JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

Anticancer Activity of Moringa *oleifera*

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Abstract

Moringa *oleifera* from the Moringaceae family is a perennial tree widely cultivated in many tropic regions and easily grown even in adverse conditions. M. *oleifera* is also known as the miracle tree, According to the holistic or traditional medicine, M. *oleifera* has very relevant therapeutic properties and applications depending on the constitution, somatic and psychological needs of patients. It is usually referred as a natural product that can treat different physical and psychological health aspects, offering an energetic action and structural rebuilder of the body and promoting emotions of highly positive attitudes towards life. These attractive properties have led researchers to look for other novel uses for the moringa tree, especially as a source of anticancer drugs. Researchers have tested extracts from various parts of the moringa tree both in vitro and in vivo on several types of cancers with varying success. This review explores the state of current research on the anticancer properties of M. *oleifera*.

Keywords: Moringa *oleifera*, Anticancer Activity

Introduction

Moringa *oleifera L* (MO) (Family: Moringaceae) is a perennial angiosperm plants, which includes several other species [1, 2]. The Moringa genus comprises 14 species: M. *arborea*; M. *longituba*; M. *borziana*, M. *pygmaea*; M. *hildebrandtii*; M. *drouhardii*; M. *longituba*; M. *peregrina*; M. *stenopetala*; M. *rivae*; M. *ruspoliana*; M. *ovalifolia*; M. *concanensis* and M. *oleífera* (Rani et al. 2018). From the Moringaceae family, M. *oleifera* is the most known, studied and used species (Anwar 2005; Olson 2011) with human and animal applications. It is a native of the Himalayan region that is widely cultivated throughout tropical and sub-tropical countries of the world including Saudi Arabia. [3-4]. The plant has numerous medicinal applications and is used as a traditional medicine for the treatment of various illnesses such as skin diseases, respiratory distress, ear and dental infections, hypertension, diabetes, anemia, and cancer [5–9].

Additionally, the pharmacological importance of the leaves extract containing bio-active compounds are well described by Leone et al (2015) [10].

The flowers, roots, leaves and bark of M. *oleifera* have long been used by the public as nutritional supplements and foods, as well as in the manufacture of perfume, skin oil and other products [11-13]. Certain parts of M. *oleifera* (leaf, stem and root) have been demonstrated to produce various biological activities, including antiatherosclerotic [14], immune-boosting [15], anticardiovascular disease [16], antiviral [17-19], antioxidant [20-22], antimicrobial [23], anti-inflammatory [24] and tumor-suppressive effects [25]. Due to its long history of usage and various biological effects, M. *oleifera* has long been the subject of research interest. A previous study reported on the therapeutic potential of the water-soluble extract from M. *oleifera* leaves (MOL) in the treatment of various types of cancers, including lung, breast and skin cancers [25].

The important characteristics features of cancer cells include the ability to proliferate, invade through the extra cellular matrix and migrate to other body parts to form secondary tumors. The migration of cancerous cells is dependent on the tumor micro environment from where they get nourishment and support by forming new-vasculature (a process called angiogenesis) and allowing them to spread [12]. It is a challenging task for Oncologists and Medical Scientists to devise the best treatment regimen that kills the maximum number of cancer cells with minimal side effect rendering maximum benefits to the cancer patients. As reported earlier, about 74% of the known anti-cancer medicines are derived from various plant species [27-28]. Indeed, there are many household dietary products exhibiting anti-cancer potential with minimal side effect that are currently under clinical trials for cancer treatment [29-30]. Among these, two important household dietary products that are very common among South Asian communities are Curcumin and Lycopene. Curcumin is a poly phenolic compound isolated from turmeric and this product exhibits anti-microbial, immune modulatory and potential cancer chemo preventive efficacy [31-32].

ANTICANCER ACTIVITY OF MORINGA OLEIFERA

Cancers are the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths (Fuglie, 1999). The number of new cases is expected to rise by about 70% over the next 2 decades. Among men, the 5 most common sites of cancer diagnosed were lung, prostate, colorectum, stomach, and liver cancer. Among women the 5 most common sites diagnosed were breast, colorectum, lung, cervix, and stomach cancer (WHO, 2015; De Martel et al., 2012).

All parts of the M. *oleifera* tree have been tested for anticancer activity, including the leaves, seeds, bark, and roots. However, the most extensive research on the anticancer activities of M. *oleifera* has focused on the leaf extracts. The biochemical compounds like benzyl carbamate, niazimicin, Benzyl isothiocyanate and sitosterol present in the leaves of M. oleifera shows a potent antitumour activity (Anwar et al., 2007). The compounds present in M. *oleifera* leaves like benzylisothiocyanide, and niazimicin exhibits a cytotoxicity activity against the cervical cancer cell lines (Varalakshmi and Nair, 2011). There has been extensive interest in exploring the anticancer activities of various parts of the M. *oleifera* tree, and

many published research articles describe promising results of in vitro and in vivo testing of various extracts from the moringa plant.

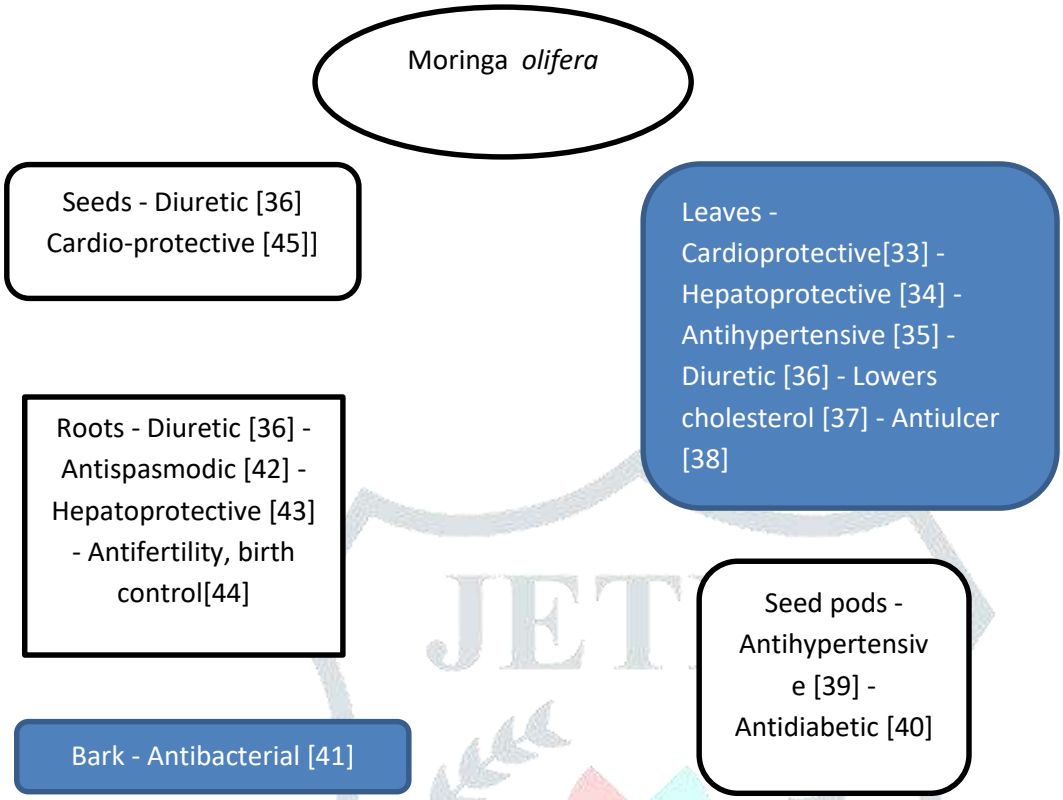

Figure 1: Medicinal Uses of Moringa *oleifera* .

A number of studies have focused on the anticancer activity of the moringa leaf extract using in vitro screening of cancer cell lines. Parvathy and Umamaheshwari (2007) [46] studied the effects of moringa leaf extracts on the human B-lymphocyte plasma cytoma U266B1 cell line. U266B1 cells were treated with serial dilutions of the methanol, ethanol, ethyl acetate, and chloroform extracts of the moringa leaf, and cytotoxicity was measured using the neutral red dye uptake assay. The methanol extract had the highest cytotoxic activity against U266B1 cells (IC_{50}: 0.32 µg/ml); this suggests that this extract has high anticancer activity, as a small amount can significantly inhibit the proliferation of U266B1 cells. In another study, Nair and Varalakshmi (2011) [47] tested the anticancer and cytotoxic potential of hot water, methanol, and hexane extracts of the moringa leaf on cervical cancer cells (HeLa cell line) and normal lymphocytes. Results of the MTT assay showed that the aqueous leaf extract caused a dose dependent decrease in HeLa cell viability (IC_{50}: 70µg/ml). In contrast, the methanol and hexane leaf extracts caused an increase in HeLa cell viability at higher concentrations. Lymphocytes treated with the different leaf extracts did not exhibit any significant decrease in cell viability. The try pan blue dye exclusion assay was performed for the aqueous leaf extract to verify the results from the MTT assay. The results of this experiment also showed a dose-dependent decrease in cell viability for the aqueous leaf extract. The HeLa cells exhibited increased numbers of detached and dead cells with increasing concentration of the aqueous leaf extract. DNA fragmentation analysis of cells treated with the aqueous leaf extract showed a DNA smear on the agarose gel compared to distinct bands for untreated cells. The DNA smear is indicative of

DNA breakage and damage. The last test performed was acridine orange-ethidium bromide staining, which can distinguish viable cells (green fuorescence glow) from nonviable cells (bright orange chromatin). These results showed that the aqueous leaf extract of moringa leaves has significant cytotoxic activity and is capable of fragmenting DNA and killing the HeLa cells. Charoensin (2014) [48] compared the anticancer activity of the leaf extract among different cancer cell lines (hepatocarcinoma (HepG2), colorectal adenocarcinoma (Caco-2), and breast adenocarcinoma (MCF-7)). First, the methanol and dichloromethane leaf extracts of M. *oleifera* were tested for their antioxidant activity using the DPPH and 2,2'- azino-bis (3-ethylbenzothiazoline-6-sulphonic acid) assays and Alternative Medicine. The results of both assays indicated that the methanol extract had better antioxidant activity. The anticancer activity of the leaf extracts was then tested on the three cell lines. The MTT assay, conducted to assess the effects on cell proliferation, showed that the dichloromethane leaf extract (IC_{50}: 112–133 µg/ml) was more effective than the methanol leaf extract (250 ug/ml) at killing cancer cells. This means that a lower dose of dichloromethane is needed to inhibit the proliferation of cancer cells by 50% compared to the methanol leaf extract. In vitro chemoprevention was also tested using the Quinone reductase (QR) induction assay on the hematomas (Hepa1c1c7) cell line. The dichloromethane leaf extract induced significant QR activity, whereas the methanol leaf extract exhibited no significant inductive activity. These results indicate that the methanol extract of moringa leaves has better antioxidant activity, but the dichloromethane leaf extract has better anticancer activity on HepG2, Caco-2, and MCF-2 cells as well as better chemoprevention activity. Khaliafalla et al. (2010) [49] tested the anticancer effects of M. *oleifera* leaf extracts on primary leukemia cells harvested from 15 patients with acute myeloid leukemia (AML) and 10 patients with acute lymphoblastic leukemia (ALL). They also tested the effects of cold water, hot water, and 80% ethanol leaf extracts on the HepG2 cell line. The leaf extracts were first tested for their antioxidant activity using the DPPH assay. The hot water and 80% ethanol extracts had the highest antioxidant activity. They showed 63% and 77% inhibition of radical formation, respectively, compared to 49% inhibition by the cold water extract. The MTT assay was then performed to determine if the extracts could inhibit the proliferation of cancerous cells. The leaf extracts showed promising results, causing 72–82% of AML cells and 77–86% of ALL cells to die after 24 hours of incubation with 20 ug/ml of the extract. After the same treatment, 69–81% of HepG2 cells died. The ethanol extract had the highest anticancer activity in both AML and ALL cells, followed by the hot water extract and then the cold water extract. For HepG2 cells, the hot water extract resulted in the strongest inhibition and the cold water extract had the weakest anticancer activity. Overall, the results showed that moringa leaf extracts had good anticancer activity in vitro against AML, ALL, and HepG2 cells.

Due to the global ongoing interest in the nanotechnology with potential applications in health and drug delivery for cancer therapy (Shoo et al., 2007; Park et al., 2008), poly D-L-lactide-co-glycoside (PLGA) decorated with chitosan (CS) and polyethylene glycol (PEG), PLGA-CS-PEG, provides unique physicochemical characteristics resulting from the nano-size effect (Sumer and Gao, 2008; Parveen and Sahoo, 2011). The nanoparticles of FDA approved biodegradable polymer, PLGA, is widely used for the delivery of various natural treatments to the target site. However, rapid opsonization by phagocytes is a

major challenge for achieving effective drug targeting by PLGA nano formulation (Greif et al., 1995). Therefore, surface coating by biodegradable and biocompatible polymers with low toxicity such as CS and PEG were used to curb the phagocytic effects and to enhance the longevity of the nanoparticles (Hu et al., 2008; Illum, 1998; Parveen et al., 2010). Intriguingly, the chemical modification of CS with PEG not only improves the biocompatibility of CS (Zhang et al., 2002), but also reduces the adsorption of circulating plasma proteins onto the material surface (Amiji, 1997). This important effect of nanotechnology used in the study to improve the effectiveness of moringa extracts against cancer cell lines. Moringa *oleifera* nano composites may have potential for use as a natural source of anti-cancer compounds against different cell lines, while sparing normal cells with minimal inhibitory effect.

Very recently, Al-Asmari et al., (2015) have investigated the remarkable effects of Moringa *oleifera* leaves and bark on breast MDA-MB-231 and colorectal HCT-8 cancerous cells. They found that Moringa *oleifera* extracts significantly exhibit apoptosis-mediated cell death and cell cycle arrest associated with remarkable changes in the cell phenotypic properties in both beast MDA-MB-231 and colorectal HCT-8 cancerous cell lines. In addition, the analyses of these extracts using GC-MS indicated considerable compounds with anti-cancer prosperities (Al-Asmari et al., 2015; Al-Sharif et al., 2013; Sui et al., 2005; Matsuda et al., 2007; Peng et al., 2008). On the other hand, Balamurugan et al., (2014) assessed the anti-tumor impact of the moringa leaf and bark extracts on hepatic cancer cell line (HepG2) using MTT experiment. They found that the leaf crude extract has a significant anticancer effect against HepG2 cells compared to that of the bark extract of moringa (Balamurugan et al., 2014).

Madi et al. (2016) [50] also investigated the mode of action of the anticancer activity of moringa leaf extract on the A549 lung cancer cell line. The leaf extract was prepared by soaking the dried leaf powder in hot water, and different concentrations of leaf extract based on the ratio of leaf powder to water were prepared (0.1% to 2.5%). Cell viability of extract-treated A549, HepG2, $CaCo_2$, Hek293, and Jurkat cells was measured and compared. Although the leaf extract caused dose-dependent reduction in viability of all tested cell types, some were more sensitive than others. A549 cells were the most susceptible to the leaf extract (IC_{50}: 0.05%) compared to the other cell lines (IC_{50}: 0.1–0.4%). The ATP bioluminescence assay revealed a significant decrease in ATP levels with increasing moringa leaf extract concentration, which indicates that treatment resulted in fewer live cells, as ATP is required for live and active cells. The p-nitro-blue-tetrazolium salt assay showed a significant increase in ROS levels with increased concentration of the leaf extract. Elevated levels of ROS cause DNA damage, which leads to cell death. The ApoGSH colorimetric test showed a significant decrease in GSH level with increasing extract concentration. The decrease of GSH together with the increase in ROS and decrease in ATP with increasing extract concentration suggests that the leaf extract compromises the mitochondrial pathway of the cell to induce cell death. Measurement of the mitochondrial membrane potential using cell-permeable lipophilic JC-1 staining showed that the leaf extract induced mitochondrial membrane potential depolarization. In just one hour of 0.05% moringa treatment, a noticeable induction in mitochondrial membrane depolarization was observed. Balamurugan et al. [51] reported the anticancer effect of MO leaf

extracts against hepatic cancer cell line (HepG2). The phytochemicals showed a dynamic role in treatment and prevention of cancer by hindering cancer cells through activating hormones and enzymes, stimulation of DNA repair mechanism, enhancing the production of protective enzymes that induce antioxidant action and enhance immunity [52–53].

CONCLUSION

This review study focused on molecules involved in anticancer activity of M.*oleifera* at different forms.

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