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FOOD FRONTIERS

REVIEW ARTICLE

Role of *Moringa oleifera* Lam. in cancer: Phytochemistry and pharmacological insights

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Abstract

Moringa oleifera Lam. (*M. oleifera*), aka "*Shigru*," "mother's best friend," "miracle tree," "horseradish tree," "drumstick tree," and "oil tree," native of the sub-Himalayan region of northern India, belongs to the Moringaceae family. The high nutritional value of *M. oleifera* makes it suitable for both nutritional and medicinal purposes. Because of its chemical constituents, *M. oleifera* is used to treat and combat malnutrition, especially in infants and nursing mothers. These days, herbal medicine and its phytocompound derivatives are also being recognized as effective complementary therapies for cancer treatment. So, in this study, *M. oleifera* is reviewed for its anticancer property. By thoroughly scanning the PubMed, Embase, SinoMed, and China National Knowledge Infrastructure databases, an extensive up-to-date report on its ethnomedicinal use, nutritional, phytochemistry, and pharmacotherapeutic potential is done. It has valuable nutrients such as vitamins, proteins, iron, calcium, antioxidants (flavonoids, carotenoids, and phenols) and ascorbic acid. Additionally, it is used as an antioxidant, anti-inflammatory, antispasmodic, antimicrobial, anticancer, and antidiabetic agent. There are also concrete evidence that this plant's bioactive constituents, numerous extracts have a high biopotential in a number of cancer cells, through its antioxidative, anti-inflammatory, antiproliferative, and cell cycle arresting properties. This extensive literature review will provide insights into several mechanisms and signaling pathways of its various phytoconstituents that can mitigate the growth of cancer cells in various experimental models, safety and toxicity concerns, and drug–drug interactions.

KEYWORDS
anticancer, *Moringa oleifera*, nutrition, pharmacological action, phytochemistry, Shigru

1 | INTRODUCTION

Globally, cancer is the leading cause of mortality, accounting for almost one in six deaths or almost 10 million deaths by 2020 (Cancer). The most common types of cancer include breast, lung, colon, rectum, and prostate (Cancer). In comparison with women, men are more likely to develop lung, prostate, colorectal, stomach, and liver cancer; however, women are more likely to develop breast, colorectal, lung, cervical, and thyroid cancers (Cancer). Prevalence of cancer among different countries are stipulated in Figure 1. Cancer have characteristic of uncontrollable growth of abnormal cells, invading adjoining parts of the body and/or spreading to other parts of the body (Cancer). Almost

FIGURE 1 Prevalence rate of cancer in 2020 in different countries according to Globocan 2020

any organ or tissue of the body can develop cancer, which contributes to a broad range of disorders (Cancer). The latter process, known as metastasizing, is a significant contributor to cancer-related mortality (Cancer). The terms "neoplasm" and "malignant tumor" are also used to describe cancer (Cancer). Though causes of cancer are numerous, intricate, and only partially understood, some common causes in development of cancer enlightened here includes external factors (chemicals, tobacco, radiation, and infectious organisms) as well as some internal factors (hormones, immune conditions, inherited mutations, and random mutations) (Mathur et al., 2015). Also numerous factors, such as dietary elements, specific diseases, lack of exercise, obesity, and environmental toxins, are known to raise the risk of cancer (Cancer). These elements may interact to start or encourage carcinogenesis in humans, making cancer (Figure 2) the main cause of death (Mathur et al., 2015). Overall, among all human diseases, cancer imposes the greatest clinical, social, and financial cost in terms of cause-specific disability-adjusted life years (DALYs) (Mattiuzzi & Lippi, 2019). The overall chance of developing cancer in people aged 0–74 years is 20.2% (24.4% in men and 18.2% in women, proportionately) (Mattiuzzi & Lippi, 2019). In 2019, it was projected that cancer would result in 250 million DALYs worldwide globally (Kocarnik et al., 2022).

There is a number of conventional treatment modalities that are used to treat cancer, including surgery, chemotherapy, and radiotherapy, while contemporary treatments include hormone therapy, immunotherapy, antiangiogenic stem cell treatments, and dendritic cell-based immunotherapy (Debela et al., 2021). The factors influencing the treatment options and progression include the type of cancer, where it is located, and how severe it is (Debela et al., 2021). Despite early discovery and advances in medical treatment, patient survival rates have increased significantly over the past three decades due to early discovery and advances in medicine (Desantis et al., 2014; Siegel et al., 2014). A large number of cancer patients benefit from treatment with anticancer medications and undergo chemotherapy or chemoradiotherapy (Siegel et al., 2014). These anticancer medications, however, cause a wide range of toxic side effects, such as anorexia, nausea, vomiting, diarrhea, and oral mucositis. These side effects are all caused by toxic effects on cells and normal tissues (Akin et al., 2010). As a result of these adverse reactions, patients often experience reduced quality of life, which makes it challenging to continue chemotherapy or chemoradiotherapy (Akin et al., 2010). Although many beneficial techniques have been created to treat or avoid these adverse effects, but they are still inadequate (Gibson et al., 2012; Jordan et al., 2014). Hence, there is a need to find the alternative cure for the management of cancer with minimal side effects.

The popularity of herbal medicine is rapidly increasing in today's time (Choudhari et al., 2020). A variety of illnesses and diseases have been treated with natural products (Sharma et al., 2022) especially plant-based remedies, since ancient times and in folklore (Choudhari et al., 2020; Dias et al., 2012). Also, traditional medicine is used by 80% of people worldwide (Lin et al., 2014). Natural products are an important source of drug discovery in a variety of therapeutic domains, notably cancer and infectious diseases, because to their medicinal properties that have drawn researchers to pinpoint their bioactive components (Atanasov et al., 2021). A majority (over 60%) of clinically available anticancer drugs are derived from natural products (Yap et al., 2021). In contemporary drug development, they provide inexpensive material and good sources of lead compounds (Ali Abdalla et al., 2022).

Numerous medicinal herbs have been found to have the power to prevent the growth or advancement of cancer, according to research (Aung et al., 2017) and one such plant is *Moringa oleifera* Lam. (*M. oleifera*) (Aung et al., 2017). Numerous names for *M. oleifera* exist, including "*Shigru*," "Mother's best friend," "the miracle tree," "the horseradish tree," "the drumstick tree," and "the oiltree" (Coppin, 2008). Small to medium-sized, deciduous or evergreen *M. oleifera* tree is also referred as the "ben tree" in English (Toma & Deyno, 2014). Early Romans, Greeks, and Egyptians employed this quickly growing tree, and it is presently commonly grown in many tropical areas (Paikra et al.). In India, it is known to be one of the most significant plant grown, also known as *Subhanjan* (Sharif et al., 2016), *Sainjna* (Sharif et al., 2016), and *Munga* (Paikra et al). *M. oleifera* nutritional and medicinal properties make it an essential multipurpose tropical tree (Coppin, 2008). The plant is renowned for having a variety of therapeutic benefits,

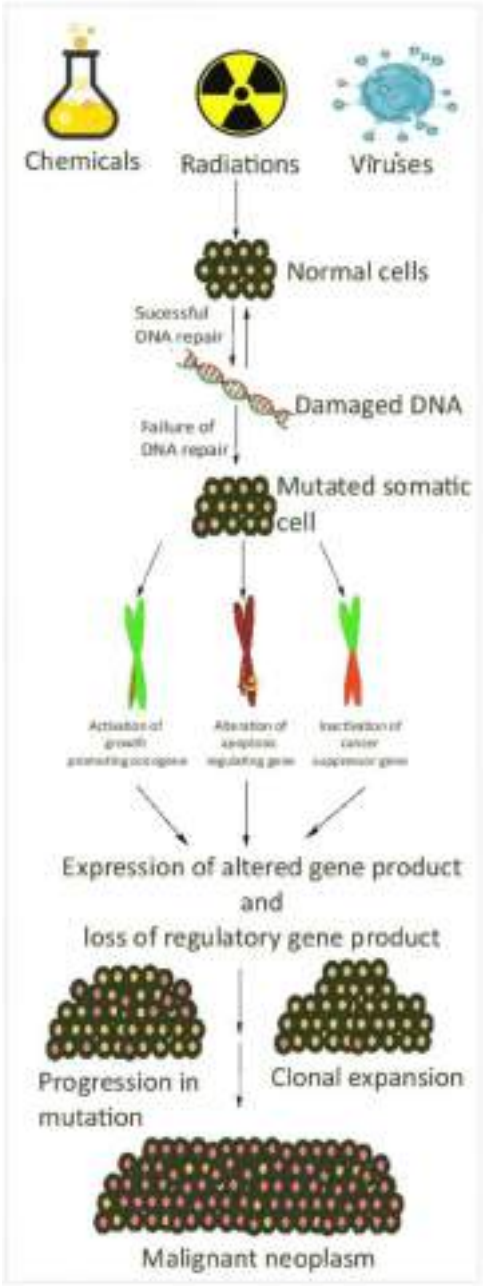

FIGURE 2 Representing the pathophysiology of cancer

including the ability to treat tumors, prevent infertility, lower blood pressure, anticancer, antioxidant, anti-inflammatory, antiproliferative, and have antimicrobial effects (Paikra et al). Various parts of *M. oleifera* plant are also traditionally employed to treat a variety of diseases including cancer (Mali et al., 2022; Paikra et al). Also there have been several reports confirming that its myriad active phytoconstituents are capable of a wide range of biological activities (Paikra et al).

There are many reviews present on *M. oleifera* suggesting its various activities but it is believed that no review is available on *M. oleifera* that specifically deals with its role as an anticancer entity and also explaining possible mechanism involved in its action. So, this study is undertaken to review and compile prevalence of cancer, epidemiology, geographical distribution, ethnopharmacology, phytochemistry, mechanism of action, and preclinical and clinical claims pertaining to the management of cancer by *M. oleifera*. This paper will help in generating new leads toward developing a new formulations for management of cancer and identifying new directions for further studies.

2 | MATERIALS AND METHODS

The search was extended from its availability till July 20, 2022. The available classical ayurvedic literature, online published articles of PubMed, Web of Science, Scopus, and Google scholar were explored for prevalence of breast cancer, epidemiology, phytochemical, industrial importance, nutritive value, ethnomedicinal uses, antioxidant, anti-inflammatory, anticancer study on breast, in vitro, in vivo model, and clinical studies by applying following key words: "Shigru," "Moringa oleifera," "breast cancer," "antioxidant," "anti-inflammatory," "antiproliferative," using conjunctions OR/AND with corresponding medical subject headings terms. Search was restricted to English language only. Research articles reporting in vitro, in vivo, clinical studies, and review articles related to cancer studies were included. In addition, the review also examined studies describing extract's anticancer effects, isolated compounds, and nanoparticles on cancer. We did not include conference proceedings, letter to the editor, gray literature, unpublished data, newspaper articles, ethnobotanical assessments with little or no support, abstracts and full texts that could not be retrieved, studies published in a language other than English, and studies not relevant to the present review.

3 | GEOGRAPHICAL DISTRIBUTION

Fast-growing softwood tree *M. oleifera* is a native of sub-Himalayan regions of northern India and belongs to the monogeneric Moringaceae family (Leone et al., 2015; Paliwal & Sharma, 2011; Pandey et al., 2011). It has a wide geographic distribution throughout tropical and subtropical climates at altitudes of up to 2000 m and shares the same genus as of 13 other species (Leone et al., 2015; Paliwal & Sharma, 2011; Pandey et al., 2011). It is a tropical deciduous perennial dicotyledonous (Leone et al., 2015; Pandey et al., 2011). The brittle, corky, whitish-gray stem of *M. oleifera* has branches that are drooping (Leone et al., 2015; Pandey et al., 2011). Its leaves are pale green in color and bipinnate or more commonly tripinnate leaves with opposite, ovate leaflet (Figure 3) (Leone et al., 2015; Paliwal & Sharma, 2011; Pandey et al., 2011). Although it can endure high temperatures up to 48°C, frost in the winter, altitude, and a wide range of soil conditions, but thrives best in 25–35°C range, under direct sunlight, at a height of 500 m, and in mildly acidic to alkaline soil (pH 5.0–9.0) (Saini et al., 2016). *M. oleifera* seeds can be sown as soon as they reach maturity, since they do not go into dormancy and maintain their vitality for a year (Saini et al., 2016). Approximately 6–8 months after the tree is planted, it begins to bear

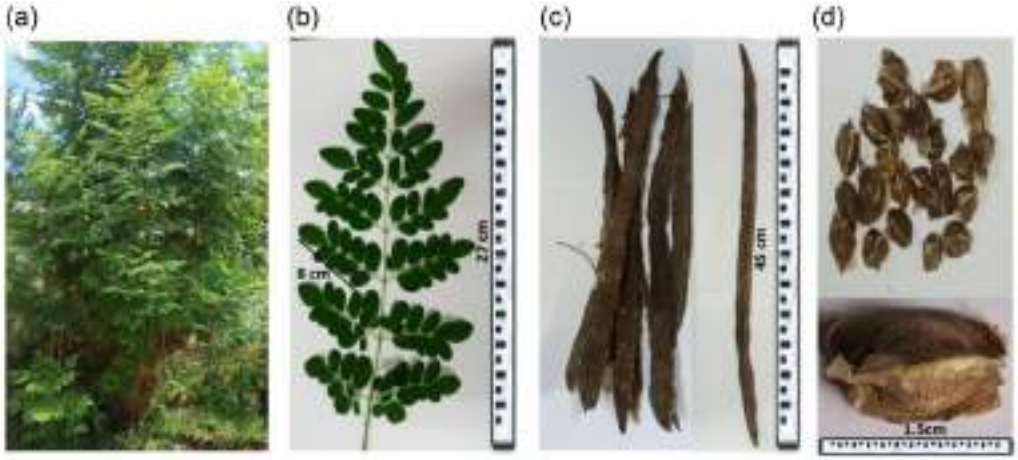

FIGURE 3 *M. oleifera*; (a) natural habitat, (B) leaves, (c) dried pods, (d) dried seeds

fruit (Saini et al., 2016). The first 1–2 years of fruit production are very slow, but later years see a rise in productivity (Saini et al., 2016).

The months of June and July are the most common times in India for this plant to be propagated using cuttings (1–2 m long). To make it easier to harvest the pods and leaves when it is being grown commercially, it is clipped up to 3 m (Autonoumus body, 1962). Northern and eastern parts of the country see leaves falling off in December and January, and new leaves and flowers appearing in March and May, with fruiting beginning in April and June (Autonoumus body, 1962). The southern states also produce fruit and flowers throughout the year, with prime harvest times in July–September and March–April (Autonoumus body, 1962). When seeds are separated from ripe pods, there is no dormancy period before they can be sowed (Pandey et al., 2011). Plant remains viable for 3–4 months in ambient conditions. Itches are caused by the gum leaked from the trunks of old trees (1–2 m) that supports swarms of hairy caterpillars (Pandey et al., 2011). Although *M. oleifera* originally came from northern India, it is now found worldwide throughout the Americas, Africa, Europe, Oceania, and Asia (Brilhante et al., 2017).

In addition, Figure 4 illustrates the distributions of this plant throughout the world, including in India, based on records from the Global Biodiversity Information Facility (Anwar et al., 2007).

4 | ETHNOMEDICINAL UPDATES ON *M. oleifera*

M. oleifera also known as miracle tree have been in use as a traditional medicine among many cultures around the world from centuries for treating various ailments such as anemia, skin infections, psoriasis, anxiety, asthma, pimples, blackheads, blood impurities, bronchitis, catarrh, cholera, conjunctivitis, cough, diarrhea, eye and ear infections, chest congestion, fever, glandular swelling, headaches, abnormal blood pressure, hysteria, and pain in joints. Also, ancient cultures have preserved medicinal benefiting evidence of moringa oil as a skin conditioner and moisturizer for the body and hair, it is highly valued for its beauty properties (Mahmood et al., 2010). Since ancient times, in Egypt, moringa oil ointments and treatments for the skin have been in use (Mahmood et al., 2010).

Every part of this plant is in use from times as a therapeutic and nutraceutical entity. Some of the ethnomedicinal uses of its different parts are stipulated in Table 1.

5 | PHYTOCHEMISTRY

The therapeutic potency of medicinal plants depends on phytochemical constituents (Fidrianny et al., 2021). The leaves, stems, bark, roots, seeds, pods, and oil of *M. oleifera* contain a variety of phytochemical components, including alkaloids, anthraquinone, saponins, tannins, steroids, terpenoids phenolic acids, anthocyanin, glucosinolates, flavonoids, terpenes, and carotenoids. Some of the important phytoconstituents along with its chemical structure and formula responsible for its anticancer properties are stipulated in Table 2 Figures 5, 6a and 6b.

A number of reports have shown that cinnamic acid and its derivatives have potent antimicrobial, antifungal, antioxidant, anticancer, antituberculosis, and antiatherogenic properties (Rai et al., 2021). In an in vitro and in silico study of phenolic compounds from *M. oleifera* leaves, Mumtaz et al. determined quercetin, gallic acid, P-coumaric acid, and 4-hydroxy 3-methoxy cinnamic acid displayed potent anticancer activity. When compared with all other phenolic compounds, quercetin displayed the best docking energy values and good interaction behavior (Zahid Mumtaz et al).

Cancer cells were found to be inhibited from proliferating, promoted from apoptosis, and metastasizing when treated with *M. oleifera* isothiocyanates (MIC-1). The cell viability examination of HepG2, Caco-2, and HEK293 after treatment with MIC-1 showed targeted cytotoxic and apoptotic responses in both human and noncancer cells. In addition, MIC-1 inhibits the growth of cancer cells by downregulating some signaling pathways involved in cell proliferation (Wu et al., 2021).

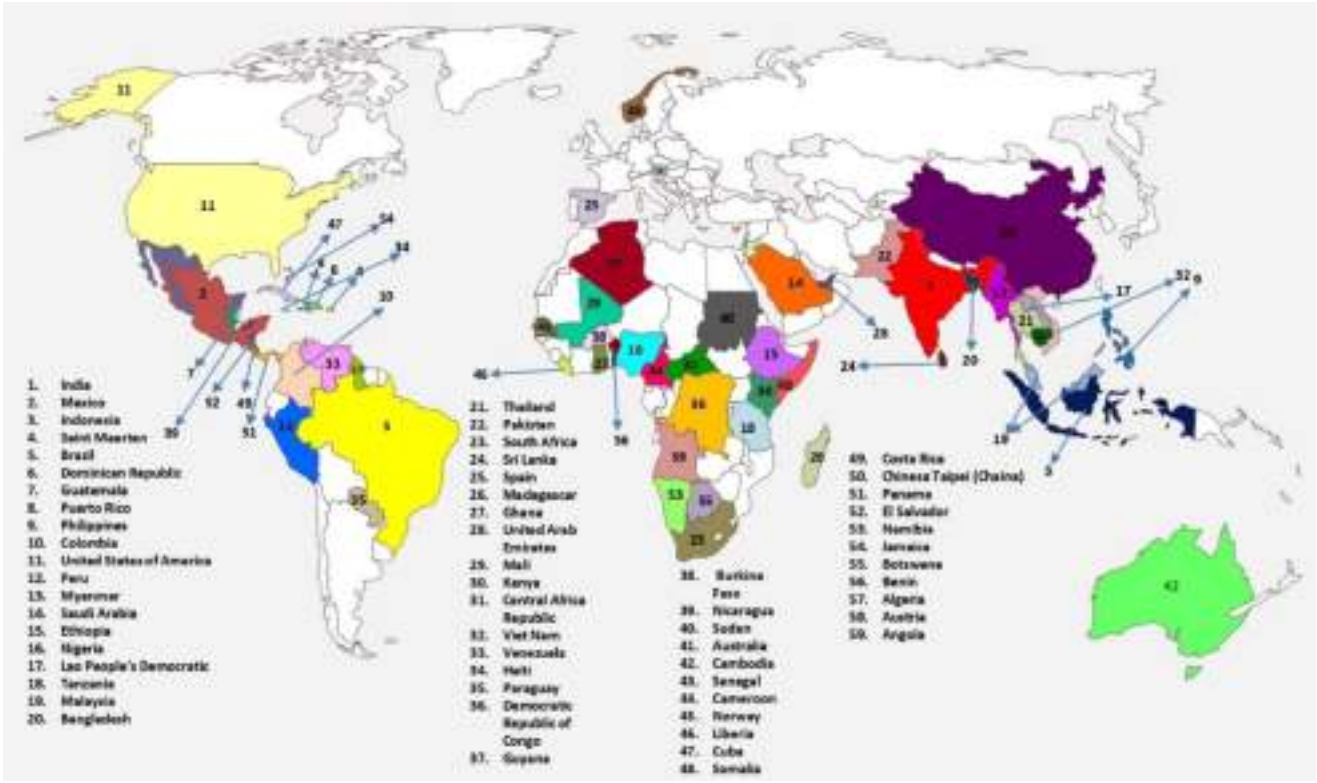

FIGURE 4 Worldwide geographical distribution of *M. oleifera*

TABLE 1 Ethnomedicinal uses of different parts/dosage forms of *M. oleifera* in various countries

Country	Part used/dosage form	Route of administration	Uses	References
India	Root	Oral	Antilithic, rubefacient, vesicant, carminative, antifertility, anti-inflammatory, act as a cardiac/circulatory tonic, used as a laxative, abortifacient, treat rheumatism, articular pains, and lower back or kidney pain, stimulant in paralytic afflictions	Anwar et al. (2007)
	Leaves	Oral	Fever, sore throat, bronchitis, eye and ear infections, scurvy and catarrh, stabilize blood pressure, control glucose levels, treat hyperthyroidism, piles, act as an anti-Herpes Simplex Virus Type-1, used as purgative	(Anwar et al., 2007)
	Poultice	Locally applied	Sores	(Anwar et al., 2007)
	Leavesdry powder	Rubbed on temples	Headaches	(Anwar et al., 2007)
	Leaves paste	Local application	Reduce glandular swelling	(Anwar et al., 2007)
	Stem bark		Rubefacient, vesicant, cure eye disease, prevent spleen enlargement, formation of tuberculous glands of the neck, helps to destroy tumors, heal ulcers	(Anwar et al., 2007)
	Root bark juice	Pour in ear	Relieve earaches	

(Continues)

TABLE 1 (Continued)

Country	Part used/dosage form	Route of administration	Uses	References
		Place at tooth cavity	Acts as pain killer	
	Seeds	Oral	Antipyretic, antimicrobial activity against bacteria and fungus, larvicidal activity against the mosquito that transmits dengue and yellow fever, anti-inflammatory, antispasmodic, diuretic	(Anwar et al., 2007)
	Pods	Oral	Antihypertensive	(Anwar et al., 2007)
USA, Maryland region	Leaves	Oral	Antimicrobial, antibacterial, antiviral, antiparasitic, antipathogenic, antitumor, prostate cancer, radioprotective, antihypertensive, antidiabetic, diuretic, used in colitis, diarrhea, dysentery, ulcer/gastritis, anemia, anti-inflammatory, antirheumatic, lactation enhancer, antiseptic, used in catarrh, scurvy	
	(Fahey & Sc, 2021)			
	Flowers	Oral	Anti-inflammatory, antitumor, antimicrobial, antibacterial, anti-infective, antiviral, antirheumatic, used in ulcers, throat infection, diuretic, antihysteric, abortifacient	(Fahey & Sc, 2021)
	Seeds	Oral	Antimicrobial, antibacterial, antiparasitic, antipathogenic, antitumor, anti-inflammatory, antirheumatic, antispasmodic, used in ulcer, gastritis, bladder disorder, scurvy	
	Pods	Oral	Antimicrobial, anthelminthic, antihypertensive, antidiabetic, anti-inflammatory, antirheumatic, skin cancer	
	Roots	Oral	Antimicrobial, antiviral, antiparasitic, antiasthmatic, antidiarrheal, anti-inflammatory, antirheumatic, antispasmodic cardiotonic, diuretic, oedema, used in dental caries, ulcers, fever	
	Bark	Oral	Antimicrobial, antiviral, antitumor, antiepileptic, antihysteric, used in dental caries, ulcers, snake bite, scorpion bite, scurvy, aphrodisiac, abortifacient	
	Gum	Oral		
	Antimicrobial, antiasthmatic, antirheumatic, diuretic, used in syphilis, typhoid, earache, fever, dysentery			
	Oil (from seeds)	Oral	Antimicrobial, antifungal, antihysteric, purgative, used in skin disorder, bladder disorder, prostate function	

(Continues)

TABLE 1 (Continued)

Country	Part used/dosage form	Route of administration	Uses	References
Africa, Kampala, Uganda region/Senegal region/Tanzania region	Leaves powder	Oral	Malnutrition, antihypertensive, antiseptic, antiasthmatic, diabetes mellitus, malaria/fever, syphilis and skin disease, bronchiasis, (human immunodeficiency virus)/(acquired immunodeficiency syndrome)-related symptoms, external sores, colitis, gastritis, impotence, syphilis, flu, heart burn, bone setting, stress, used to deworm	(phytochemicals & uses of moringa oleifera leaves in ugandan rural communities - Google Search 2022)
	Leavesjuice mixed with honey followed by coconut milk two to three times a day	Oral	Cure diarrhea, dysentery, colitis	(Silver)
Leaves				
Bark				
Seeds				
Roots	Oral	Detoxification, skin diseases, rheumatism, headache, inflammation	(A. & K., 2012)	
Nigeria, Nsukka, Enugu State region	Leaves	Oral	Cure fever malaria, typhoid ear infections, lower blood sugar, hypertension, common cold cough, diarrhea, cure male impotency, cure skin infection, decrease viral load in HIV positive, lactation enhancer in newly delivered mothers, treat indigestion, used in snake bite poison	(Stevens et al., 2013)
	Stem	Oral	Cure typhoid, malaria, ear infection, eye infection, tooth ache, common cold cough, diarrhea, catarrh, viral load in HIV positive, worm expeller, cure male impotency, lactation enhancer in newly mother, treat indigestion, used in snake bite poison	
	Root	Oral	Cure typhoid, malaria, eye infection, ear infection, tooth ache, purgative, common cold cough and catarrh, decrease viral load in HIV positive, worm expeller, cure male impotency, lactation enhancer in newly mother, treat indigestion, used in snake bite poison	
Philippines	Whole plant	Oral	Helps in milk production in lactating women, anemia	(Pandey et al., 2019)
Thailand, Bangkok region	Leaves	Oral	Antipyretic, antihypertensive, poisons antidote	(Sahakitpichan et al., 2011)
	Leavespowder in capsules			
	Spray-dried plant extracts in capsules			
	Herbal tea from leaves or seeds			

(Continues)

TABLE 1 (Continued)

Country	Part used/dosage form	Route of administration	Uses	References
Pakistan, Faisal-abad region	Root Bark Gum Leaves fruit (pods) Flowers Seed Seed oil	Oral	Used to treat inflammation, infectious diseases, cardiovascular, gastrointestinal, hematological, hepatorenal disorders	(Anwar et al., 2007)

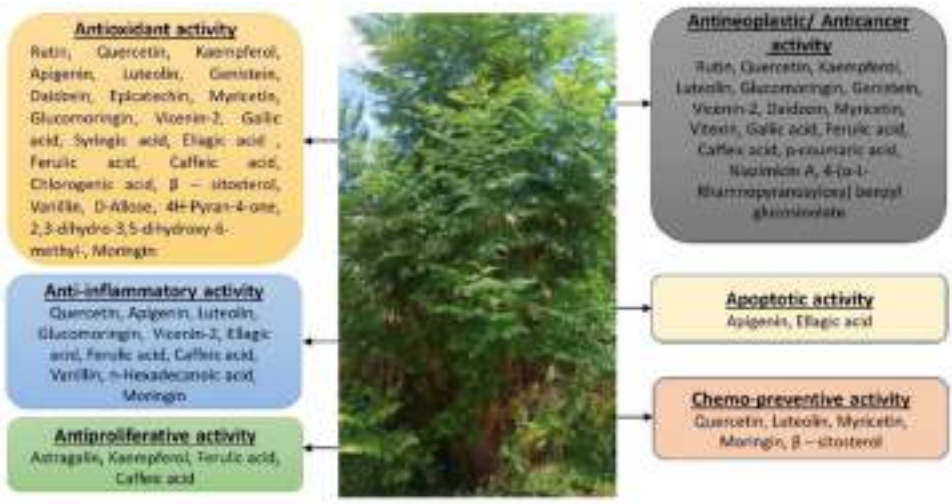

FIGURE 5 Phytoconstituents responsible for anticancer activity of *M. oleifera*

6 | PHARMACOLOGICAL PROFILE

M. oleifera leaves have been utilized as tonic, antibacterial, anti-herpes simplex virus, anti-infection, antipyretic, hepatic, headache, antioxidant, antitumor, lactation, scurvy, and antiseptic since ancient times (Toma & Deyno, 2014). The flowers of *M. oleifera* are traditionally used as a tonic, cure throat infection, antitumor, anthelmintic, and a remedy for rheumatism and common colds. Traditional applications of *M. oleifera* roots include dental caries, common cold, cardiotonic, antispasmodic, diuretic, epilepsy, headache, carminative, and gout (Rani et al., 2018). *M. oleifera* bark is traditionally used for toothache, dental caries, common cold, abortifacient, birth control, snakebite, scorpion bite, as well as scurvy (Aney et al., 2009). *M. oleifera* pods have pharmacological effects that include anthelmintic, antihypertensive, antidiabetic, and joint pain. They are also helpful nutritionally (Mali et al., 2022) (Figure 7).

7 | ANTICANCER PROFILE OF *M. oleifera*

Many different forms of cancer have been successfully treated using appropriate therapeutic strategies; nevertheless, toxicity and/or resistance make it necessary to find new, more potent therapies. Breast, pancreatic, and colorectal cancer cell growth has been successfully inhibited by leaf and bark extracts of *M. oleifera* (Al-Asmari et al., 2015; Berkovich et al., 2013).

Al-Asmari et al. (2015) revealed that *M. oleifera* contains 12 different compounds by gas chromatography–mass spectrometry (GC–MS) and three of these have anticancer properties. The precursor form of isothiocyanates, glucosinolates, which has been identified as a powerful anticancer agent, is found naturally in an entire plant. Isothiocyanates, which have been claimed as a powerful anticancer chemical, are the precursor form of glycosylates that occur naturally in the *M. oleifera*. When the intact plant is disrupted, glucosinolates are hydrolyzed to create isothiocyanate in a mechanism mediated by the enzyme myrosinase (Fahey et al., 2001).

The anticancer effects of isothiocyanates have been thoroughly investigated. According to Xiao et al. (2003), Alyl isothiocyanates (AITC) inhibit both androgen-dependent (LNCaP) and androgen-independent (PC-3) human prostate cancer cells.

In the presence of AITC, gap2/mitosis (G2/M) cells accumulated along with apoptosis, resulting in reduced PC-3 cell growth. A reduction in the levels of cyclin-dependent kinase CDK1 (cyclin-dependent kinase 1), cell division cycle protein 25B (CDC25B), and CDC25C was

TABLE 2 Phytoconstituents of *M. oleifera* having anticancer properties

Part	Constituents		Chemical formula	Medicinal profile	References
	Groups	Compounds			
Leaves	Flavanoids and flavanol glycosides	Rutin	$C_{27}H_{30}O_{16}$	Antioxidant, antihepatocellular carcinoma	(Rutin | C27H30O16 - PubChem 2022) (Xiang et al., 2013)
		Quercetin	$C_{15}H_{10}O_7$	Chemo-preventive activity, decreased p53 protein and p21-ras oncogene expression, anti-inflammatory, synergetic impact in reversal of the multidrug resistance phenotype in in vitro when combined with chemotherapeutic drugs, anticancer, antineoplastic, antioxidant	(Quercetin | C15H10O7 - PubChem 2022)
		Isoquercetin	$C_{21}H_{20}O_{12}$	Antioxidant, suppresses apoptosis, subsequent regeneration of nontransformed liver cells	(Isoquercitrin | C21H20O12 - PubChem 2022) (Fujii et al., 2013)
		Astragalin	$C_{21}H_{20}O_{11}$	Antiproliferative against gastric cancer cell line	(Espacenet - Bibliographic data 2022)
		Kaempferol	$C_{15}H_{10}O_6$	Antioxidant, antiproliferative, enhanced bioavailability of oral tamoxifen due to an inhibition of CYP3A and P-gp, adjuvant therapy in the treatment of pancreatic cancer, potent colorectal cancer management	(Kaempferol | C15H10O6 - PubChem 2022) (Zhang et al.)
		Apigenin	$C_{15}H_{10}O_5$	Antioxidant, anti-inflammatory, new therapy against malignant tumors with tumor necrosis factor-related apoptosis-inducing ligand	(Apigenin | C15H10O5 - PubChem 2022) (Lee et al., 2007)
		Luteolin	$C_{15}H_{10}O_6$	Antioxidant, anti-inflammatory, immunomodulator, antineoplastic agent, active against several cancers, free radical scavenger, chemo-preventive	(Luteolin | C15H10O6 - PubChem 2022)
		Genistein	$C_{15}H_{10}O_5$	Antineoplastic activity, antiangiogenic, antioxidant, antitumor agent	(Genistein | C15H10O5 - PubChem 2022)
		Daidzein	$C_{15}H_{10}O_4$	Antineoplastic agent, antioxidant	(Daidzein | C15H10O4 - PubChem 2022)
		Epicatechin	$C_{15}H_{14}O_6$	Antioxidant	((-)-Epicatechin | C15H14O6 - PubChem 2022)

(Continues)

TABLE 2 (Continued)

Part	Constituents		Chemical formula	Medicinal profile	References
		Myricetin	$C_{15}H_{10}O_8$	Antineoplastic agent, antioxidant, potent chemo-preventive activity by targeting Fyn in skin carcinogenesis	(Myricetin | C15H10O8 - PubChem 2022) (Sung et al., 2008)
		Glucomoringin	$C_{20}H_{28}KNO_{14}S$	Anticancer activity, anti-inflammatory activity	(Rajan et al., 2016) (Galuppo et al., 2014) (Glucomoringin | CAS:316165-49-8 | Miscellaneous | High Purity | Manufacturer BioCrick 2022)
		Vitexin	$C_{21}H_{20}O_{10}$	Antineoplastic agent	(Anzano et al., 2021) (Vitexin | C21H20O10 - PubChem 2022)
		Vicenin-2	$C_{27}H_{30}O_{15}$	Antioxidant, anti-inflammatory, anticancer	(vicenin-2 - Google Search 2022) (Singhal et al., 2017) (No Title)
	Phenolic acid	Gallic acid	$C_7H_6O_5$	Antioxidant, antineoplastic agent	(Gallic acid | C7H6O5 - PubChem 2022)
		Syringic acid	$C_9H_{10}O_5$	Antioxidant	(Syringic acid | C9H10O5 - PubChem 2022)
		Ellagic acid	$C_{14}H_6O_8$	Antioxidant, anti-inflammatory, and apoptotic signal transduction pathways in the tumor milieu	(Ellagic acid | C14H6O8 - PubChem 2022) (Shah et al., 2021)
		Ferulic acid (4-hydroxy 3-methoxy cinnamic acid)	$C_{10}H_{10}O_4$	Anti-inflammatory, antioxidant, free radical scavenger, anticancer activity	(Ferulic acid | C10H10O4 - PubChem 2022) (Zahid Mumtaz et al.)
		Caffeic acid	$C_9H_8O_4$	Antioxidant, antineoplastic anti-inflammatory, antiproliferative	(Caffeic acid | C9H8O4 - PubChem 2022)
		Chlorogenic acid	$C_{16}H_{18}O_9$	Antioxidant, chemo-preventive activity	(Chlorogenic acid | C16H18O9 - PubChem 2022)
		p-Coumaric acid	$C_9H_8O_3$	Anticancer activity	(p-coumaric acid pubchem - Google Search 2022) (Zahid Mumtaz et al.)
	Alkaloid and sterol	β-Sitosterol	$C_{29}H_{50}O$	Antioxidant, reduces side-effects of radiation-induced toxicity	(beta-Sitosterol | C29H50O - PubChem 2022)
		Niazimicin A	$C_{16}H_{23}NO_6S$	Pancreatic cancer cell growth inhibitor, potential anticancer agent	(Tiloke et al., 2018) (Pangastuti et al., 2016)
		β-Sitosterol-3-O-β-D-glucopyranoside	$C_{35}H_{60}O_6$	Pancreatic cancer cell growth inhibitor	(Tiloke et al., 2018) (Vergara-Jimenez et al., 2017)
		4-(α-L-Rhamnosyloxy) benzyl Isothiocyanate	$C_{16}H_{19}NO_6S$	Pancreatic cancer cell growth inhibitor	(Tiloke et al., 2018) (4-(4-O-Acetyl-alpha-L-rhamnopyranosyloxy)benzyl isothiocyanate | C16H19NO6S - PubChem 2022)

(Continues)

TABLE 2 (Continued)

Part	Constituents		Chemical formula	Medicinal profile	References
	Others	Vanillin	$C_8H_8O_3$	Anti-inflammatory, antioxidant, antimutagenic	(Vanillin | C8H8O3 - PubChem 2022)
		D-Allose	$C_6H_{12}O_6$	Antioxidant	(D-Allose | C6H12O6 - PubChem 2022)
		4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl-	$C_6H_8O_4$	Antioxidant	(4H-Pyran-4-one, 2,3-dihydro-3,5-dihydroxy-6-methyl- | C6H8O4 - PubChem 2022) (Bhalla et al., 2021)
		n-Hexadecanoic acid (palmitic acid)	$C_{16}H_{32}O_2$	Anti-inflammatory	(Palmitic acid | C16H32O2 - PubChem 2022) (Bhalla et al., 2021)
Stem	Flavanoids and flavanol glycosides	4-(α-L-Rhamnopyranosyloxy) benzyl glucosinolate	–	Anticancer activity	(Fahey, 2017)
Bark	Alkaloids and sterol	4-(α-L-Rhamnopyranosyl benzylglucosinolat	–	Anticancer activity	(Fahey, 2017)
Seeds	Isothiocyanate	Moringin	$C_{14}H_{17}NO_5S$	Chemo-preventive, antioxidant, anti-inflammatory, antitumor effect	(Borgonovo et al., 2020; Moringin | C14H17NO5S - PubChem 2022; Michl et al., 2016; Rajan et al., 2016)

–: No published data available.

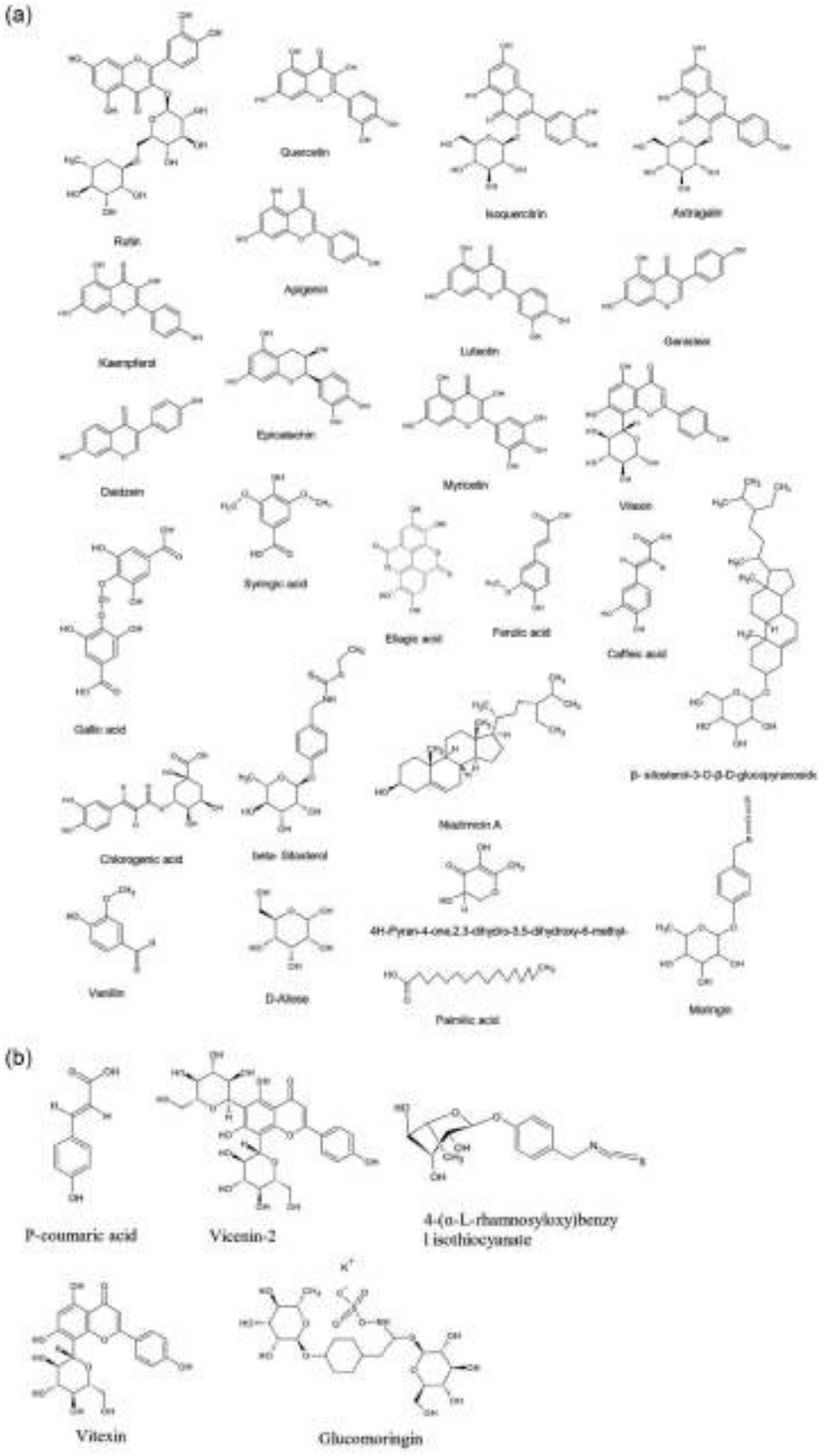

FIGURE 6 (a) Chemical structure of key phytoconstituents of M. oleifera. (b) Chemical structure of phytoconstituent of *M. oleifera*

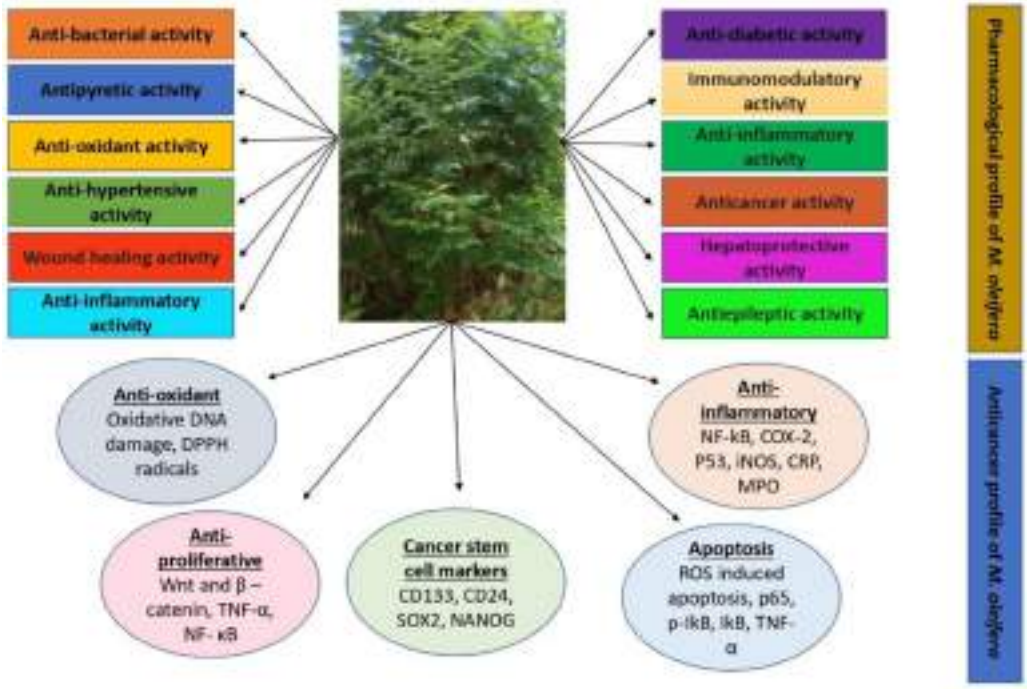

FIGURE 7 Pharmacological and anticancer profile of *M. oleifera*

observed following treatment with AITC for 24 h for PC-3 and LNCaP cells. Benzyl isothiocyanates (BITCs) slowed the growth of tumors in mice implanted with BxPC-3 tumor xenografts by 43%, according to (Boreddy et al., 2011) BITC treatment also reduced protein kinase B (AKT), mammalian target of rapamycin, forkhead box O3A, phosphorylation of phosphatidylinositide 3-kinase, FOXO1, and pyruvate dehydrogenase kinase. By inhibiting AKT, phenyethyl isothiocyanates have been proven to decrease the growth of cancer (Gao et al., 2011). Moringa isothiocyanates have been studied extensively in vitro but our preliminary in vitro studies, as well as studies involving other isothiocyanates, suggest they may be useful as cancer therapeutics.

Some important in vitro and in vivo studies conducted on different parts, extracts, and isolated compounds from *M. oleifera* for evaluating its anticancer properties are stipulated in Tables 3 and 4 respectively.

7.1 | Antioxidant potential of *M. oleifera*

In the multistage process of carcinogenesis, oxidative stress plays a key role in tying environmental toxicities to carcinogenesis. In response to both endogenous and exogenous stimuli, reactive oxygen species (ROS) are generated (Ziech et al., 2010). Environmental factors like radiation, chlorinated chemicals, and xenobiotics have been shown to be important inducers of cellular damage via ROS-mediated toxicity in both in vitro and in vivo investigations (Marnett, 2000). Superoxide dismutase, catalase, and glutathione peroxidase are examples of endogenous enzymatic antioxidant defences that can balance out oxidative microenvironments by various peroxides and chelating superoxide (Marnett, 2000). Additionally, nonenzymatic endogenous antioxidants such coenzyme Q, glutathione, vitamins E and C, and b-carotene can reduce ROS activity (Marnett, 2000). Ting with other cellular elements, such as phospholipids, leads to the production of secondary reactive intermediates, which then irreversibly link to DNA bases to form DNA adducts (Marnett, 2000). The process of creating DNA adducts is essential for the development of cancer because these adducts could result in mutations if they evade cellular repair mechanisms and persist (Wogan et al., 2004). The etiology of cancer has been linked to oxidative damages. The (8-oxo-dG) lesions are an important biomarker of oxidative DNA damage (Cooke et al., 2003; Dizdaroglu et al., 2008; Evans et al., 2004; Valko et al., 2004).

Numerous studies demonstrate that antioxidant supplementation leads to longer survival times, improved tumor response, or both, as well as less toxicities than controls; in some recent systematic reviews on this subject, there is no evidence that antioxidants interfere with chemotherapy mechanisms, with a potential that antioxidants may potentially enhance tumor response or patient survival (Block et al., 2007).

Free radicals are one of the main elements required for DNA mutation in the etiology of cancer, which then initiates the carcinogenesis stage (Johnson, 2004). The endogenous antioxidant system, which guards against free radicals in the body, can perform better when exogenous antioxidants from natural sources are used (Johnson, 2007). Polyphenol contents of *M. oleifera* extracts are reported to exhibit potent antioxidant activities (Luqman et al., 2012; Santos et al., 2012). Polyphenols and DPPH radical scavenging activities in the aqueous extract of *M. oleifera* leaves have been recently discovered (Luqman et al., 2012; Santos et al., 2012). Additionally, some research asserts that *M. oleifera*

TABLE 3 Anticancer claims of *M. oleifera* based on in vitro reports

Dosage form	In vitro model	Dose	Standard	Activity	References
Five fractions of methanol extract of its leaves: n-hexane, chloroform, ethyl acetate, butanol, and distilled water	MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) reduction assay by 96-well plates containing Hela cancer cell lines	26, 52, 104, 208, and 416 μg/ml	–	Reduction in Hela cancer cell viability, anticancer property	(Mumtaz et al., 2021)
Aqueous extract of leaves	Ehrlich ascites carcinoma (EAC) and human laryngeal carcinoma (Hep-2) cell culture	0.05, 0.1, 0.25, 0.5, and 1 mg/ml	Control (no treatment)	Anticancer	(Barhoi et al., 2020)
	Trypan blue dye exclusion assay	0.05, 0.1, 0.25, 0.5, and 1 mg/ml	Control (no treatment)	Dose-dependent decrease in viable cells	
	MTT assay	0.05, 0.1, 0.25, 0.5, and 1 mg/ml	Control (no treatment)	Dose-dependent decrease in viable cells	
	Lactate dehydrogenase (LDH) release assay	0.05, 0.1, 0.25, 0.5 and 1 mg/ml	Control (no treatment)	Dose and time dependent release of LDH	
	Cell cycle assay	0.05, 0.1, and 0.2 mg/Ml	Control (no treatment)	No cell cycle arrest but showing a dose and time-dependent accumulation of cells at sub-G1	
	Annexin V-FITC/PI (propidium iodide) staining	0.05, 0.1, and 0.2 mg/ml	Control (no treatment)	Increases apoptosis percent	
	Mitochondrial membrane potential	(0.05, 0.1, and 0.2 mg/ml)	Control (no treatment)	Apoptosis due to change in mitochondrial membrane potential	
Sequential leaf extract with hexane, ethyl acetate, and ethanol	MDA-MB-231 cells, colony formation assay	75, 100, and 150 μg/ml	Control (no treatment)	Clonogenic growth of cell line was completely inhibited	(Wisitpongpun et al., 2020)
	MTT assay	75, 100, and 150 μg/ml	Control (no treatment)	Cell viability decreased in time-dependent manner	
	Annexin V/7-AAD (7-Aminoactinomycin D) staining	150 μg/ml	Control (no treatment)	Induce apoptosis	
	Cell cycle assay	150 μg/ml	Control (no treatment)	Promote cell cycle arrest	
7-Octenoic acid	Cell migration assay (in vitro scratch assay)	1.5 mg/ml	Doxorubicin (1.5 μM)	Migratory cells number decreases across the wound suggesting its antimigratory effect	

(Continues)

TABLE 3 (Continued)

Dosage form	In vitro model	Dose	Standard	Activity	References
Oleamide		40 μg/ml	Doxorubicin (1.5 μM)	Migratory cells number decreases across the wound suggesting its antimigratory effect	
1-Phenyl-2-pentanol		250 μg/ml	Doxorubicin (1.5 μM)	Migratory cells number decreases across the wound suggesting its antimigratory effect	
7-Octenoic acid	Hoechst staining	2.5 mg/ml	Control (no treatment)	Apoptosis	
Oleamide		70 μg/ml	Control (no treatment)	Apoptosis	
1-Phenyl-2-pentanol		600 μg/ml	Control (no treatment)	Apoptosis	
Ethanol extract of leaves, bark, and seeds	HCT-8 and MDA-MB-231 cell line	250 and 500 μg/ml	Control (no treatment)	Leaves and bark inhibit cell survival	(Al-Asmari et al., 2015)
	Motility assay	250 and 500 μg/ml	Control (no treatment)	Leaves and bark decrease motility rate	
	Clonogenic survival assay	250 and 500 μg/ml	Control (no treatment)	Leaves and bark decrease colony formation	
	Cell viability assay	250 and 500 μg/ml	Control (no treatment)	Leaves and bark decrease cell survival	
	Apoptosis assay	250 and 500 μg/ml	Control (no treatment)	Apoptotic cells increase from 27 to 46% in leaves and from 27 to 29% in bark	
	Cell cycle assay	500 μg/ml	Control (no treatment)	G2/M enrichment was observed in leaves and bark showing cell cycle arrest	
Syringic acid	SW 480 cell line (Trypan blue assay)	0–2000 μg/ml	Control (no treatment)	Inhibitory effect at 1200 μg/mL	(Mihanfar et al., 2021)
	MTT assay	0–2000 μg/ml	Control (no treatment)	Decrease cell viability at 800–2000 μg/ml	

(Continues)

TABLE 3 (Continued)

Dosage form	In vitro model	Dose	Standard	Activity	References
	Cell proliferative assay	0–2000 μg/ml	Control (no treatment)	Antiproliferative activity at dose dependent manner (max at 1000–1200 μg/ml concentration)	
	TUNEL	0–2000 μg/ml	Control (no treatment)	Apoptosis at 1200 μg/ml	
	Anexin -V/PI flow cytometery	0–2000 μg/ml	Control (no treatment)	Increase apoptosis at 1000 and 1200 μg/ml	
	Lactate dehydrogenase release assay	0–2000 μg/ml	Control (no treatment)	Apoptosis at 1200 μg/ml	
	ROS (reactive oxygen species) evaluation	0–2000 μg/ml	Control (no treatment)	ROS generation at 1200 μg/ml	
	Antioxidant enzymes	0–2000 μg/ml	Control (no treatment)	Lower activity of catalase, reduce superoxide dismutase, inhibit glutathione reductase activity, reduce glutathione peroxidase at 1200 μg/ml, that is, leads to cell death	
	DNA damage	0–2000 μg/ml	Control (no treatment)	Increase in 8-oxo-dG, increased apurinic sites at 1200 μg/ml	
	Western blotting	0–2000 μg/ml	Control (no treatment)	Increase p53, decrease ERK1/2, P13K, AKT, and NF-kB	
M. oleifera, *T. tuberosum*, and *A. cherimola* ethanolic seeds extracts	Human CRC cells HCT-15, T84, SW480, CCD-18, HT-29	2.5–12 μg/ml	5-Fluorouracil	Dose-dependent proliferative inhibition	(Fuel et al., 2021)
	Antioxidant capacity	2.5–3 mM	–	Shows antioxidant activity	
	Glutathione S-transferase assay	2.5 μg/ml *M. oleifera*, 2 μg/ml *T. tuberosum*, 1. 5 μg/ml *A. cherimola*	Sulforaphane	Induce glutathione S-transferase activity	
	NAD(P)H: quinone oxidoreductase (QR) assay	25 μl of each sample	Sulforaphane	Induction of QR	
	Cell viability assay	–	Control (no treatment)	Inhibit cell viability	
	Cell cycle analysis	–	Control (no treatment)	Increase in SubG1 phase	
	Western blot analysis	–	Control (no treatment)	Increased cleaved caspase expression and microtubule-associated protein light chain 3	
	Lysotracker labeling	–	Control (no treatment)	Form autophagic vesicle	

(Continues)

TABLE 3 (Continued)

Dosage form	In vitro model	Dose	Standard	Activity	References
	Cellular reactive oxygen species	–	Control (no treatment)	Increased intracellular reactive oxygen species production	
	Real time PCR (polymerase chain reaction) analysis of cancer stem cells	–	Control (no treatment)	Shows strongest effect on CD24, CD133 (prominin-1), SOX2, NANOG markers	
Aqueous methanol, ethanol, ethyl acetate and chloroform extract of *M. oleifera* and *Vinca rosea* leaves	U266B1(Human B-lymphocyte plasmacytoma), myeloma cell culture	200 to 0.5 μg/ml	–	Shows cells apoptosis	(Cytotoxic Effect of Moringa oleifera Leaf Extracts on Human Multiple Myeloma Cell Lines 2022)
	Cytotoxicity Studies	200–0.5 μg/ml	–	Shows cytotoxic effect more than *Vinca rosea* extract	
	Neutral red dye uptake assay	200–0.5 μg/ml	–	Reduced cells viability	
Aqueous extract of leaves	HeLa cell line, cytotoxicity assay	10 to 100 μg/ml	Control (no treatment)	Concentration-dependent cytotoxic effect, decrease cell viability	(Varalakshmi & Nair, 2011)
	Trypan blue dye exclusion	1–100 μg/ml	Control (no treatment)	Cell count of HeLa cells decreased	
	DNA fragmentation-based apoptosis analysis	1–100 μg/ml	Control (no treatment)	Increase in internucleosomal DNA fragmentation	
	Ethidium bromide–acridine orange staining	1–100 μg/ml	Control (no treatment)	Apoptosis, appearance of cell shrinkage	
Methanol and dichloromethane extracts of leaves	DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate), radical scavenging assay	–	Quercetin	Methanol extract shows higher potential in radical scavenging, antioxidant	(Suphachai, 2014)
	ABTS radical cation decolorization assay	–	Trolox	Methanol extract shows higher potential in radical cation, antioxidant	

(Continues)

TABLE 3 (Continued)

Dosage form	In vitro model	Dose	Standard	Activity	References
	Human hepatocellular carcinoma (HepG2), colorectal adenocarcinoma (Caco-2) and breast adenocarcinoma (MCF-7) cell lines, and human dermal fibroblast, antiproliferative assay	0–250 μg/ml	Cisplatin	Exhibit antiproliferation on cancer cell lines, but showed no cytotoxicity on normal cells	
	Quinone reductase induction assay	0–100 μg/ml	β-Naphthoflavone	Dichloromethane significantly increased the quinone reductase induction ratio	
Hot water, cold water, or ethanol extracts of leaves	Antioxidant activity	5–20 μg in 50 μl	Quercetin	Ethanol extract shows highest antioxidant activity by inhibiting radical formation	(Khalafalla et al., 2010)
	Cell viability of HpG2 cell cultures	5, 10, and 20 μg/ml	Control (no treatment)	Ethanol extract shows remarkable destruction of lymphoblasts	
Ethyl acetate fraction of ethanol extract of flowers	MTT-assay, HePG2 (liver cancer cell line)	62.5, 125, 250, 500, and 1000 μg/ml	–	Shows cytotoxicity, anticancer	(Rajeshkanna et al., 2020)
Hydro ethanolic extract of leaves, seeds, stems, and root	DPPH scavenging capacity	100 μl	–	Leaf extracts Higher antioxidant activity in leaves extract	(Wang et al., 2020)
	FRAP assay	5.0 μl	Control (FeSO4)	Higher antioxidant activity in leaves extract	
	ABTS scavenging ability	80 μl	BHA	Higher antioxidant activity in leaves extract	
	CAL27 and CNE-1 cell line, Cell viability	0.005–8 mg/ml	–	–	
	Colony formation assay	0.12 mg/ml	Control (no treatment)	Colonies decreased, antiproliferative	

(Continues)

TABLE 3 (Continued)

Dosage form	In vitro model	Dose	Standard	Activity	References
	Annexin V-FITC/PI staining	0.12 mg/ml	Control (no treatment)	Induced apoptosis	
	Western blot analysis	–	–	Downregulated BCL-2 expression, while upregulated BAX expression	
Successive fractions from methanol extract of leaf by column chromatography	HCT 116	–	–	Inhibit cell growth	(Tragulpakseerojn, et al., 2017)
	MTT assay	–	Astragalin isoquercetin	Shows cytotoxicity, antiproliferative	
	Cell extraction and western blotting	–	Adriamycin, cisplatin	Decreased p-ERK1/2 and little decreased AKT expression, but not p38 MAPK (mitogen-activated protein kinases) in a concentration dependent manner	
Quercetin on A549 cells	Cell proliferation	0.1, 0.5, 1, 5, 10,20,50 70, 100, and 200 μM	Control (no treatment)	Showed a concentration-dependent cytotoxicity at higher concentrations (50–200 μM)	(Robaszkiewicz et al., 2007)
	Cell viability	0, 0.5, 5, 10, 50, 100, and 200 μM	–	At above 50 μM concentrations, concentration dependent decline in viability	
	Apoptosis Generation of reactive oxygen species in the cells	0, .5, 5, 10, 50,100, and 200 μM	–	Above 50 μM concentration decrease the fraction of live cells, increase the share of apoptotic and necrotic fractions	

–: No published data available.

TABLE 4 Anticancer claims of *M. oleifera* based on in vivo reports

Dosage form	In vivo model	Animal	Dose	Activity	Reference
Hydro methanolic and methanolic extract of leaves	Melanoma model	Mouse	1 g/kg b.wt.	Increase tumor volume doubling time, growth delay	(In vivo anticancer activity of the leaves & fruits of Moringa oleifera on mouse melanoma 2022)
Hydro methanolic and methanolic extract of fruits	Melanoma model	Mouse	500 mg/kg b.wt	Increase tumor volume doubling time, growth delay	(In vivo anticancer activity of the leaves & fruits of Moringa oleifera on mouse melanoma 2022)
Moringa oleifera alkaloids	Xenograft model	Nude mice	Control group: Saline 150 mg/kg 300 mg/kg	Inhibited prostate cancer (PC-3) cell xenograft tumor growth via the COX-2 (Cyclooxygenase-2)-mediated Wnt/β-catenin signaling pathway	(Xie et al., 2020)
Water soluble *M. oleifera* leaves extract	Hollow fiber assay	Nude mice	50 mg/kg, 100 mg/kg, 200 mg/kg, p.o.	Antiproliferative against human liver and lung cancer, produce stronger cytotoxicity in the HepG2 cells	(Jung et al., 2015)
M. oleifera flower trypsin inhibitor	Sarcoma 180-bearing mice	Mice	15 mg/kg 30 mg/kg, i.p. for 1 week	Antitumor activity	(Patriota et al., 2020)
Ethanol extract of leaf	Liver cancer induced by diethyl nitrosamine	Rat	Control group: corn oil test group: 500 mg/kg	Chemoprotective against hepatocellular carcinoma, antioxidant	(Sadek et al., 2017)
Boiled freeze-dried *M. oleifera* pods	Colitis-related colon carcinogenesis model induced by azoxymethane (AOM) and dextran sodium sulfate (DSS)	Mice	1.5, 3.0, and 6.0% of basal AIN-76 diet	6.0% helps to reduce tumor incidence, chemo-preventive agent	(Suppressive effects of Moringa oleifera Lam pod against mouse colon carcinogenesis induced by azoxymethane & dextran sodium sulfate - PubMed 2022)
Hydroethanolic extract of *M. oleifera* and isolated saponin	DMBA (7,12-dimethylbenz[a]hosphore)-induced renal carcinogenesis	Swiss albino mice	200 mg/kg, 400 mg/kg	Potential anticarcinogenic	(Aboulthana et al., 2021)
M. oleifera pods hydro-ethanolic extract	DMBA-induced hepatocarcinogenesis	Swiss albino mice	200 mg/kg, 400 mg/kg	Extract shows total antioxidant capacity at 0.1–1 mg/ml concentrations, hepatoprotective activity	(Hepatoprotective & antioxidant potential of Moringa oleifera pods against DMBA-induced hepatocarcinogenesis in male mice - Google Search 2022)

(Continues)

TABLE 4 (Continued)

Dosage form	In vivo model	Animal	Dose	Activity	Reference
Hydro-alchoholic drumsticks extract of *M. oliefera*	DMBA-induced skin papilloma	Female Swiss albino mice	5 mg/kg body weight topical application	Significant decrease percentage of tumor incidence, the average number of papillomas per mouse	(Chemomodulatory effect of Moringa oleifera, Lam, on hepatic carcinogen metabolising enzymes, antioxidant parameters & skin papillomagenesis in mice - PubMed 2022)
Aqueous extracts of *M. Oleifera* leaves	EAC solid tumor model	Balb/c mice	200 mg/kg, 400 mg/kg	Life span of tumor-bearing mice increases at both doses level, shows tumor growth regression, physiology of normal mice does not alter	(Barhoi et al., 2021)
Ethyl acetate extract of *M. oleifera* (F1 fraction)	DLA model	Swiss albino mice	F1 at the dose of 5 mg/kg, 10 mg/kg p.o.	Significant increase in mean survival time in mice	(Krishnamurthy et al., 2015)
Ethanol extract of moringa leaves (*Moringa oleifera* L.) and ethanol extract of papaya leaves (Carica papaya L.) combination	Tumor-induced DMBA (7,12-dimethylbenz(a)anthracene)	Sprague–Dawley rat	150 and 200 mg/kg BW	Slowing tumor tissue formation at a dose of 150 mg/kg BW	(Arif et al., 2020)
Aqueous extract of *M. oleifera* leaves	Carrageenan-induced paw edema	Sprague–Dawley rats	10, 30, and 100 mg/kg	Shows anti-inflammatory activity	(Sulaiman et al., 2009)
Niazimicin	DMBA as initiator and TPA as tumor promoter induced two-stage carcinogenesis in mouse skin using	Mice	Niazimicin 85 nmol in acetone 0.1 ml topically applied	Potent antitumor promoter in chemical carcinogenesis	(Guevara et al., 1999)
n-Hexane, dichloromethane (DCM), ethyl acetate (EtOAc), n-butanol and aqueous fractions of *Moringa oleifera* (*M. oleifera*) leaves methanol extract	Carbon tetrachloride (CCl4)-induced liver injury	Sprague–Dawley rat	100 mg/kg b.wt. orally in olive oil	n-Hexane, DCM and aqueous fraction of *M. oleifera* methanol extract ameliorates CCl4-induced pathological changes	(Atta et al., 2018)
Ethanol extract of *M. oleifera*	Benzene-induced leukemia	Wister rats	0.2 ml of 100 mg/ml	Increased expression TNF-α enhanced apoptosis	(Akanni et al., 2014)

(Continues)

TABLE 4 (Continued)

Dosage form	In vivo model	Animal	Dose	Activity	Reference
Aqueous silver *M. oleifera* nanoextract	Colon cancer induced by azoxymethane	Wister rat	687.50 mg/Kg b.w	Tumor (CEA and CA 19-9) levels decreased inflammatory (CRP (C-reactive protein) and MPO (myeloperoxidase)) markers normal levels	(W. Aboulthana, … W. S.-… J. of C., & undefined 2021 2022)
Crude ethanol extract of *M. oleifera* dried seeds, hexane, butanol and water fraction	Carrageenan-induced inflammation in the hind paw	Mice	3 mg/g body weight	Shows anti-inflammatory activity, antitumor-promoting activity	(Anti-inflammatory & antitumor activities of seed extracts of malunggay, Moringa oleifera L. (Moringaceae) 2022)
M. oleifera leaves ethanolic extract	Cobalt-triggered apoptosis	Sprague–Dawley male rats	400 mg/kg body weight	Reduced Cobalt dichloride ($CoCl_2$)-induced genotoxicity and oxidative injury, more effective when administered as prophylactic regimen in $CoCl_2$ exposure	(Khalil et al., 2020)
Syringic acid	Colon cancer	Rat	–	Tumor volume and incidence Reduction	(Mihanfar et al., 2021)
Dietary quercetin and rutin, phenolic flavonoids	Azoxymethanol-induced colonic neoplasia	CF1 female mice	0.1, 0.5, or 2.0% quercetin and 1.0 or 4.0% rutin	Both 2% quercetin and 4% rutin suppressed tumor multiplicity	(Deschner et al., 1991)
Quercetin and rutin added to standard AIN-76A diet	Azoxymethane-treated mouse colon	CF1 mice	Unmodified AIN-76A or AIN-76A supplemented with either 2% quercetin or 4% rutin	Markedly increased in number of apoptotic cells/column and apoptotic indices, increased number in colonic epithelial cells per crypt column	(Yang et al., 2000)

–: No published data available.

leaves are abundant in polyphenols and flavonoids and possess antioxidant action (Luqman et al., 2012; Santos et al., 2012). In accordance with the previous works, *M. oleifera* leaves extracted with methanol and dichloromethane also showed antioxidant activity (Santos et al., 2012).

Free radicals can be successfully scavenged by phenolic acids and flavonoids, which often have antioxidant properties in vitro (Zhang et al., 2015). There was a significant positive study found that leaf extracts had the highest content of phenolic compounds, such as gallic acid, kaempferol, ellagic acid, chlorogenic acid, catechin, isoquercitrin (Oboh et al., 2018), quercetin, and epicatechin (Saini et al., 2016). This suggested that the phenolic acids might mainly be responsible for the antioxidant properties of leaves.

7.2 | Anti-inflammatory potential of *M. oleifera*

Inflammation plays a critical role in cancer management (Rayburn et al., 2009). Inflammation is also linked to various cancers, indicating that reducing inflammation is a viable method to prevent or treat cancer (Rayburn et al., 2009). Chronic inflammation causes an increase in angiogenic factors, tissue destruction, fibrosis, and infiltration of mononuclear immune cells (Rayburn et al., 2009). Chronic inflammation also results in an increase in angiogenesis and invasion, genomic damage, DNA synthesis, cellular proliferation, disruption of DNA repair pathways, and suppression of apoptosis (Rayburn et al., 2009). A number of these processes are implicated in the initiation and progression of cancer. Proinflammatory molecules, such as cytokines, inducible nitric oxide synthase, ROS, and NF-kB, are also upregulated during chronic inflammation (Rayburn et al., 2009). Together, malignant cells grow exponentially in a microenvironment favored by these processes. It might therefore be possible that inflammation produces both key mutations and provides an appropriate environment for tumor development (Rayburn et al., 2009). Many studies show that cancer incidences and recurrences can be reduced and patients' prognoses can be improved by using anti-inflammatory agents (Rayburn et al., 2009). A new therapeutic approach to cancer treatment may be proposed by combining anti-inflammatory agents with traditional anticancer therapies (Rayburn et al., 2009). *M. oleifera*'s different parts, extracts, and isolated compounds exhibit anti-inflammatory properties in various experiments (Aboulthana & undefined, 2022; Anti-inflammatory & antitumor activities of seed extracts of malunggay, 2022; Rajan et al., 2016; Shah et al., 2021; Sulaiman et al., 2009) indicating its demonstrating as an anticancer agent.

7.3 | Regulation of cell proliferation

The growth and spread of cancer rely greatly on proliferation. Cells with a high basal level of proliferation and regeneration are killed by cytotoxic medicines used in cancer therapy.

The antiproliferative activity of *M. oleifera* has been demonstrated in previous studies, including the proliferation of breast cancer MDA-MB-23, human liver cancer HepG2, colon cancer HCT-8, and lung cancer A549 cells (Al-Asmari et al., 2015; Karim et al., 2016).

Interestingly, up to 95% of the proliferation of neuroblastoma SH-SY5Y cells are inhibited by *M. oleifera*. A remarkable 95% inhibition rate is observed when *M. oleifera* is applied to neuroblastoma SH-SY5Y cells. Additionally, the leaves extract also inhibited proliferation of KB cells, as assessed by changes in viability and cell morphology, and by fragmentation of DNA (Sharma & Martins, 2020; Sreelatha et al., 2011).

7.4 | Cycle arrest and apoptosis

It has been shown that apoptosis plays an important role in maintaining homeostasis by eliminating damaged cells. One important mechanism of some antitumor medications is their capacity to induce apoptosis. Previous researches have demonstrated that *M. oleifera* leaf extract isolated isothiocyanates induce apoptosis in various cancer cells (Sreelatha et al., 2011; Waterman et al., 2014). *M. oleifera* extract inhibits the proliferation of cancer cells, according to these studies, although the underlying mechanisms are unclear. When *M. oleifera* is used, a strong correlation is shown between the activation of caspase signaling and other apoptosis-related signaling pathways or related mechanisms. The average sub-G1 populations in A549 lung cancer cells can increase after 6 h of treatment of *M. oleifera* extract at different concentrations. When *M. oleifera* leaf extract is administered, cleaved caspase-3 is upregulated and caspase-3 is downregulated in a dose-dependent way (Jung, 2014). Furthermore, the application of *M. oleifera* leaf extract engendered a time-dependent rise in phosphor-extracellular signal-related kinase (p-ERK) and, phosphor-c-Jun N-terminal kinase (p-JNK) without affecting total JNK or ERK protein, suggesting that *M. oleifera* induces apoptosis in human melanoma A2058 cells via activating these kinases (Guon & Chung, 2017). Cholangiocarcinoma (CCA) cells treated with *M. oleifera* seed extract showed enhanced activation of hosphor-p44/42 MAPK (ERK1/2) and hosphor-p38 MAPK, suggesting that the concentration of pro- and antiapoptotic signaling proteins may define the apoptotic characteristics of this drug (Leelawat & Leelawat, 2017).

MDA-MB-231 (breast cancer cell line) and HCT-8 cells (colorectal cancer cell lines) were treated with *M. oleifera* bark and leaves extracts that increased apoptosis and effectively arrested cell cycle progression at the G2/M phase. Isopropyl isothiocynate, eugenol, hexadeconoic acid ethyl ester, and D-allose are some of the compounds that are responsible for its bioactivity (Al-Asmari et al., 2015).

A failure of the cell cycle's checkpoint frequently results in DNA mutations and genomic rearrangements, contributing to cancer development through genetic instability. Numerous anticancer drugs have been found to cause apoptosis in cancer cells by arresting cell cycle at a specific junction (Khan et al., 2012; Khan et al., 2012). In addition, Jung discovered that there was a dose-dependent decrease in cyclin D1 was discovered in cells treated with aqueous leaf extract of *M. oleifera*. Observations show that leaf extract of *M. oleifera* is capable of arresting cell cycle in human pancreatic cancer cells (PANC-1 cells) and reducing the expression of p65, p-IkB, and IkB proteins in a dose-dependent

manner suggests the leaf extract of *M. oleifera* has potential as a phytochemical for targeting cancer cells by arresting cell cycle (Kou et al.,; Rai et al., 2021).

7.5 | Effect on chemotherapeutic drugs

The major cause of chemotherapy failure is multidrug resistance (MDR). As a result of MDR to chemotherapy drugs, treatment efficacy is often reduced and the likelihood of cancer recurrence is increased (Kou et al., 2017). There are many advantages to phytochemical compounds, such as their low toxicity, minimal side effects, numerous targets, and low tumor resistance, as well as their ability to inhibit tumor growth and regulate the immune system (Kou et al., 2017). Research into natural compounds that have reversed MDR has become a focus in the fight against cancer. When doxorubicin is combined with *M. oleifera* callus and leaf extracts, a strong interaction occurs over cell proliferation inhibition, which is also associated with triggering apoptosis. There are no commercially available chemo-preventive agents derived from *M. Oleifera* (Jafarain et al., 2014). Employing *M. oleifera* along with currently available anticancer medications could be a potential therapeutic approach for cancer.

7.6 | Regulating enzyme activity

Maintaining a balance and activating drug metabolizing enzymes in phase I and II is a well-known way to protect against chemical carcinogens (Singh et al., 2000). The pod extract of *M. oleifera*, which has a significant protective role in carcinogenesis, is capable of restoring lost activity of GSH and GST (glutathione s-transferase) (Sharma et al., 2012; Singh et al., 2000). An extract of hydro-alcoholic Drumstick *M. oleifera* is able to induce not only phase I but phase II enzyme production in the liver, increasing cytochrome B5 levels, cytochrome P450 levels, and GST levels (Dasgupta et al., 2003). Additionally, it has been shown that *M. oleifera*'s potential as a chemo-preventive agent is strongly associated with its antioxidant activity. Additionally, by successfully reducing renal oxidative stress and toxicity, it has been shown in mice that pod extracts *M. oleifera* (200 and 400 mg/kg body weight; p.o.) and its saponin isolated from its pods (50 mg/kg body weight; p.o.) can reduce DMBA-induced kidney carcinogenesis (Sharma & Paliwal, 2014).

According to the above thorough analysis from various angles, a wide range of signaling pathways may be involved in the antitumor effect of *M. oleifera*, such as the induction of cell apoptosis, cell cycle arrest, inhibition of cell proliferation, inhibition of angiogenesis, and collaboration with chemotherapeutic agents (Kou et al., 2018).

7.7 | Potential of *M. oleifera* microRNA in anticancer

MicroRNA (miRNA) are small noncoding RNAs (ncRNAs) measuring about 22 nucleotides in length (He et al., 2020). miRNA plays an important role in gene regulation, and their dysregulation is implicated in cancer (He et al., 2020). Since an imbalance in miRNA expression levels is associated with tumorigenesis, miRNA-based cancer therapies are primarily focused on restoring miRNA function and inhibiting overexpressed miRNA (Fu et al).

Authors found presence of miRNA in leaves, callus, and seeds (Pirrã et al., 2019). Besides providing essential nutrients, plants can also regulate human gene expression in a cross-kingdom manner (Minutolo et al). Gismondi et al. (2022) found that developing in vitro cultures able to accumulate miRNAs with high nutraceutical properties may be crucial for the understanding of the parameters that can modify miRNA pools in *M. oleifera* tissues, since plant miRNAs have cross-kingdom activity on human organisms which are introduced by diet.The bioinformatic analysis of miRNA in *M. oleifera*, belonging to 18 conserved families, found that they target BCL2 (B-cell lymphoma 2), IL2RA (interleukin-2 (IL-2) receptor alpha), TNF (tumor necrosis factor), and VAV1 (proto-oncogene vav) at high affinity, all of which regulate apoptosis, cell cycle, and immune responses (Minutolo et al). Pirrã et al. (2019) reported in their research that miR159 miRNA levels were high under all experimental conditions. A study by Chin et al. (2016) reported that miR159 inhibited breast cancer growth. In another study, computer-based approaches were used to investigate the mechanistic action and influence of *M. oleifera* seed miRNA on vital human target genes (Bhadresha et al., 2022). Bhadresha et al. (2022) found that there is promising role for *M. oleifera* seed-derived miRNA-targeted genes in bone-associated biological processes, with notable bone disease implication and the ability to control vigorous downstream signaling pathways in various functional processes and bone.

Researchers found a total of 48 genes are regulated by miRNA derived from *M. oleifera* seeds among 12 genes that are associated with epidemiologically prevalent malignancies such as pancreatic cancer, cervical cancer, neuroendocrine tumors, tongue cancer, somatic, hepatocellular carcinoma, squamous cell carcinoma, breast cancer, ovarian cancer, prostate cancer, systemic sclerosis, and lung cancer (Hou et al., 2017; Ju et al., 2007; Kreis et al., 2019; Meng et al., 2006). The results of these studies pave the way for future research that could uncover a role for *M. oleifera* miRNA in inhibiting cross-kingdom regulation in cancer prevention and treatment.

7.8 | Proteins inhibited by *M. oleifera*-molecular docking

M. oleifera phytocompounds with affinities for inhibiting DHFR and BCL-2, known as disease proteins in cancer proliferation, were shown to have therapeutic potential in a molecular docking study using a computational approach (Aslam, 2005).

The ADMET profiling is carried out to provide insight into the efficacy of these inhibitors as prospects for new medication development. By not breaking the Lipski Rule of Five (RO5), ML2 and ML4 also demonstrated the best drug-likeness in their ADMET profiles. Small molecules drug-likeness can be determined by Lipinski RO5. Comparatively, MS2, ML5, and ML13 are less harmful than other possible inhibitors, according to a wealth of information on hazardous

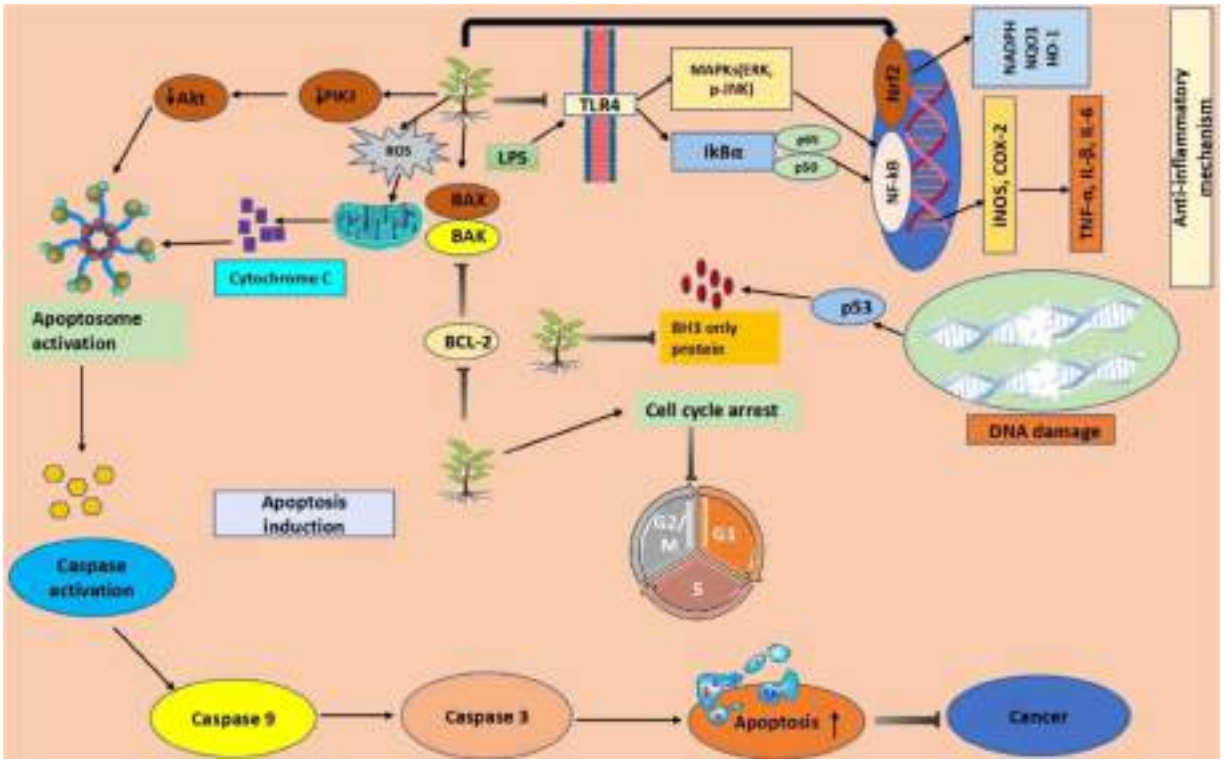

FIGURE 8 Mechanisms underlying the bioactivity of *M. oleifera* against cancer

endpoints and lethal dose values. In the compound, TPSA (topological polar surface area) describes the surface of polar atoms. It has been shown that compounds with higher TPSA have a reduced permeability to membranes and are more effective substrates for p-glycoprotein (evidence for drug efflux from the cell) than those with lower TPSA (Blake 2000). Therefore, lower TPSA was favorable for drug-like properties among potential inhibitors. It has also been predicted that a molecule that is more effective at permeating the BBB should also have a lower TPSA value (Chico et al., 2009). In the light of these, the Lipinski RO5 is not violated by ML4 and ML5, so ML4 and ML5 may be more likely to be effective therapeutically than all possible inhibitor (Aslam, 2005).

8 | MECHANISTIC ROLE OF *M. oleifera* AS AN ANTICANCER DRUG

Recent studies have demonstrated the anticancer potential of various *M. oleifera* extracts in a variety of animal models by potentially intervening multiple mechanisms such as the expression of TNF-α, CRP, MPO, CD133, CD24, SOX2, and NANOG markers, change in mitochondrial membrane potential, ROS generation, downregulation of COX-2, Wnt and β-catenin, NF-κB (nuclear factor kappa B), catalase activity, superoxide dismutase, glutathione reductase activity, glutathione peroxidase and BCL-2 expression, G2/M enrichment and upregulation of BAX, 8-oxo-dG, apurinic sites, p53, GST, p-ERK1/2, AKT and QR expression (Figures 7 and 8).

The growth, differentiation, oncogenesis, invasion, and metastasis of tumors are all significantly influenced by the COX-2, Wnt, and β-catenin signaling system. Previous research found that therapy suppressed the Wnt and β-catenin signaling pathway, which reduced cancer cell proliferation and elevated apoptosis. Additionally, antiproliferative and apoptotic activities are observed in the *M. oleifera* plant, which is related to the downregulation of the COX-2, Wnt, and β-catenin signaling pathways (Han et al., 2020).

Because TNF-α has a cytotoxic effect on a variety of tumor cells, it has been found to be an effective anticancer therapy. TNF-α has prometastatic properties and unfavorable effects of activating NF-κB signaling, however, restrict its therapeutic use in the treatment of cancer. The use of TNF-α-mediated apoptosis therapy for cancer patients must therefore be made possible by sensitizing drugs that can mitigate this unfavorable effect. A variety of pharmacological activities, including anti-inflammation, antibacterial, antivirus, and anticancer, have been demonstrated for the *M. oleifera* plant. We found that the *M. oleifera* plant could suppress NF-κB signaling and thus inhibit the activated T lymphocytes. Here, we demonstrated that *M. oleifera* plant significantly reduced TNF-α-induced NF-κB activation and the expression of its target genes involved in cancer cell proliferation, thereby potentiating TNF-α-mediated cell death in cancer (Akanni et al., 2014; Kam et al., 2013; Mihanfar et al., 2021). Ethanolic extracts of *M. oleifera* were able to stimulate GST and QR activity, which are both protective mechanisms against chemically induced carcinogenesis and can be employed to lessen the toxicity and side effects of various chemotherapy drugs (Fuel et al., 2021).

Furthermore, *M. oleifera* ethanolic extracts reduced the expression of cancer stem cell markers like CD133, CD24, SOX2, and NANOG (Fuel et al., 2021). Cancer stem cell removal is thought to have the potential to completely remove the disease. By employing therapeutic antibodies, cancer stem cell surface markers offer molecularly targeted treatments for a variety of cancers (Kam et al., 2013).

CRP is a positive protein during the acute phase of tissue damage and inflammation, and an increase in its level correctly indicated persistent tissue damage and inflammation compared with other biochemical markers. Additionally, the MPO activity is a reliable indicator of tissue damage brought on by inflammatory responses. According to research, *M. oleifera* significantly reduced the levels of these inflammatory markers (CRP level and MPO activity) (Aboulthana & undefined, 2022; Hall et al).

Many oxygen-centered free radicals, as well as other physiological and biochemical activities within the human body, can result in the production of ROS. High concentrations of these free radicals can lead to oxidative stress, which eventually causes a number of chronic diseases in people, including diabetes, cancer, atherosclerosis, and other degenerative conditions. Because of their higher metabolic rate, gene mutations, and relative hypoxia, tumor cells produce more ROS than normal, which are then suppressed by the cells' enhanced antioxidant enzymatic and nonenzymatic mechanisms. But ROS can also cause cell death that has been specifically programmed. Therefore, medications can be created as part of therapeutic approaches based on controlling ROS levels to treat cancer. Compelling evidence indicate the role of *M. oleifera* in modulating the ROS levels to treat cancer (Fuel et al., 2021; Perillo et al., 2020).

9 | ANTICANCER CLAIMS OF *M. oleifera* BASED ON CLINICAL STUDIES

Though many clinical studies are available on different parts, extract, and isolated compounds from *M. oleifera*, but only few are related to anticancer evaluation. Clinical studies related to anticancer properties are only discussed here. A phase I clinical trial was conducted on flavonoid quercetin. In this study, patients of median age 56 (range 23–78 years) years having history of tumor histologies in large bowel (14), ovary (10), pancreas (seven), melanoma (six), stomach (five), renal (two), hepatoma (three), nonsmall cell lung cancer (two), testicular teratoma (one), and gastrinoma (one) were treated with quercetin, intravenously at different doses (60,120, 200,300, 420, 630, 945, 1400,1400, 1700, and 2000 mg/m^2) (Phase I clinical trial of the flavonoid quercetin: pharmacokinetics & evidence for in vivo tyrosine kinase inhibition - PubMed, 2022).

A moderate level of local pain was observed at the initial dose level (60 mg/m^2) at the site of injection for 10 s, which is further followed by brief period of flushing, affecting the whole body accompanied by sweating for 3 min but there was no drop in blood pressure observed. Quercetin at 945 mg/m^2 and above doses concentration produced severe pain on site of injection in the upper arm. Two patients who received 50 ml RIMSO bolus injections suffered from pain and flushing as a result of this injection. A dose of 630 mg/m^2 of quercetin administered via a Hickman catheter causes no pain, but a slight flush when administered. A further dose increases to 1400 mg/m^2 caused dyspnea during and for a few minutes, but a dose increases to 2000 mg/m^2 caused severe dyspnea that lasted for 5 min. At 1400 mg/m^2 dose, two out of 10 treated patients had shown renal toxicity, one at grade 2 and one at grade 4. In nine out of 11 patients, quercetin treatment at 1 h demonstrated a significant reduction in lymphocyte protein tyrosine phosphorylation that lasted 16 h after treatment. An ovarian cancer patient who was refractory to cisplatin after two courses of quercetin (420 mg/m^2) showed a decline in CA 125 from 295 to 255 units/ml following two courses of quercetin, and a similar decrease in serum a-fetoprotein in another patient with hepatocellular carcinoma. It is safe to administer quercetin intravenously. Interestingly, it was found that the plasma levels achieved inhibited lymphocyte tyrosine kinase activity and inhibited tumor growth (Phase I clinical trial of the flavonoid quercetin: pharmacokinetics & evidence for in vivo tyrosine kinase inhibition - PubMed, 2022).

For a thorough understanding of the efficacy of *M. oleifera*, a multicentric study is required, which is crucial to understand its efficacy. The traditional medical systems of Ayurveda, Chinese medicine, and Iranian medicine follow an individual approach to treatment according to the constitution of the patient, which is based on the physician's well-defined wisdom. While personalized medicine has gained popularity in the last decade, it is not a new concept since it is based on ancient medicinal practices. As a rapidly advancing therapeutic approach, personalized medicine is poised to revolutionize and improve healthcare systems across the globe. In personalized medicine, treatment strategies are tailored to each individual based on their clinical, genomic, epigenetic, proteomic, and environmental profiles. Modern biomedical science offers hope that symptomatic treatment approaches can be transformed into personalized, predictive therapies based on genetic makeup. To shape the future of medicine, *M. oleifera* should be studied for personalized medicine (Sharma & Prajapati, 2020).

10 | INDUSTRIAL SIGNIFICANCE

Almost every part of the moringa tree is edible and has been consumed by humans for centuries. There are many applications for it, including pharmaceuticals, nutraceuticals, functional foods, biodiesel production, and water purification (Saini, 2022). Additionally, it is among the finest solutions for treating malnutrition in children under the age of 3 years (Global Moringa Products Market Size & Share | Industry Report, 20252022). Biodiesel can be made from moringa seed oil, which meets all the main specifications of US, German, and European standards (Mofijur et al., 2014). Moringa seed oil contains high levels of monounsaturated fatty acids in the form of oleic acid (C18:1) and is used in the manufacture of biodiesel as a source of fatty acids. It is also known as "Ben oil" and can yield 30–40% of weight (Azam et al., 2005; Rashid et al., 2008). The unique properties of moringa oil have made it highly valued in cosmetic industry for its ability to spread easily on the skin. Consequently, it is a good choice for massage and aromatherapy. Since

the oil has such a strong ability to capture and hold even the most elusive odours, perfume makers highly regard it. In order to meet the growing industrial demand for gums, it has been required to investigate newer sources of gum. It has been claimed that the tree *M. oleifera*'s gum has the ability to produce gel when applied topically (Rashid et al., 2008). Due to the plant's widespread availability, the exudates from the *M. oleifera* tree's stem were looked into for potential use as a suspending agent in pharmaceutical formulations (Mulugeta & Fekadu, 2014). The wood provides a pulp that is regarded as good for newsprint, wrapping, printing, and writing sheets. Moringa seed has oil in it. In the food industry, it serves as a preservative. It makes a great salad dressing oil. *M. oleifera* leaves and seeds are used as animal forage. The market is seeing an increase in demand for these items because of all the aforementioned considerations (Global Moringa Products Market Size & Share | Industry Report, 20252022). There are several classes of secondary metabolites found in plants that determine bioactivity of *M. oleifera* (Kou et al., 2018). Using standardized growth conditions for *M. oleifera* in vitro cultures, researchers developed a biotechnological system that could be used to produce antioxidant molecules in a controlled, rapid, and guaranteed manner for pharmaceutical applications (Hassanein et al., 2019; Zanella et al., 2019). As a result, it is quite important from a commercial and industrial standpoint. Some of the important formulations available in the market along with their uses are stipulated in Table 5.

11 | NUTRITIONAL PROFILE

Leaves, flowers, immature pods, and fruits of *M. oleifera*'s are traditionally eaten as a highly nutritious vegetable in a variety of cultures, especially in India, Pakistan, Hawaii, Philippines, and several African countries (Table 6) (Valdez-Solana et al., 2015). In developing countries, *M. oleifera* is used to treat and combat malnutrition, especially in infants and nursing mothers, due to its chemical constituents. Vitamins, minerals, protein, antioxidants, and other vital substances that your body needs to keep healthy are all naturally found in moringa, a whole-food source (Dhakar et al., 2011). Minerals like calcium, potassium, zinc, magnesium, iron, and copper are abundant in *M. oleifera* leaves (Kasolo et al., 2010). *M. oleifera* also contains vitamins such beta-carotene of vitamin A, vitamin B such as pyridoxine, nicotinic acid, and folic acid, vitamins C, D, and E (Mbikay, 2012). Saini et al. (2012) found in their study that *M. oleifera* derived from tissue culture had a higher lutein, b-carotene, a-tocopherol, and total carotene content than conventionally grown plants. *M. oleifera* contains phytochemicals like flavonoids, sterols, alkaloids, terpenoids, tannins, saponins, anthraquinones, and reducing sugar (Berkovich et al., 2013). According to claims, moringa has 15 times more potassium than bananas, seven times more vitamin C than oranges, 10 times more vitamin A than carrots, 17 times more calcium than milk, 25 times more iron than spinach, and nine times more protein than yoghurt (Rockwood et al., 2013). The tiny leaves of moringa pack a powerful nutritional punch, containing more calcium than milk, more iron than spinach, and more protein than eggs (Islam et al., 2021). Palmitic acid is saturated fatty acid (Carta et al., 2017). Researchers have found that all parts of moringa leaf, seed, and bark contain palmitic acid, which shows cytotoxicity against human leukemic cells as well as antitumor activity in mice (Harada et al., 2002). High fiber content in moringa leaves facilitates digestion and prevents colon cancer (Gopalakrishnan et al., 2016). Moringa tea, tablets, capsules, powder, soaps, and face washes are just a few of the many items made from the moringa plant by several companies throughout the globe (Singh & Singh, 2022). It is referred as the miracle tree because of its nutritional properties.

There is no doubt that nutrient content varies with plantation site (Aslam, 2005) and season (Meireles et al., 2020).

12 TOXICITY AND SAFETY CONCERNS OF *M. oleifera*

As of yet, no adverse effects have been reported in any human studies, which will be discussed in greater detail in the text. Additionally, various preparations continue to be used around the world as food and as medicine with no reports of adverse effects. *M. oleifera* have also been subjected to multiple studies on the potential toxicity of various preparations. Results of different studies are stipulated in Table 8. Overall studies depict no adverse upto the dose of 2000 mg/kg orally.

12 | ABSORPTION, DISTRIBUTION, AND EXCRETION OF *M. oleifera*

No study on pharmacokinetic profile of complete *M. oleifera* plant is available; however, various studies are conducted to study the absorption, metabolism, and excretion of its isolated compound. Some of the important studies are discussed below.

In a study, four male and two female volunteers received 4 g of quercetin orally over a 24-h period. Within 24 h, neither quercetin nor its derivatives were detected in blood or urine. However, 53% was recovered in feces within 72 h. The blood plasma levels of six volunteers were decreased biphasically with half-lives of 8.8 min and 2.4 h after receiving 100 mg of quercetin intravenously. Protein binding was greater than 98%.

Within 9 h after the injection, 0.65% of the intravenous dose was excreted unchanged, while 7.4% was excreted as conjugate; no other excretion took place for 24 h after the injection (Quercetin | C15H10O7 - PubChem, 2022).

In another study, ACI rats were administered 14C-quercetin orally, and absorbed about 20% of the dose, decomposed more than 30% into 14-CO2, and excreted unchanged about 30% in feces (Quercetin | C15H10O7 - PubChem, 2022). The glucosides of quercetin in a diet (64.2 mg expressed as aglycone) were administered to both males and females in a separate study. After 2.9 h of ingestion, quercetin reached its peak plasma concentration of 196 ng/ml. The plasma concentration of quercetin had a biphasic time-course. During the distribution phase of quercetin's plasma concentration, the half-life was 3.8 h and during

TABLE 5 Formulations containing *M. Oleifera*

Dosage form	Route of administration	Aliment/use	References
Shigru churna	Oral	Worms, headache, running nose	((PDF) AYURVEDIC MEDICINE: A REVIEW ON MEDICINAL IMPORTANCE OF SHIGRU (Moringa oleifera Lam) IN SAMHITAS 2022)
Shigru lepa	Topical	Swelling, itching, skin disease	
Vyoshadya Saktu	Oral	Diabetes	
Shigru tail	Topical	Skin diseases, itching	
Kanak kshiri tail	Topical	Helps in deworming, different skin disease, itching	
Agurvadya Taila	Topical	Fever	
Shigru varti	Topical	Eye diseases	
Mulakadya Taila	Topical	Reduce joint pain	
Sanjivana Agada	Topical/oral	Poisoning	
Vasisth Haritaki	Oral	Reduce cough	
Kshara taila	Topical	Mouth, ear, throat disease	
Shigru ghrita	Oral	Epilepsy, schizophrenia, weakness	
Moringa tea	Oral	Antioxidant, helps in digestion, healing, delay aging,	(Meireles et al., 2020)
Naturinga Moringa capsules	Oral	Anti-inflammatory, helps in lowering cholesterol level, helps to improve diabetic condition	
Moringa kids multivitamin complex	Oral	Immunomodulatory, rich source of vitamins and minerals	
Moringa powder	Oral	Improves physical condition, rich source mineral, vitamins, fibers	
Bio-hera Moringa capsules	Oral	Increase natural body defence, improves skin health, helps to reverse aging process	
Moringa syrup	Oral	Improve immunity, general health	
Moringa powder organic	Oral	Boost energy level, rich source of vitamin C, amino acid, iron, calcium	
Moringa organic tea	Oral	Reduces stress, antioxidant, build stamina	
Organic Moringa superfood supplements—capsules	Oral	Nutritional whole food, restore diet imbalances	
Iswari Moringa Superfood Powder Bio	Oral	Nutrient-rich super food	
Nutrabasics—Moringa	Oral	Helps to maintain blood glucose levels	

TABLE 6 Edible plant parts and their usage

Country	Form of usage	Parts of plant	Reference
Nigeria	Herbal tea Vegetable soup Leaves are chewed as snack Salad Spice	Leaves, stem, roots	(Stevens et al., 2013)
Philippines	Mixed in chicken or shellfish soups to enhance breast milk production	Leaves	([PDF] A double-blind, randomized controlled trial on the use of malunggay (Moringa oleifera) for augmentation of the volume ofbreastmilk among non-nursing mothers of preterm infants | Semantic Scholar 2022)
India	Used as vegetable Moringa squash Use as a pickle Cooked roasted seed as a snacks Immature green pods prepared as green bean Moringa chocolate bars Salad dressing Moringa seed flour added in wheat/rice flour Cooked leaves as *Bhaaji* Smoothies	Tender pods, flowers, young leaves	(Drumstick (Moringa oleifera): A Multipurpose Indian Vegetable on JSTOR 2022; Sonewane et al., 2022)
Mexico	Vegetable Snacks such as *Sopes*, *Tortillas*	Leaves	(Chiu et al., 2021)
Pakistan	Soups, tea, salad, juices	Leaves	(Anwar et al., 2007)
Bangladesh	Uses as vegetable	Leaves pods	(Islam et al., 2021)
Philippines	Uses as vegetable	leaves, fruit, flowers, immature pods	(Anwar et al., 2007)

According to the United States Department of Agriculture (USDA) database, nutritional values of edible plant parts leaves and raw pods are mentioned in Table 7 (Meireles et al., 2020).

the elimination phase, it was 16.8 h. Forty-eight hours after ingesting quercetin, it was still present in plasma (Quercetin | C15H10O7 - PubChem, 2022). Autoradiography of a fasted rat revealed that although most of the radiolabel remained in the digestive tract, it also appeared in the blood, lungs, kidneys, liver, and ribs 3 h after the oral dose of 2.3 mg/kg (4-(14)C)quercetin (Quercetin | C15H10O7 - PubChem, 2022). In another study, rats were given 630 mg/kg of the labeled compound orally. Within 24 h, 34% of the radiolabel was expelled as expired CO_2, 12% as bile, and 9% as urine, 45% was recovered in the feces within 48 h. Unmetabolized quercetin accounted for roughly 60% of the radiolabel found in the feces (Quercetin | C15H10O7 - PubChem, 2022).

Study on its compound, kaempferol, was also conducted in healthy individuals following eating of beans (*Phaseolus vulgaris* L.) by tracking excretion in response to intake. From cooked bean, kaempferol was given to healthy seven subjects. After 2–8 h, there was the highest excretion of hydrolyzed flavonol. It was observed that women and men excreted 6.10 ± 5.50% and 5.40 ± 5.40% of the kaempferol dose, respectively, as intersexual differences. The highest and lowest excretion concentrations were observed to vary amongst people by 6.72-fold, while the excretion profiles of all the individuals were similar. Additionally, a 0.80 correlation score was found to show a direct association between the participants' body mass index and the percentage of kaempferol excreted. Two hours after ingestion, all individuals showed a first peak in kaempferol excretion except two individuals. After kaempferol consumption, the study provides details on interindividual excretion capacity (Kaempferol | C15H10O6 - PubChem, 2022). Furthermore, the pharmacokinetics of kaempferol were assessed in a study of four healthy males and four healthy females. Kaempferol (9 mg) was absorbed from endive in a time-dependent manner with a mean maximal plasma concentration (0.1 M) after 5.8 h, suggesting that it was absorbed from the small intestine or colon. Despite the fact that there was a 7.5-fold interindividual variance between the highest and lowest maximum plasma concentration, the majority of people had extremely consistent pharmacokinetic profiles. Flavonoids such as rutin, which are absorbed primarily from the large intestine, have

TABLE 7 Nutritional values of the edible portion of *M. oleifera* leaves and pods per 100 g

Components	Raw leaves	Dried leaves	Raw pods
Protein (g)	9.40	24 ± 5.8	210
Energy (kcal)	64	304 ± 87	37
Carbohydrate, by difference (g)	8.28	36 ± 9.2	8.53
Water	78.66	0.0074 ± 0.0029	88.20
Total lipid (g)	1.40	6 ± 2.5	0.20
Fiber, total dietary	2.0	20.6–28.6*	3.2
Fatty acids, total monounsaturated (g)	–	–	0.102
Fatty acids, total monounsaturated (g)	–	–	0.033
Fatty acids, total saturated (g)	–	–	0.033
Fatty acids, total trans (g)	0.000	–	0.000
Vitamin A (RAE) (μg)	378	3639 ± 1979.8	4
Vitamin D (IU)	0	–	0
Vitamin D (D2+D3) (μg)	0	–	0.0
Cholesterol(mg)	0	–	0
Riboflavin (mg)	0.660	1.29–20.5*	0.074
Thiamin (mg)	0.257	2.6	0.053
Niacin (mg)	2.220	8.2	0.620
Vitamin B-6 (mg)	1.200	2.4	0.120
Vitamin B-12 (μg)	0.00	–	0.00
Vitamin C, total ascorbic acid (mg)	51.7	172 ± 37.7	141.0
Vitamin E (mg)	–	56–113*	–
Folic acid (μg)	0	–	0
Folate total (μg)	40	540	44
Iron (mg)	4.00	32.5 ± 10.78	0.36
Phosphorus (mg)	112	297 ± 149.0	50
Magnesium (mg)	42	473 ± 429.4	45
Potassium (mg)	337	1467 ± 636.7	461
Sodium (mg)	9	220 ± 180.0	42
Calcium (mg)	185	1897 ± 748.4	30
Manganese (mg)	1.063	–	0.259
Iron (mg)	4.00	32.5 ± 10.78	0.36
Copper (mg)	0.105	0.9 ± 0.48	0.084
Selenium (μg)	0.9	–	0.7
Zinc (mg)	0.60	2.4 ± 1.12	0.45

–: No published data
*: Only two values were found.

different profiles. In addition to the endive containing 14% kaempferol-3-glucoside, early absorption was also noted in most subjects. The main compound found in plasma and urine was kaempferol-3-glucuronide. Quercetin in plasma or urine indicates that kaempferol was not hydroxylated in phase I. Even at modest oral doses, kaempferol is more well absorbed by humans than quercetin. In plasma, 3-glucuronide conjugates dominate, and interindividual differences in absorption and excretion are low, suggesting that for exposure urinary kaempferol could serve as a biomarker.

Using liquid chromatography coupled to electrospray mass spectrometry (LC–ESI–MS), the flavonoids quercetin and kaempferol metabolism were analyzed by rat hepatocytes. After incubation it is detected that with the compounds, four glucuronides of quercetin and two of kaempferol, quercetin and kaempferol were metabolized extensively. Quercetin and kaempferol glucuronides were identified as being the same ones that emerged following incubation with rat hepatocytes with UDP-glucuronosyltransferase 1A9. Additionally, human volunteers who had consumed Ginkgo biloba capsules, a plant abundant in

TABLE 8 Results of different type of toxicity study conducted on various dosage forms of *M. oleifera*

Dosage form	Type of toxicity study	Animal	Standard	Dose	Observations	References
Aqueous extract of leaves	Acute toxicity	Wistar rat	Control group: distillated water (3 ml/kg p.o.) only.	400, 800, 1600, 2000 mg/kg	No toxicity at even 2000 mg/kg, at 1600, 2000 mg/kg dose slight dullness for first 5 h	(Adedapo et al., 2009)
	Subacute toxicity	Wistar rat	Distilled water	400, 800, 1600 mg/kg	At 400 mg/kg: significant increase in PCV, WBC, significant increase in the levels of ALT and AST At 800 mg/kg: significant decrease in PCV, hemoglobin, red blood cells, liver enzymes significant increase in WBC At 1600 mg/kg: significant decrease in PCV, significant increase in the levels of liver enzyme 800 mg/kg safest dose for medicinal purpose, weight gain in all animals however decreased with graded dose	
Aqueous extract of leaves	Cytotoxicity	Human peripheral blood mononuclear cells	Control	5–10 mg/ml	At 20 mg/l cytotoxic	(Asare et al., 2012)
	Acute toxicity	Sprague–Dawley rats	Negative and positive control rats (0.9% saline and 10 mg/ml N-ethyl-N-nitrosourea-administered i.m., respectively).	1000, 3000 mg/kg b.wt, respectively) per o.s.	Significant ($p = .020$) low dose and high dose ratios, no mortality at the highest dose level of 3000 mg/kg b.wt.	

(Continues)

TABLE 8 (Continued)

Dosage form	Type of toxicity study	Animal	Standard	Dose	Observations	References
Sandard livestock feed (Grower mash) mixed with Powdered *M. oleifera* leaves	93 days fed with amended diet	Albino (Wister stains) rat	Control group: standard diet	Group I: 25% (w/w) amended diet Group II: 50% (w/w) amended diet Group III: 75% (w/w) amended diet	Observable microscopical lesions some organs in treated animals, indiscriminate large consumption for a long time period food and medicine is not safe	(Ambi et al., 2011)
Aqueous leaf extract	Acute toxicity	Wistar albino mice	Control group: distilled water	Orally: up to 6400 mg/kg Intraperitoneal: up to 2000 mg/kg	On oral administration no mortality at different doses of 400 mg/kg to 6.4 g/kg, after 2 h post treatment at higher doses of 3200 and 6400 mg/kg reduced locomotion, dullness in some animals, at the higher doses of 1000 and 2000 mg/kg 20% and 80% mortality on i.p. administration LD_{50}: 1585 mg/kg	(Awodele et al., 2012)
	Sub chronic toxicity (60 days)			250, 500, 1500 mg/kg orally	Treated with extract at 250 to 1500 mg/kg dose dependently food consumption reduction, hematological, biochemical parameters, and sperm quality: No significant difference ($p \geq .05$)	
Methanolic extract of leaves	8 weeks (56 days) drug given	Male Wistar rats	Group I: (vehicle) corn oil (2 ml/kg body weight b.w.)	Group II: 50 mg/kg Group III: 100 mg/kg Group IV: 200 mg/kg b.w.	In a dose-dependent manner at dose of 200 and 400 mg/kg b.w. significant increase in serum total protein and globulin, significant increase in serum ALT, AST, creatinine and BUN which pointed to kidney and hepatic damage	(Oyagbemi et al., 2013)

(Continues)

TABLE 8 (Continued)

Dosage form	Type of toxicity study	Animal	Standard	Dose	Observations	References
Aqueous extract of leaves	Acute toxicity	Swiss albino mice	Control (vehicle): 10 ml/kg	200, 400, 800, 1600, 3200, 6400 mg/kg orally	LD_{50} > 6.4 g/kg. p.o., After 2 h of administration at high doses reduced locomotion and quiescence, no visible delayed toxicity and mortality	(Bakre et al., 2013)
Extract of *M. oleifera* leaves	Acute toxicity	Male Sprague–Dawley rats	–	Orally 5000 mg/kg single dose	LD50 greater than 5000 mg/kg, no adverse drug reaction	(Asiedu-Gyekye et al., 2014)
	Subacute toxicity		Control: vehicle (distilled water)	Dose range: 0–1000 mg/kg for 14 days	No adverse drug reaction, lower creatinine levels, elevations in liver enzymes (ALT, ALP)	
Aqueous seed extract	Acute toxicity study	Swiss albino mice	–	2000 mg/kg	All animal survived, no sign of systemic toxicity	(Araújo et al., 2013)
Methanol extract of seeds	Acute toxicity	Wistar rats	–	1000 mg/kg, 2000 mg/kg, 3000 mg /kg	Signs of acute toxicity at 4000 mg/kg, mortality at 5000 mg/kg, concentrations lower than 3000 mg/kg no adverse effect, median lethal dose 3873 mg/kg	(Ajibade et al., 2013)
	Subacute toxicity			3000 mg/kg, 4000 mg/kg, 5000 mg/kg	At 1600 mg/kg: significant ($p < .05$) increase in levels of alanine and aspartate transferases (ALT and AST), significant ($p < .05$) decrease in weight of experimental rats	

(Continues)

TABLE 8 (Continued)

Dosage form	Type of toxicity study	Animal	Standard	Dose	Observations	References
Methanolic extract of roots	Liver, kidney toxicity	Male guinea pigs	Control: 0 mg/kg of plant extracts	Doses of 3.6, 4.6, 7.0 mg/kg, i.p. injection	At 3.5 mg/kg: no difference in kidney histological sections from control, balloon degeneration in liver histological sections 4.6 mg/kg: kidney show mild tubular damage with interstitial inflammations, liver show balloon degeneration 7 mg/kg: kidney infiltration of interstitium with inflammatory cells as well as tubular lumina filled with amorphous eosinophilic materials. liver balloon degeneration with microvessicular steatosis	(Paul & Didia, 2012)
M. oleifera leaf powder	Acute toxicity	Sprague–Dawley rats	–	2000 mg/kg p.o. (3 animals per step)	LD50 greater than 2000 mg/kg, no changes in gross pathology or clinical signs	(Moodley, 2017)
Aqueous-methanolic leaf extract	Acute toxicity	Female Wistar albino rats	Control group	2000 mg/kg dose p.o.	LD50 greater than 2000 mg/kg, mean levels of AST increase, mean levels of total bilirubin nonsignificant increase, hepatic index of the treatment group relative to the control nonsignificant increase	(Okumu et al., 2016)

No published data available.

flavonoid glycosides were analyzed for their plasma samples by LC–MS. Flavonoid glycosides are present in samples of plasma is reported evidence. For the metabolism of flavonoids, UGT1A9 is a key UDP-glucurosyltransferase isoform and that it is possible to absorb intact flavonoid glycosides (Kaempferol | C15H10O6 - PubChem, 2022).

In the absence of external metabolizing systems, kaempferol, a flavonoid that is extensively present in food plants, has been demonstrated to be genotoxic to V79 cells. Its genotoxicity increases in the presence of an external metabolizing system, such as rat liver homogenates (S9 mix), as a result of quercetin's biotransformation into a more genotoxic flavonoid via the cytochrome P450 (CYP) monooxygenase system. The human metabolites of kaempferol include kaempferol-3-glucuronide and (2S,3S,4S,5R)-6-[3,5-dihydroxy-2-(4-hydroxyphenyl)-4-oxochromen-7-yl]oxy-3,4,5-trihydroxyoxane-2-carboxylic acid (Kaempferol | C15H10O6 - PubChem, 2022). A known human metabolite of galangin and kaempferide is kaempferol (Kaempferol | C15H10O6 - PubChem, 2022).

13 | DRUG–DRUG INTERACTION

As these plants remedies not use singly for the treatment, so it become necessary to study, if it interacts with some other medications. So, studies in which it is used as a combination therapy are discussed here. An intensive pharmacokinetics sampling was performed in adults taking steady-state doses of nevirapine after a 21-day washout period with herbal medicines. A repeat blood sampling was conducted after 14 days of coadministration of moringa (1.85 g leaf powder per day) and nevirapine. Liquid chromatography–tandem mass spectrometry was used to determine the plasma concentration of nevirapine. In order to assess the influence of moringa on nevirapine pharmacokinetics, the change in nevirapine's AUC (area under the plasma concentration–time curve) was determined. There was no clinically significant interaction between nevirapine and moringa found following concomitant administration over 14 days. Adding *M. oleifera* leaf powder to nevirapine at the usual dose did not change its long-term pharmacokinetics significantly (Monera-Penduka et al., 2017).

M. oleifera is frequently utilized even by those who test positive for HIV. A study evaluates whether extracts of *M. oleifera* influence CYP3A4-mediated 6ß-hydroxylation of testosterone, since herbal components might inhibit the metabolizing enzymes involved in medication metabolism. Testosterone and mixed-sex human liver microsomes were treated with methanolic and aqueous extracts of the leaves and roots of *M. oleifera* at doses ranging from 0.01 to 10 mg/ml in the presence of NADPH. HPLC was used to measure the amounts of metabolites in which significant CYP3A4 inhibitory actions were discovered. Cytotoxicity was only observed in the leaf-water extract (IC50 = 6 mg/ml). It is unclear from in vitro research if giving *M. oleifera* to HIV/AIDS patients concurrently with antiretroviral medication would cause a clinically relevant interaction (Monera et al., 2008).

In another study, effects of *M. oleifera* leaves powder on the pharmacokinetics of amodiaquine in human subjects were examined in a different investigation. The three-period study included 20 healthy volunteers. After an overnight fast, a single dose of amodiaquine (10 mg/kg) was given during the first phase. Amodiaquine was coadministered with *M. oleifera* after a 7-day washout period. Each subject took 3 g *M. oleifera* once daily for 7 days and *M. oleifera* was coadministered with amodiaquine on the 8th day for the third period. There was a significant decrease in amodiaquine C_{max} after concurrent administration with *M. oleifera*. There was a 32% decrease in amodiaquine C_{max} after pretreatment. The study discovered a pharmacokinetic interaction of amodiaquine and *M. oleifera* with concurrent administration and pretreatment that may have clinical implications for the treatment of malaria. The study also revealed that the interaction may have more to do with metabolic regulation than with amodiaquine absorption, which made it necessary to look into the enzymes that might be involved in the metabolic regulation (Olawoye et al., 2018).

According to some reports, quercetin slows down the proliferation of human myelogenous leukemia cells by enhancing the uptake of the chemotherapeutic drug vincristine (Quercetin | C15H10O7 - PubChem, 2022). Also, in in vitro study quercetin binds to the DNA gyrase site. Potentially, it could act as an inhibitor of quinolone antibiotics that bind here as well. Those taking cisplatin in combination with quercetin should avoid quercetin supplements due to the risk of genotoxicity. In general, bromelain and papain promote quercetin absorption (Quercetin | C15H10O7 - PubChem, 2022). Due to its prooxidant properties, quercetin will increase the bleomycin-induced iron-dependent DNA damage. In order for bleomycin to more easily combine with oxygen and cause more effective DNA damage, qurecetin may convert iron to the ferrous form. It has been shown that bleomycin has a biphasic prooxidant action. DNA damage was identified at low concentrations, while at increasing levels, less DNA damage was observed (Quercetin | C15H10O7 - PubChem, 2022).

Also, kaempferol suppressed the expression of inflammatory cytokines IL-6, monocyte chemoattractant protein-1, and chemokine IL-8, and on activation, normal T-cells were expressed and secreted. In a ROS-dependent manner, kaempferol reduced the migration of glioma cells. It was found that kaempferol increased ROS toxicity and decreased doxorubicin efflux, which potentiated the toxic effects of doxorubicin. Kaempferol and doxorubicin both are toxic when they are used together; their toxic effects are amplified. It is suggested that using redox perturbation as an approach to kill glioma cells could be the basis for combinatorial therapy (Kaempferol | C15H10O6 - PubChem, 2022).

14 | GREEN NANOPARTICLES

In recent years, nanobiotechnology has become an important interdisciplinary area of research (Deepak et al., 2019). Various varieties of life-threatening cancers can be treated more effectively with it (Ratanpal, 2022). There are numerous drawbacks and adverse effects associated with conventional cancer treatments (Ratanpal, 2022). Nanomaterials can be utilized in place of these conventional approach (Ratanpal, 2022). In the study by Kiran et al. (2021), in order to synthesize gold nanoparticles (AuNPs), *M. oliefera* leaf extract was used as a bioreductant. An antioxidant activity of *M. oliefera* leaf extract-mediated

AuNPs (MO-AuNPs) has been demonstrated. According to the findings of cytotoxicity studies on MCF-7 (Michigan Cancer Foundation-7) cells, MO-AuNPs have an IC50 value of 67.92 μg/ml and are potent anticancer agents (Kiran et al., 2021).

In another study, an MTT assay was used to test the cytotoxicity of *M. oleifera* leaf extract and *M. oleifera*–AgNPs against HTC116 and SW480 (colon-cancer cells). Cell viability was reduced by both solutions in a dose-dependent manner with increasing concentrations. A 70 μg/ml IC50 was recorded for *M. oleifera*–AgNP against HTC116 while a 100 μg/ml IC50 was recorded for SW480. As a result of regulating the expression of many of the key genes associated with oxidative stress, cell proliferation, DNA damage, as well as the arrest of cancer cell cycle, AgNPs possess excellent antitumor potential (Althomali et al., 2022). These studies suggested that *M. oleifera* nanoparticle may be a useful tool in cancer therapeutics.

15 | FUTURE PERSPECTIVE

The current review offers a wealth of details regarding ethnomedicinal applications, commercial formulations, geographical distribution, chemical components, toxicological profile, nutritional significance, pharmacological effects of crude, methanolic, ethanolic, aqueous extracts, hydro-alcoholic, n-hexane, ethyl acetate, as well as pure compounds, and clinical research coupled with *M. oleifera*'s effect on cancer. Various signaling pathways were found to be involved in *M. oleifera* extracts and compounds' anticancer activity, but the specific mechanism of action remains unclear. Therefore, more research is needed to explain the potential mechanisms. Its anticancer effects are also recognized to exist in some of its compounds. Although it is necessary to conduct scientific research on more substances in order to determine their molecular mechanisms of action and potential bioactivities, which could lead to the development of new treatments. Despite having achieved such remarkable outcomes in animal models, there is paucity of information available from clinical trials about *M. oleifera*'s anticancer properties so it is necessary to conduct additional systematic, well-planned, multicenter clinical studies to assess *M. oleifera* anticancer properties therapeutically. This could spur the discovery of novel therapeutic anticancer drug and also it could be employed as an adjuvant to the recognized targeted medications.

One another focus of *M. oleifera* research is its industrial use as a biocoagulant and a fortifier for snacks. Using the tree's potential as a source of extremely nutritious food and conducting additional research to support previous studies, researchers and industries can make it a significant source of wealth for India.

16 | CONCLUSION

Presently, extensive research identifies and characterizes the *M. oleifera* and its functions. A rich source of phytoconstituents with nutritional value that can be used to make nutraceuticals and functional foods has been found in *M. oleifera*. The *M. oleifera* plant is the most affordable, practical choice. It is a highly valued plant that is produced globally and used in many food compositions. Also, it is used for industrial purposes and for the treatment and prevention of various diseases. All parts of this plant exhibit a broad spectrum of anticancer capabilities through the inhibition of cancer cells as well as through anti-inflammatory, apoptotic, antiproliferative, and cell cycle arresting effects. The *M. oleifera* plant's leaves, however, are the component that has been examined the most. *M. oleifera* extracts and its isolated phytoconstituents have also exhibited anticancer properties in various experimental models. Application of *M. oleifera* as a natural component for medicine supplements may encourage the discovery of new drugs. Combining synthetic drug use with *M. oleifera* could reduce its adverse effects. *M. oleifera* could be used safely as many toxicity studies have found that doses up to 2000 mg/kg have no harmful effects.

AUTHOR CONTRIBUTION

Conceptualization and writing the original draft: J. S.; *supervision*: D. N. S. G.; *Editing and proof reading*: S. S. and R. S.

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CONFLICT OF INTEREST

All authors declared that there is no conflict of interest.

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