leaves of *M. oleifera* on postprandial blood glucose response on Saharawi people living in refugee camps and confirmed *M. oleifera* leaf powder as a possible hypoglycemic herbal drug. Several other reports have validated the antidiabetic activities of *M. oleifera* leaf and seed extracts in diabetic rats (62,110-112). Overall, *M. oleifera* leaves were confirmed to lower postprandial blood pressure (50).

Cardioprotective and anti-hypertension activity

Articles retained on anti-hypertension activities of *M. oleifera* suggest a positive correlation between consumption of raw leaves/extracts of *M. oleifera* and reduction in blood pressure of tested animals. Globally, hypertension, heart failure, and their associated risk factors have been a major cause of death without restriction to age (113) while almost half the losses in dialysis patients are ascribed to heart disease (114). High blood pressure is a typical symptom of hypertension with severe complications and increases the risk of heart disease, stroke, and death (115,116). Findings of different health interventions by the University College Hospital (UCH), Ibadan, Nigeria, indicated that hypertension is the commonest disease after the age of 40 (117). Management and cure for cardiac arrest and hypertension are cumbersome using synthetic drugs and usually with side effects. Thus, natural remedies that reverse hypertension and lowers high blood pressure are being sought after as plausible solutions to cardiovascular ailments. In this regard, our review outcome indicates that *M. oleifera* is a good candidate useful to treat hypertension. Its parts show cardiac protective effects in spontaneously hypertensive rats (115). Several studies have also provided

scientific proof in support of ethnopharmacological uses of *M. oleifera* as the antihypertensive plant with strong cardiac protective effects (118,119). Cheraghi et al (50) investigated the cardioprotective property of *M. oleifera* isolated magnetic hydrogel nanocomposite loaded N, α -L-rhamnopyranosyl vincosamide (VR) on rats induced with doxorubicin cardiac toxicity. It was shown that VR levels of malondialdehyde (MDA) and superoxide dismutase (SOD) in heart tissues were reduced and heart failure biomarkers were inhibited. The studies of Nandave et al (120) also highlighted the cardioprotective capabilities of *M. oleifera* in isoproterenol (ISP)-induced model of myocardial infarction. Their findings indicated that the effects of ISP-induced hemodynamic perturbations and a rise in lipid peroxidation were significantly repressed when tested organisms treated with *M. oleifera* extracts. The cardioprotective/antihypertension capacities of the plant might not be unconnected to the high content of antioxidant, antiperoxidative, and myocardial preservative activities (130). Previous studies and personal experiences of one of us (JOP) also validate the consumption of *M. oleifera* raw leaves or extracts to lower the blood pressure, enhance sleep and prevent cardiac arrest (2,24).

Wound healing and anti-ulcer activities

Wound healing and anti-ulcerative pharmacological capabilities of *M. oleifera* have been severally reported and associated with rich phytochemical contents of alkaloids and antioxidants (59,77,121,122). Ulcer is one of the neglected tropical diseases affecting millions of people in many countries of the world (123). It is caused by infection with *Mycobacterium ulcerans*. Valuable anti-ulcer, anti-secretory and cytoprotective activities of *M. oleifera* were shown in albino Wistar rats using *M. oleifera* ethanolic root-bark extract, which aligns with the preponderance ethnobotanical information on the plant (24,122). Studies of Ruckmani et al (124) revalidated the anti-ulcerative properties of *M. oleifera* root and leaves in alkali preparation with healing effects. The evaluation of polyherbal concoction of *M. oleifera*, *Raphanus sativus* and *Amaranthus tricolor* leaf extracts in an experimental model of gastric ulcer in male albino Wistar rats also confirmed the use of *M. oleifera* as anti-ulcer therapy (56). Their findings concluded that polyherbal concoction exhibited significant anti-ulcerative activity, efficacious in preventing stomach sores caused by reperfusion and ischemia, ethanol and indomethacin. In another study, *M. oleifera* extract was compared with a commonly used drug for the ulcer, famotidine, and found out that the extract and famotidine significantly reduced the free acidity and total acidity of gastric juice (125). Thus, *M. oleifera* preparations, particularly in alkali form, can treat and cure ulcers without any adverse effect. The presence of both tannins and flavonoids has been implicated for the antiulcer activity of *M. oleifera* (39,125,126).

Wound healing has been described as a complex process of tissue repair in response to injury. It is characterized by hemostasis, inflammation, fibroplasia, and maturation (121,127). An aqueous fraction from *M. oleifera* was reported to heal wounds on diabetic Wistar rats induced with STZ and nicotinamide (NAD) (54). The study established that *M. oleifera* aqueous fraction inhibited the growth of bacteria associated with chronic wounds of diabetes. The bioactive compound Vicenin-2 was implicated to enhance wound healing in diabetic rats by downregulating proinflammatory cytokines and promoting angiogenesis (54). Alcoholic preparation of *M. oleifera* leaves was also confirmed as an effective therapeutic agent in healing skin wound and improved fibroblast proliferation and spread thereby increasing wound closure rate (121).

Anti-malaria activities

Malaria is a leading and probably the most upsetting infectious disease with an increased incidence of mortality in sub-Saharan Africa (128,129). The mosquito vector, *Plasmodium falciparum*, is the cause of malaria infection. Though one study indicated that there is a decline in malaria in many parts of Africa, the estimations are not reliable with many deaths recorded recently (130,131). Malaria challenge is compounded by widespread resistance to artemisinin combination therapies by malaria parasites (132). However, as the threat of antimalarial drug resistance increases, persistent efforts are also being expended in developing alternative therapies coupled with the sustainability of existing treatments and control methods. Over the centuries, the use of herbal combinations or preparations as active antimalarial drugs have been seen as an effective approach to treat recurrent malaria infections (133,134). *M. oleifera* in combination with other plants has been actively used as antimalarial in many parts of Africa and Asia (2,24). For instance, *M. oleifera* and *Gynostemma pentaphyllum* leaf extracts were combined with Artesunate in mice infected with *Plasmodium berghei* and adjudged effective in the treatment of malaria (135). The infected mice were subjected to artesunate treatment (6 mg/kg) in combination with *M. oleifera* and *G. pentaphyllum* using standard doses. Their findings showed a significant curative effect and high percentage suppression in a dose-dependent manner. Several other studies have established the efficacy of polyherbal preparations containing *M. oleifera* in combination with other plants, which also inhibited the growth of *P. falciparum*. This holds enormous potential to serve as an excellent source of herbal drug to combat malaria (112,135,136). The crude preparation of the plant leaves in aqueous form also demonstrated antimalarial activities by suppressing *P. berghei* ANKA infection in mice (137). Very recently, Olawoye et al (138) studied the actions of *M. oleifera* powdered leaves on

amodiaquine (AQ) pharmacokinetics in healthy twenty human volunteers and established a positive interaction between AQ and *M. oleifera* suggesting a possible combinatorial therapy for malaria. The methanolic seed extract of *M. oleifera* also exhibited significant insecticidal activities, which could be exploited for integrated pest management to control the Anopheles mosquito (139).

Other activities

The aphrodisiac effect of *M. oleifera* is gaining scientific attention as a supplement to enhance sexual performance, although the precise underlying mechanisms are yet to be understood (140). The leaf extracts of *M. oleifera* inhibited 6- β -hydroxylation of testosterone with monoamine modulation effects, which could help to overcome stress-induced male sexual dysfunction (140,141). A significant correlation between increased sexual urges, erectile function, and consumption of *M. oleifera* methanolic leaves extract in rats has been reported and attributed to its soluble epoxide hydrolase inhibitory actions (142). In many local communities in Africa and elsewhere, *M. oleifera* parts have been used in the fight against HIV/AIDs and other viral infections due to its immunostimulatory effects (24,143,144). A study on the impact of leaf powder of *M. oleifera* as a supplement administered to patients with HIV and on antiretroviral therapy significantly enhanced their nutritional intake and boosted their immune system (145). Thus, the antioxidants in *M. oleifera* can be carefully utilized to fight free radicals and boost immunity in HIV and other related patients.

Toxicity, human studies, and safety of *M. oleifera*

The study of Reddy et al (146) clearly demonstrated the non-toxic nature of *M. oleifera* bark extracts on rats without records of lethality. Adedapo et al (44) also reported no adverse effect on studied organs and organisms suggesting that *M. oleifera* could be safe on the experimental animals. Likewise, the different tested doses on rats showed no lethality and significant differences in genotoxicity parameters, thus the study confirmed the suitability of *M. oleifera* as a safe herbal drug (62). Asare et al (20) reported that half-maximal lethal dose (LD₅₀) of *M. oleifera* aqueous leaf extract was not toxic and observed no changes in the behaviour of the studied rats. In other related studies involving the administration of high dosages of methanolic extract of the plant in male Wistar rats, no toxic reaction or mortality was observed among the rats (147). The toxicity of *M. oleifera* aqueous extract was investigated in both acute and subchronic studies where mice were orally given an extract of 6400 mg/kg, 250, 500, and 1500 mg/kg, respectively, and intraperitoneally supplied a dose of 1500 mg/kg and found to be safe (58). In another toxicity evaluation involving different standard doses of *M. oleifera* methanolic extracts for a period of 2 months, there was no negative toxicity reaction on the

liver and kidneys of the tested animals (63). According to the findings of the study, all experimental rats fed with *M. oleifera* leaf extract did not show any symptoms of genotoxicity; however, there was an increase in body weight in a dose-dependent manner. Studies of Asiedu-Gyekye (148) also established the safety of a single dose of 5000 mg/kg and an oral dose of 1000 mg/kg of *M. oleifera* in tested rats with no overt adverse effects. Recently, the safety of Moringa isothiocyanate-1 enriched hydro-alcoholic Moringa seeds extract was demonstrated in mid-low rats groups without toxic reactions on the organs (42). Wang et al (105) reported that phenolic glycosides compound 1, 4 and 5 may be developed as new safe hypoglycemic drugs from *M. oleifera*, thus validating its safety as a safe therapeutic agent. The therapeutic effect of *M. oleifera* consumption on diabetic rats also indicated its possible use and safety as an antidiabetic preparation (40,149). Other studies have also reported and confirmed the safety of *M. oleifera* as an herbal drug to treat many ailments (59,61,64,148).

Several trials demonstrating potential benefits for the treatment of diabetes, ulcer, and asthma and enhancing the immune system of HIV/AIDS patients have been reported (56,150). However, very few clinical trials involving the safety of different preparations of *M. oleifera* parts have been published. Kushwaha et al (150) studied 30 women at post-menopause supplemented daily with 7 g leaf powder of *M. oleifera* for 12 weeks and compared with another 30 post-menopause women as a control group. There was a corresponding increase in biomarkers of antioxidant properties showing significant anti-hyperglycemic and anti-dyslipidemia activities without toxic effects. Moringa leaf powder could have served as an appetite stimulant in HIV/AIDS patients, thereby improving their immune systems (60). Agrawal and Mehta (64) also investigated clinical trial and safety of the seed kernel of *M. oleifera* to treat bronchial asthma and demonstrated that the extracts were safe with no adverse effects recorded. Maurya et al (151) conducted a clinical trial of *M. oleifera* stem bark on 30 patients with urinary tract infection and reported its safety in humans with no adverse effects reported on the patients. Although genotoxicity at the high dose of the supplement was reported in human peripheral blood mononuclear cells, such doses greatly exceeded commonly used doses as demonstrated by the studies of Asare et al (20). However, at recommended doses administered on rats, *M. oleifera* was found to be safe without genotoxicity observed in the organs tested. Shreds of evidence from the literature and articles retained for this review imply that *M. oleifera* (leaves, stem and bark or whole leaves) could be safe for consumption as a vegetable, as well as a therapeutic agent to fight diseases and possibly enhance healthy living. Combining the rich pharmacological activities with the safety of *M. oleifera*, this systematic review concludes that *M. oleifera* could be further explored in the search

for cheaper and safer therapeutic agents against diseases especially in Africa and other resource poor nations.

Conclusion

This review highlighted the multifaceted pharmacological potentials and safety of *M. oleifera* as a multi-purpose medicinal plant which can be exploited by man in the search for more potent drugs to fight diseases. The increased usage and research efforts on the pharmacological capabilities of the plant (*in vivo*, *in vitro* and clinical trials), clearly lend credence to the safety reported in many works of literature and cultures. Though scientific breakthrough has been recorded on many fronts including, identification, isolation, and elucidation of the structure of pharmaceutical principles responsible for many therapeutic actions of *M. oleifera*, more research efforts are needed to ascertain its safety in humans, as well as the safety of current and future potential herbal formulations of Moringa origin. Many Moringa products are already in the market, which requires quality assessment for their safety and consumption. The importance of *M. oleifera* cannot be overemphasized in the search for new bioactives that could be harnessed for therapeutic potentials, and for exploring future research options to be engaged in pharmaceutical and allied companies.

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Authors' contributions

Authors JOP, OSA, OLO, and OOA prepared the manuscript while author OOO supervised the research. All authors contributed equally in planning and carrying out this study. All authors read the manuscript and confirmed the publication for the final version.

Conflict of interest

We declare no conflicts of interest.

Ethical considerations

Ethical issues have been observed by the authors.

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