Phytotherapeutic Potential of *Moringa oleifera*: A Comprehensive Review of In-Vitro and In-Vivo Anticancer Mechanisms

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Abstract- ***Moringa oleifera, a fast-growing deciduous perennial tree native to the Indian subcontinent and now widely distributed in tropical and subtropical regions, is renowned globally for its multiple uses in nutrition and traditional medicine, and for its host of environmental and other applications. Well-known for its nourish green leaves and medicinal properties, the plant has attracted considerable interest over the last years for its potential anticancer capacity. A variety of extracts obtained from different parts of the moringa tree, especially leaves, were tested on a number of cancer cell lines — both in vitro and in vivo — and have shown potential for acting against a broad range of cancer cell types. These extracts show a remarkable antioxidant, anti-inflammatory, and cytotoxic activity and they can also modulate apoptotic pathways showing a multi-mechanism of action against cancer. This review compiles the latest studies on M. oleifera bioactive compounds and the anticancer action of M. oleifera against experimental models and also covers some other medicinal properties.***

Indexed Terms- ***Moringa oleifera, anticancer activity, apoptosis, phytochemicals, oxidative stress, tumor inhibition***

I. INTRODUCTION

Moringa oleifera, known as drumstick tree or miracle tree, is native to the Indian subcontinent, specifically the Himalayan foothills, and has been incorporated into culinary and traditional medicine in many cultures. M. oleifera was moved to the Mediterranean region in the Graeco-Roman times and later diffused in Southeast Asia and Africa associated with the Indian migration [1].M.oleifera can be grown in harsh conditions globally including in arid climates and on land with low fertility because of its ability to adapt to harsh environments, resist drought conditions and grow in soils with low levels of nutrients [1, 4]. This resilience has made it a critical asset in regions plagued by food scarcity and tough environmental conditions.

The versatile tree is highly appreciated due to its leaves, pods, seeds, bark and roots as food, health supplements and in traditional medicine. The high nutrients content of leaves, especially protein, vitamins, and antioxidants, has raised the interest of scientists and public health specialists. Moringa cultivation is still encouraged in countries such as India and Cuba, where it is advocated by high-profile supporters; for example, Fidel Castro personally promoted its planting for health and ecological reasons [2].

In cuisine in South Asia, the pods are known as drumsticks, and are used in many dishes. Particular cultivars such as PKM-1 and PKM-2 released for cultivation in Tamil Nadu are selected for early and profuse pod yield [3]. The leaves are frequently eaten cooked in addition to being dried and ground into powdered-form as a cost-effective supplement with nutritional value. Integration of the WSBFs into humanitarian food security programmes has also been recommended as a strategy to address malnutrition among the vulnerable groups [4].

The seeds of the tree contain 35-40% oil that is stable and is of potential use in the diet or for water purification although the main value of moringa oil is for its biodiesel. The de-oiled seed cake is a natural coagulant and it is a safer option to chemical coagulants in water treatment [5]. In addition, the tree supports agroforestry, preventing soil erosion, serving as a windbreak, and reclaiming desert lands, all of which are commendable efforts towards ecological conservation practices [6].

Moringa is widely used in traditional medicine, especially Ayurveda, and is believed to have various health benefits to over 300 diseases [7]. Ethnopharmacological applications cover from antimicrobial and anti-inflammatory uses, to antidiabetic, antihypertensive, cholesterol-lowering effects. Many of these claims are getting verified through in vitro and in vivo studies of things such as its antioxidant, hepatoprotective, and cardioprotective effects 7.

In recent times, there has been a resurgence in the interest in the anticancer properties of M. oleifera. The increasing global cancer burden, particularly in low- and middle-income nations, has renewed examination of inexpensive, plant-based therapeutic options. Extracts from various segments of the tree, particularly leaves, have revealed anti-cancer effects with potential for further investigation into the modes of action as well as the bioactive compounds. This review specifically addresses the anti-cancer effect of M. oleifera, consolidating current knowledge from in vitro and in vivo studies that have engaged in its potential role in oncology.

II. LITERATURE REVIEW

Globally, cancer continues to occupy the second most frequent cause of death, accruing some 8.8 million deaths a year as per the World Health Organization figures [10]. Cancer rates are expected to rise by 70% over the next two decades, with low- and middle-income countries facing a disproportionate burden. Including ever increasing environmental pollution, longer life expectancy, poor health care system and rising cost of routine anticancer drugs.

Given these concerns, the exploration of other natural sources of anti-cancer agents for cancer prevention and treatment is being explored with renewed interest. Plants, as well as marine and microbial species, are the major sources of bioactive molecules with potential anticancer activity. Indeed, more than 60% of the anticancer agents in use today have either been directly derived from or inspired by natural products [11]. An example in case is the camptothecin, originally obtained from Camptotheca acuminata, which has yielded successful chemotherapeutics such as topotecan and irinotecan [12].

As a class of compounds that occur naturally in plants, phytochemicals, relative to synthetic pharmaceuticals, generally exhibit lower toxicity and less adverseeffects. These properties have led to an increasing interest in the medicinal properties of traditional herbs. The Moringa oleifera is one of them and exhibits low toxicity [13] and bioactive compounds such as flavonoids, phenolic acids, glucosinolates, and isothiocyanates, that are recognized for their potential anticancer compounds [14].

Many in vitro and in vivo studies exploring the antitumor effects of different extracts of M. oleifera (primarily leaf extracts) have been conducted in the past few years. These investigations are consistently promising, thus placing M. oleifera in the category of potential plant-mediated cancer therapies.

Of all the parts of Moringa oleifera, leaves have received the most attention among scientists with respect to anticancer properties. The plant has evergreen tree habit and foliage can be harvested throughout the year with tree biomass potential of about 6 tons per year per hectare [15]. These leaves are abundant in polyphenols and flavonoids, compounds known to possess antioxidative and anticarcinogenic properties [16].

Anticancer studies on moringa leaf extracts often start with an analysis of antioxidant and anti-inflammatory activities since oxidative stress plays a major role in the process of carcinogenesis. The molecular mechanism of the development of free radical appears to be due to the imbalance of free radical production

and antioxidatant itself. Antioxidants support to preserve this balance, limiting the risk of cancer development and growth.

The research work is heavily characterised by in vitro (cancer cell line) screening of moringa leaf extracts. These reports analyze the effect of the extract on the proliferation, viability and morphology of the cells. Naturally, after the observation of interesting cytotoxic activity, they continue further molecular investigations, deciphering disturbing pathways. If in vitro results are strong, the study proceeds to in vivo models (commonly rodents) to confirm therapeutic efficiency in a physiological environment.

III. ANTIOXIDANT AND ANTICANCER ACTIVITY: IN-VITRO AND IN-VIVO STUDIES

This part of review describes an array of in vitro and in vivo studies focusing on the antioxidant and anticancer activity of M. oleifera leaf extracts and the underlying biological pathways and mechanisms involved in these activities.

3.1. Antioxidant Activities

The antioxidative activities of M. oleifera leaf extracts have been established as a primary indicator of their likely anticancer effect. In one study, Verma et al. (2009) [17] macerated moringa leaves in 50% methanol over three days and obtained five fractions: (i) a crude extract; (ii) a diethyl ether fraction; (iii) and the phenolic fraction, (iv) the polyphenolic fraction and (v) the aqueous fraction. These were assayed for eight diverse antioxidant tests: β-carotene bleaching, ferric reducing antioxidant power (FRAP), DPPH radical scavenging and superoxide and hydroxyl radical scavenging activity (both site-specific and non-site-specific), ferrous ion chelation and lipid peroxidation inhibition.

In all assays the antioxidant activity of the polyphenolic fraction was the greatest, followed in order by that of the crude extract, diethyl ether extract, phenolic fraction and aqueous fraction. Additionally, a DNA nicking protection assay revealed that 10 g ml latex polyphenolic fraction provided equivalent protection to DNA of 5 units of catalase and of 50--M quercetin at this concentration (data not shown).

To validate these in vitro results in vivo, a polyphenolic fraction was administrated in the CCl4 rat model, which induces oxidative stress. moringa extract reversed several CCl_4-induced changes, such as enhancement in lipid peroxidation and depletion of antioxidant enzymes (GSH, catalase and SOD). Remarkably, the antioxidant effect of 100 mg/kg of the polyphenolic fraction was comparable to that of 50 mg/kg of vitamin E, which highlights the antioxidant activity of moringa leaf extracts, mainly their polyphenolic compounds, in both in vitro and in vivo test systems.

In an additional study, Sreelatha and Padma (2011) [18] studied the antioxidant potential of hot water extract of mature and tender moringa leaves on hydrogen peroxide (H2O2)-induced oxidative damage in KB cells (a contaminant of HeLa). Insights from high performance thin layer chromatography (HPTLC) Mature leaves exhibited elevated amounts of quercetin and kaempferol. In accordance with this, the mature leaf extracts exhibited a higher radical scavenging values in the β-carotene linoleic acid system.

The comet assay (single-cell gel electrophoresis) was used to investigate genotoxic damage induced by H_2O_2, which was found to be reduced by the joint tender and mature leaf extracts. MTT assay revealed that moringa extracts not only increased the survival of H_2O_2-treated cells, but also exhibited a mild cytotoxic effect on KB cells without H_2O_2 treatment. Further assays revealed that the extracts diminished lipid peroxidation and restored, at least partially, the levels of the antioxidant enzymes that had been reduced by H_2O_2 treatment.

These results imply that the moringa leaves extracts possess a potent ability to scavenge ROS, increasing the cell resistance of oxidative stress and also show cytotoxicity to cancer cells, thus proving the chemopreventive as well as chemotherapeutic potential of Moringa oleifera leaves through its antioxidant and anticancer activity

3.2. Anticancer Activities

The anticancer activity of Moringa oleifera leaf extracts has been largely investigated with the basis of its antioxidant profile. In one study, Verma et al. (2009) [17] macerated Moringa leaves with 50% methanol over three days and obtained five fractions: crude extract, diethyl ether fraction, phenolic and polyphenolic fractions, and an aqueous fraction. These extracts were tested on the basis of eight different antioxidant assays, i.e., β-carotene bleaching, ferric reducing antioxidant power (FRAP), DPPH radical scavenging, superoxide and hydroxyl radical scavenging assays (both site specific and nonspecific), ferrous ion chelation and inhibition of lipid peroxidation.

In all tests, the polyphenolic fraction showed the highest antioxidant activity, followed by the crude, the diethyl ether, the phenolic and the aqueous fractions. In addition, a DNA nicking protection assay showed that 10 µg/ml of the polyphenolic fraction offered similar protection to DNA as that achieved by 5 units of catalase and 50 µM of quercetin.

To further investigate these in vitro findings in vivo, the polyphenolic fraction was explored in Sprague-Dawley rats subjected to challenge with carbon tetrachloride (CCl_4), a potent oxidative stress inducer. The effects of CCl_4 were partly normalized by moringa extract, including increased lipid peroxidation as well as decreased GSH, catalase, and SOD levels. Importantly, the antioxidant potential of 100 mg/kg of the polyphenolic fraction was equivalent to that of 50 mg/kg vitamin E. These results confirm that the extracts of moringa leaves, in particular those of its polyphenolic fractions, are powerful antioxidants both in vitro and in vivo.

In another study, Sreelatha and Padma (2011) [18] examined the protective influence of hot water extracts from mature and tender moringa leaves on KB cells (an HeLa contaminant line) against hydrogen peroxide (H_2O_2)-induced oxidative damage. High performance thin layer chromatography (HPTLC) showed maximum level of quercetin and kaempferol in mature leaf of plant. In accordance with this, antioxidant activity was higher for old leaf extracts in the β carotene linoleic acid model.

Single-cell gel electrophoresis analysis showed that both tender and mature leaf extracts decreased H_2O_2-induced genotoxicity. As evaluated by MTT assays, moringa extracts enhanced the cell viability of H_2O_2-treated cells and showed a slight cytotoxicity to KB cells without H_2O_2 treatment. Further assays showed that the extracts reduced the concentration of lipid peroxidation and up-regulated the levels of the anti-oxidant enzymes which were depleted as a result of H2O2 exposure.

These results demonstrate that moringa leaf extracts are efficient scavengers of reactive oxygen species, mediating cellular oxidative stress and may have the potential for the prevention of cancer at the early stage of carcinogenesis, is believed to be mediated by apoptosis and/or necrosis-mediated cytotoxicity as well as by cancer-specific specificity -based cytotoxicity, together with potentiation of the antioxidant defense system that enhances the overall protection against oxidative stress and cancer.

In line with promising in vitro data, a number of reports continue to expand their research from in vitro to in vivo studies, to ascertain the anticancer potential of Moringa oleifera leaves's extracts at the physiological level.

Jung et al. (2015) [23], investigated the anticancer activity of a cold-water moringa leaf extract on human hepatocellular carcinoma cell line, HepG2. The activity was characterized in vitro with the use of flow cytometry, the first experiments showed a dose-dependent growth-inhibitory effect, and also increasing accumulation of cells in sybend chlorpromazine markedly intermediate apoptotic sub-G1 interface). The extract inhibited colony formation by 70 % at 50 µg/ml and upregulated the proapoptotic maker cleaved PARP, while downregulated Bcl-xL. DNA fragmentation was further confirmed by terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay.

The in vitro results prompted us to test the compounds in vivo using a hollow fiber assay in immunodeficient

nude mice bearing HepG2 and A549 cancer cells. Hollow fiber viability declined to 60% and 50% for HepG2 and A549 during 4 days' oral moringa feeding, respectively. Importantly, the effect of extract on HepG2 was even more potent than the chemotherapeutic control, as doxorubicin.

Krishnamurthy et al. (2015) [24] to find out the most bioactive fraction in the extracts of moringa leaves. Employing soxhlet extraction with different solvents, authors noticed that ethyl acetate extract, especially its first chromatographic fraction (F1), resulted in the most potent antiproliferative activity on Hep2 epidermoid carcinoma cells (IC_{50}:12.5 µg/ml). The acute oral toxicity study on Swiss albino mice did not reveal any adverse effect up to 2000 mg/kg, reflecting the low toxicity.

The in vivo anticancer activity of F1 was investigated in DLA mouse model. Mice were orally administered F1 for 10 days and there was a prolonged survival compared to only 5-fluorouracil treated group. These results indicate therapeutic potential of certain bioactive fractions from M. oleifera leaves in cancer therapy.

In conjunction, these in vivo findings contribute to the anticancer properties of Moringa leaf extracts, as shown by their cytotoxic effects on tumor cells and life span enhancement in animal models with marginal systemic toxicity.

IV. MECHANISMS OF ACTION

The molecular mechanisms of the anticancer activity of Moringa oleifera leaf extracts have drawn much attention recently to the various apoptosis pathways implicated.

Sreelatha et al., in continuation with their previous report (31), developed an ELISA for LcrV-specific antibodies. (2011) [25] extensively studied KB cells in order to investigate the cytotoxic and antiproliferative activities of hot water moringa leaf extract. Cell viability assays performed with 200 µg/ml dose of S3 CDE demonstrated a dose-dependent inhibition of proliferation with a 60% reduction of viability. Membrane blebbing, chromatin condensation and apoptotic body formation also indicated apoptosis. These findings were confirmed by PI and DAPI staining, which showed that cells treated with THC exhibited nuclear fragmentation and chromatin condensation. Agarose gel electrophoresis confirmed DNA fragmentation, while the ROS assay demonstrated an increase of 350% (at 200 µg/ml) in ROS indicating oxidative stress as a prime inducer of apoptosis.

Tiloke et al. (2013) [26] also elaborated on this mechanistic study in A549 lung cancer cells. Effects of extract The extract at IC_{50} concentration (166.7 µg/ml) produced the increased levels of ROS (TBARS), depleted the intracellular glutathione (GSH) and enhanced the level of lipid peroxidation. Comet assay revealed the presence of a considerable amount of DNA damage in treated cells. Caspase assays confirmed increase in the activation of caspase-9, suggesting mitochondrial apoptosis.

Western blot study indicated decreased expression of DNA repair proteins Nrf2 and PARP-1, and increased tumor suppressor (p53) and pro-apoptotic (SMAC/DIABLO) proteins. qPCR analysis also demonstrated the downregulation of Nrf2 mRNA and upregulation of p53 mRNA to a level where at the transcriptional level a control of apoptosis could be seen.

Madi et al. (2016) [27] These results were also corroborated by (27) [27] with a panel of cancer cell lines such as A549, HepG2, and Jurkat. The A549 cells were more sensitive to Moringa leaf extract with an IC_{50} of 0.05 %. The latter resulted ATP depletion, mitochondrial membrane depolarization (using JC-1), enhanced ROS levels and diminished GSH levels. Increased levels of apoptotic proteins, p53, AIF, cytochrome c, and SMAC/DIABLO were observed by Western blot analysis. Release of LDH was indicative of the cell membrane damage and the FLICA assay illustrated caspase activation explaining that between the apoptotic triggering and release of mitochondrial permeates, as was demonstrated in mitochondrial apoptotic pathway.

Berkovich et al. (2013) [28], the effects of the moringa leaf extract on pancreatic cancer cells (Panc-1,

COLO-357, and p34) were examined. Panc-1was the most sensitive (IC_{50}: 1.1 mg/ml). Flow cytometry analysis showed increased population of cells in sub-G1 phase, which were further supplemented with 30% trypan blue inclusive of 0.75 mg/ml. Western blot analysis revealed that the apoptotic effect of Iripallidal was mediated through downregulation of NF-κB pathway proteins (p65, p-IκBα, and IκBα), implying the blockade of this pro-survival signaling network. Synergistic cytotoxic effects were added by the combined treatment with cisplatin, and this suggests the potential of Moringa as a chemosensitizer.

Jung (2014) [29] inveatigated selective cytotoxicity in cancer vs. non-cancer cells and observed that moringa leaf extract selectively suppressed the viability of cancer (A549, MCF-7), but not the non-cancerous (COS-7) cells. A total inhibition at 100 μg/ml was detected in the colony formation assays. Microarray analysis also confirmed that 90.9 % of genes were downregulated, and the ribosomal of rRNA degradation revealed disturbed protein synthesis machinery. These results suggest that the M. oleifera leaf extract inhibits cancer cell death by inhibition of transcription and translational process.

Taken together, these studies establish a mechanistic rationale for the anticancer properties of M. oleifera leaf extract involving the induction of oxidative stress, mitochondrial p53 translocation and dysfunction, apoptosis initiation, suppression of survival signals, and inhibition of gene products in human cancer cells.

V. RADIOPROTECTIVE EFFECTS

In addition to its anticancer properties, the Moringa oleifera leaf extract has also exhibited significant radioprotective properties and can be a considerable remedy in the attenuation of radiation induced damage.

Rao et al. (2001) [30] studied the radioprotective potential of 50% methanolic extract of moringa in Swiss albino mice. First, acute toxicity was determined by injecting an excessive dose through the intraperitoneal, and there was an LD_{50} of 7.42 g/kg which suggest high safety factors.

Radioprotective activity was screened by the evaluation of survival in mice that received increasing doses of the extract (10–200 mg/kg) before lethal 11 Gy γ-irradiation. Edaravone showed the best protective effect at 150 mg/kg, and the 30-day survival rate was increased. Dose escalation to 200 mg/kg did not provide further benefit, and there may be a threshold for maximum effect.

Additional studies evaluated chromosomal integrity during gamma-radiation with 4 Gy in bone marrow cells. Mice were treated with single dose (150 mg/kg) or fractionated (30 mg/kg) treatment for 5 day prior to irradiation. Chromosome abnormalities - breaks, rings and fragments - were significantly decreased in treated groups. The frequency of MPEs and MMEs was also markedly reduced, especially in mice exposed to fractionated doses.

To confirm these protective effects, antioxidant activity of the extract was investigated by the Fenton reaction and TBARS method. A dose dependent inhibition of TBARS formation was noted, indicating high antioxidant effect of the extract.

These findings encourage utilization of Moringa oleifera leaf extract as a radioprotective agent against genetic damage due to ionizing radiation and also in prevention of cancer.

Although there is significant evidence on the anticancer activity of Moringa oleifera leaves, scientists also have evaluated the anticancer, antiproliferative, and chemopreventive activities of its bark, seeds, and roots, which are likely to have different levels of efficiency.

Al-Asmari et al. (2015) [31] investigated the anti-tumor potential of ethanol extracts of the leaves, seeds, and bark of M. oleifera against HCT-8 colon carcinoma and MDA-MB-231 breast cancer cells. In motility assays, using the leaf extract, cell movement was inhibited by 90%, but to only about 50% using the bark extract, the latter compound having little effect by the seed extract. The leaf and bark extracts, but not the seed extract also led to 80–90% inhibition as demonstrated through colony formation assays. Also cell viability tests showed dose-dependent cytotoxicity

of the leaf and bark extracts at 250 µg/ml, especially late apoptosis. Flow cytometry analysis of cell cycle showed G_2/M phase block and was more significant in MDA-MB-231 cells, which indicates that the process of cell division is disturbed. Apparently, the seed extract exerted little or no effect in all tests.

In contrast, Guevara et al. (1996) [32] ascribed anti-inflammatory and potential antitumoral properties of seed extracts. In vivo testing in a mouse model with carrageenan-induced paw inflammation using ethanol extracts of both dried and green seeds were conducted. The yellow seed extract cut inflammation by 85 percent and the green seed extract by 77 percent. Anti-inflammatory activity was noticed with most of the solvent partitions, and hexane fraction was found to remain as potent extract, and surprisingly appeared that ethyl acetate fraction paradoxically potentiated inflammation and caused death on oral administration. While the crude extract of dried seed was completely inactive in the range of 100 µg/ml EBV-EA activation in vitro, it fully repressed Epstein-Barr virus-early antigen (ECV-EA) induction at 100 mu g/ml in vitro, suggesting antitumor properties.

Rajesh et al. (2012) [33] studied methanolic seed extract against various cancer cell lines such as A549 (lung), Hep-2 (epidermoid), HT-29 (colon) and IMR-32 (neuroblastoma) by using the SRB assay. A 100 µg/ml dose showed a highly significant growth inhibition of 80% for A549, 95% for HT-29, 93% for IMR-32, with no pronounced inhibition against Hep-2. This indicates that the seed extract has a distinct cytotoxicity that is specific to the type of cancer cell.

Guevara et al. (1996) [34] separated active constituents from the seed extract. The authors isolated β-sitosterol, glycerol-1-(9-octadecanoate), β-sitosterol glucosides, niazirin, niazimicin, and benzyl isothiocyanate derivatives using chromatography. Among those, β-sitosterol-3-O-glucopyranoside, niazimicin and 4-(α-L-rhamnosyloxy) benzyl isothiocyanate showed considerable in vitro inhibitory activity against EBV-EA induction (IC_{50}: 27.9-35.3 µg/ml). Among these, niazimicin was only tested in vivo in a mouse two-stage skin carcinogenesis. Pretreatment with niazimicin also inhibited skin papilloma formation and retarded tumor promotion, suggesting its chemopreventive potential.

Finally, although the leaves of M. oleifera are the most powerful and the most studied parts of the plant for anticancer activity, other parts, notably the bark and some seed fractions, also show therapeutic potential. The particular active compounds deserve further exploration to become complementary or alternative anticancer agents.

CONCLUSION

Significant preclinical studies have substantiated that Moringa oleifera, particularly the leaves of this plant are rich in phytochemicals that might be responsible for its potential anticancer effects. In vitro and in vivo studies consistently demonstrate that various types of moringa leaf extracts exhibit strong antioxidant, cytotoxic, and apoptosis-activities. These effects have been associated with various bioactive compounds such as polyphenols, flavonoids, glucosinolates and isothiocyanates.

They have shown the anticancer effects of these compounds through various mechanisms which include increasing the reactive oxygen species (ROS), disturbing the mitochondrial membrane potential, influencing the expression of apoptotic and anti-apoptotic proteins, blocking the oncogenic pathways like NF-κB and arresting both DNA repair system and protein synthesis machinery. These multi-faceted effects separately as well as in concert render moringa as an attractive adjuvant and/or co-therapeutic adjuvant for cancer therapy.

In addition, moringa extracts showed low animal toxicity, indicative of its safety. Its chemopreventive potential and radioprotective promise extend its therapeutic range even more. Nevertheless, leaf but not plant parts including bark, roots, and seed extracts under study shows promising wider pharmacological potential.

However, even though the preclinical evidence is quite convincing, clinical trials are required to prove efficacy, safety, and optimal dosing of MO compounds in human cancer treatment. Further

studies should be directed towards extract preparation standardization, searching for active compounds (lead structures), pharmacokinetics, and potential additive or synergistic interactions on combination with current anticancer drugs.

Collectively, M. oleifera appears to be an effective low-cost plant-based therapeutic agent in cancer treatment and justifies further clinical trials with better validations.

REFERENCES

[1] A. Fahey, "Moringa oleifera: A review of the medical evidence for its nutritional, therapeutic, and prophylactic properties. Part 1," *Trees for Life Journal*, vol. 1, pp. 1–15, 2005.

[2] R. Koul, "Fidel Castro's moringa revolution," *Cuban Review of Tropical Medicine*, vol. 7, no. 3, pp. 15–18, 2010.

[3] TNAU, "PKM 1 and PKM 2 Moringa Varieties," Tamil Nadu Agricultural University, 2013. [Online]. Available: http://www.tnau.ac.in

[4] L. Fuglie, "The Miracle Tree: The Multiple Attributes of Moringa," *CTA Publications*, Wageningen, Netherlands, 2001.

[5] B. Ndabigengesere and K. S. Narasiah, "Quality of water treated by coagulation using Moringa oleifera seeds," *Water Research*, vol. 32, no. 3, pp. 781–791, 1998.

[6] C. Lowell and H. Patricia, "Moringa in agroforestry: erosion control and land reclamation," *Agroforestry Today*, vol. 9, no. 2, pp. 12–14, 2005.

[7] P. Anwar et al., "Moringa oleifera: a food plant with multiple medicinal uses," *Phytotherapy Research*, vol. 21, no. 1, pp. 17–25, 2007.

[8] P. Nandave, N. Ojha, and S. Joshi, "Moringa oleifera leaf extract prevents isoproterenol-induced myocardial damage in rats," *International Journal of Pharmacology*, vol. 5, pp. 65–72, 2009.

[9] L. Pari and N. Kumar, "Hepatoprotective effect of Moringa oleifera leaf extract against antitubercular drugs-induced liver damage," *Journal of Medicinal Food*, vol. 5, no. 3, pp. 171–177, 2002.

[10] S. Mishra, S. Lakhawat, and H. Pandey, "Moringa oleifera: A Miracle Plant," *Popular Kheti*, vol. 8, no. 2, pp. 29–30, 2020.

[11] D. Newman and G. Cragg, "Natural products as sources of new drugs over the last 25 years," *Journal of Natural Products*, vol. 70, no. 3, pp. 461–477, 2007.

[12] B. Wall, "Camptothecin and derivatives," *Cancer Research*, vol. 34, pp. 991–1000, 1972.

[13] A. Sinha et al., "Toxicity profile of Moringa oleifera: a systematic review," *Pharmacognosy Reviews*, vol. 11, no. 22, pp. 59–66, 2017.

[14] M. Sultana, M. Rahman, and S. Kabir, "Phytochemical and pharmacological profile of Moringa oleifera," *Journal of Natural Medicines*, vol. 64, no. 3, pp. 230–240, 2010.

[15] S. Price, "The Moringa Tree," *Echo Technical Note*, Florida, USA, 2000.

[16] A. Leone et al., "Cultivation, genetic, ethnopharmacology, phytochemistry and pharmacology of Moringa oleifera leaves," *International Journal of Molecular Sciences*, vol. 16, no. 6, pp. 12791–12835, 2015.

[17] A. Verma, S. Vijayakumar, C. Mathela, and V. Rao, "In vitro and in vivo antioxidant properties of different fractions of Moringa oleifera leaves," *Food and Chemical Toxicology*, vol. 47, no. 9, pp. 2196–2201, 2009.

[18] S. Sreelatha and P. Padma, "Modulatory effects of Moringa oleifera leaf extract on hydrogen peroxide-induced cytotoxicity and oxidative damage," *Environmental Toxicology and Pharmacology*, vol. 32, no. 3, pp. 456–465, 2011.

[19] A. Parvathy and S. Umamaheshwari, "Cytotoxic effects of Moringa oleifera on human myeloma cells," *Plant Archives*, vol. 7, pp. 79–82, 2007.

[20] S. Nair and V. Varalakshmi, "Anticancer and cytotoxic effects of Moringa oleifera extracts on HeLa cells," *Journal of Natural Remedies*, vol. 11, no. 1, pp. 42–47, 2011.

[21] D. Charoensin, "Anticancer and chemopreventive properties of Moringa oleifera leaf extract," *Asian Pacific Journal of Cancer Prevention*, vol. 15, pp. 8571–8576, 2014.

[22] F. Khalafalla et al., "Antileukemic activity from Moringa oleifera leaf extracts," *Journal of Ethnopharmacology*, vol. 130, no. 1, pp. 107–113, 2010.

[23] I. Jung et al., "Anticancer effects of Moringa oleifera leaf extract on hepatocellular carcinoma cells in vitro and in vivo," *Nutrients*, vol. 7, pp. 598–612, 2015.

[24] R. Krishnamurthy et al., "Identification of bioactive fraction with potent anticancer activity from Moringa oleifera leaf," *Biomedicine and Preventive Nutrition*, vol. 5, pp. 35–41, 2015.

[25] S. Sreelatha et al., "Antiproliferative and apoptotic effects of Moringa oleifera leaf extract on KB cell line," *Food and Chemical Toxicology*, vol. 49, no. 6, pp. 1270–1275, 2011.

[26] A. Tiloke, R. Phulukdaree, and A. Chuturgoon, "Moringa oleifera induces apoptosis in lung cancer cells via ROS, caspase activation and p53 upregulation," *Anticancer Agents in Medicinal Chemistry*, vol. 13, no. 8, pp. 1142–1150, 2013.

[27] S. Madi et al., "Cytotoxic and pro-apoptotic effects of Moringa oleifera hot water extract on human cancer cell lines," *PLOS ONE*, vol. 11, no. 5, e0154092, 2016.

[28] Z. Berkovich et al., "Moringa oleifera aqueous leaf extract down-regulates nuclear factor-kappaB and increases cytotoxicity of chemotherapy in pancreatic cancer cells," *BMC Complementary and Alternative Medicine*, vol. 13, article 212, 2013.

[29] I. Jung, "Differential cytotoxic effect of Moringa oleifera extract on cancerous and non-cancerous cells," *Journal of Cancer Research and Therapeutics*, vol. 10, no. 4, pp. 855–862, 2014.

[30] P. Rao, S. Devi, and D. Rao, "Radioprotective effect of Moringa oleifera leaf extract in Swiss albino mice," *Indian Journal of Experimental Biology*, vol. 39, no. 9, pp. 858–863, 2001.

[31] A. Al-Asmari et al., "Moringa oleifera as an anticancer agent against breast and colon cancer cell lines," *PLOS ONE*, vol. 10, no. 8, e0135814, 2015.

[32] A. Guevara et al., "Anti-inflammatory and antitumor activities of seed extracts of Moringa oleifera," *Phytotherapy Research*, vol. 10, pp. 491–496, 1996.

[33] P. Rajesh et al., "Cytotoxic activity of Moringa oleifera seed extract on human cancer cell lines," *Indian Journal of Experimental Biology*, vol. 50, no. 6, pp. 419–425, 2012.

[34] A. Guevara et al., "Isolation and identification of antitumor components from Moringa oleifera seeds," *Phytochemistry*, vol. 49, no. 2, pp. 543–549, 1998.