Journal of Ayurvedic and Herbal Medicine

Review Article

ISSN: 2454-5023
J. Ayu. Herb. Med.
2024; 10(3): 94-101
Received: 17-07-2024
Accepted: 27-09-2024

www.ayurvedjournal.com
DOI: 10.31254/jahm.2024.10305

Unveiling the Role of *Moringa oleifera* in Targeting the PI3K/AKT/mTOR Pathway in Ovarian Cancer

Mutthuraj D[1], Arjun KR[1], Sahana HD[2], Abhishek MK[3], Brunda M[1], Kanthesh M Basalingappa[1]

[1] Division of Molecular Biology, School of Life Sciences, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India

[2] Department of Biochemistry, Oxford Medical College, Hospital and Research Centre, Yadavanahalli, Bangalore, Karnataka, India

[3] Department of Biochemistry, Coorg Institute of Dental Science, Kodagu, Karnataka, India

ABSTRACT

The moringa tree grows little and quickly. Traditional medicine uses the leaves, flowers, seedlings, and roots to treat a variety of ailments. To create a powder, moringa seeds and leaves are pulverized. Both pills and capsules are formed from the powder. Moreover, you can make drinks by combining moringa powder with liquids. *Moringa oleifera* has a wide array of bioactive compounds that can function as antioxidants, anti-inflammatory substances, antibiotics, antineoplastic agents and other such categories. These ITCs are a type of these active constituents in *Moringa oleifera* which can suppress cancer development through many signal transduction pathways like PI3K-AKT-mTOR resulting in apoptosis of cancer cells and thus preventing metastasis and migration of cancer cells without harming normal ones. Moreover, *Moringa oleifera* contains varying concentrations of bioactive chemicals; for example, carbohydrates are most prevalent in the roots and least in the leaves. Additionally, the primary material composition changed depending on the treatment. In the raw leaf powder, the predominant phenolic acids were chlorogenic and gallic acids, whereas in the pretreatment leaf powder, the amounts of caffeic and gallic acids were higher. Studies demonstrating that *Moringa oleifera* extract has strong anti-cancer effects on cells with melanoma *in vitro* involving mitochondria indicate that *Moringa oleifera* extract can also encourage cancer apoptosis through mitochondria.-mediated apoptotic mechanisms that are both caspase enzyme dependent and independent.

Keywords: *Moringa oleifera*, Bio-compound, Ovarian Cancer, PTEN, PI3K.

INTRODUCTION

Moringa oleifera, known as “Shigru” in ayurveda, has been mentioned in traditional texts for its various medicinal applications. This miracle tree species belongs to the Moringaceae family with 13 different species which are distributed in tropical and sub-tropical regions (Table 1), in recent days they also can be found all around the world. This wonder species herb has a various range of nutritional, medicinal, and traditional values. Moringa’s different plants are used in treating numerous ailments like diabetes, disinfectant, fever, constipation, wound healing, burns, malaria, labor pain, slimness, muscle pains, asthma, skin problems, stomach problems, and so on [1]. In recent days herbal products are playing a vital role in managing diseases with minimal side effects. Whereas the origin of using herbs/plant products in medicine dates back to mid-paleolithic age which is 60,000 years ago [2]. Until now 391,000 vascular plant species had been identified out of this only 6% of plants were screened for their biological activity and in the future 15% for their phytoconstituents properties [3]. Out of all of the identified species around the world, the moringa genus plays an vital role in medicinal as well as economical importance.

As history stands witness in using herbal medicine to treat very serious disorders. Various civilizations like Indian, Greek, and Egyptian were used for hundreds and thousands of years [5].

Overview of ovarian cancer incidence and mortality rates

One of the main reasons why women die from cancer is ovarian cancer. The lifetime risk of ovarian cancer for a woman is around 1 in 87. She has a roughly 1 in 130 lifetime probability of passing away from ovarian cancer. (These figures do not include ovarian tumors with minimal potential for malignancy). Most cases of this malignancy affect elderly women. When ovarian cancer is detected, around half of the affected women are 63 years of age or older. White women experience it more frequently than Black women. The past several decades have seen a gradual decline in the number of ovarian cancer diagnoses. Between 1990 to the mid-2010s, the incidence rate decreased by 1% to 2% a year; between 2015 and 2019, it decreased by about 3% annually. This is probably because fewer people are using menopausal hormone

***Corresponding author:**
Dr. Kanthesh M Basalingappa
Associated Professor, Division of Molecular Biology, School of Life Sciences, JSS Academy of Higher Education & Research, Mysuru, Karnataka, India
Email: kantheshmb@jssuni.edu.in

treatment and more people are using oral contraceptives. Additionally, fewer women are dying from ovarian cancer, perhaps as a result of improved therapies and a decline in the number of cases. Since 1975, the number of fatalities from ovarian cancer has dropped by 40% [6].

Table 1: Thirteen different species of genus Moringa [4]

Moringaarborea	*Moringaperegrina*
Moringaborziana	*Moringapygmaea*
Moringaconcanensis	*Moringarivae*
Moringadrouhardii	*Moringaruspoliana*
Moringahildebrandtii	*Moringastenopetala*
Moringalongituba	*Moringaoleifera*
Moringaovalifolia	

The significance of the PI3K/AKT/mTOR pathway in cancer biology

A major cause of death worldwide, cancer is a serious public health concern. Additionally, it prevents global improvements in life expectancy. In addition, the number of cancer-related deaths and incidence worldwide is steadily rising. Patients' choices for treatment are now inadequate, and the intricacy and variety of tumors require focused therapy or tailored medication. Finding promising treatment targets for cancer is essential. One important factor in the development of cancer is inappropriate activation of the PI3K/AKT/mTOR pathway. The mTOR forms two different complexes: the mammalian target of rapamycin complex 1 (mTORC1) and the mammalian target of rapamycin complex 2 (mTORC2) [7]. The signaling pathway of mTOCR1, which is made up of mTOR, Raptor, the MLST method8, PRAS40, and DEPTOR, is influenced by growth factors, rapamycin, the hormone insulin, phosphatidic acid, specific amino acids, and oxidative stress. S6K and 4EBP1, which are crucial for protein synthesis, the dietary reaction, and tumor formation, are the most well-known targets downstream of mTOCR1. DEPTOR, mTOR, RICTOR, mLST8, PROTOR1/2, mSIN1, and mTOR make up mTORC2. AKT is phosphorylated by mTORC2 in response to its interaction with PDK1. Additionally, mTORC2 is essential for the survival, cell cycle, and actin cytoskeleton [8]. Oncogenic activation of the PI3K/Akt/mTOR pathway is facilitated by changes in PIK3CA and its effectors, decreased PTEN expression, and receptor tyrosine kinases (RTKs).

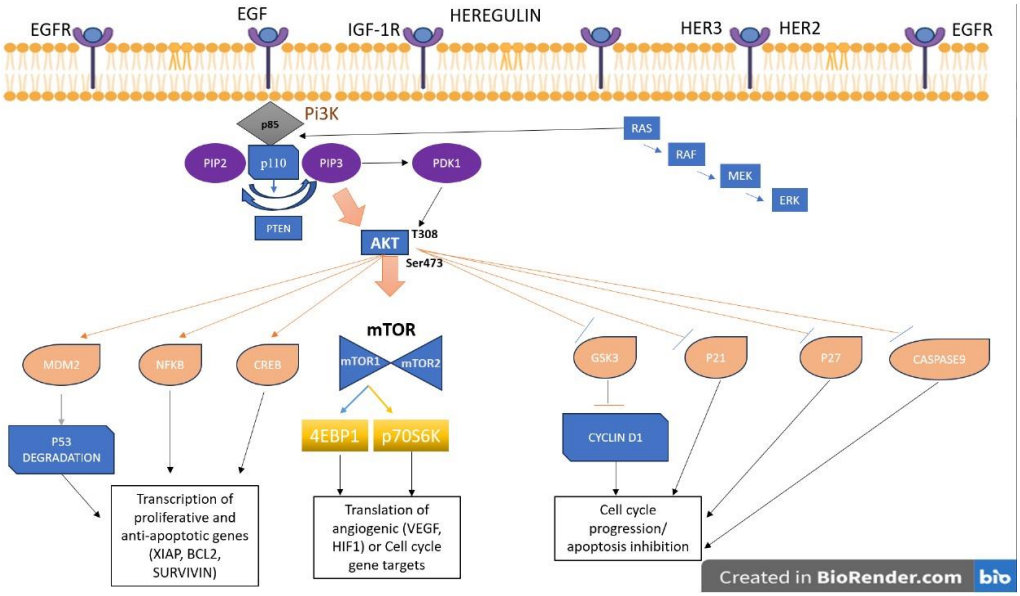

Figure 1: Mechanism of PI3K/AKT/mTOR Signaling pathway and its fate

Changes in the PIK3CA Gene's Genetics: which can be seen in the most often changed catalytic subunit of phosphatidylinositol 3-kinase (PI3K) isoform in malignancy is the p110 α (p110α) subunit, which is encoded by the PIK3CA gene. A family of lipid kinases called PI3K is made up of the catalytic subunit p110α and the regulatory subunit p85α. It is involved in several cellular processes such as cell growth, migration, survival, and proliferation. PI3K is bound to the plasma membrane by a variety of receptor tyrosine kinases, including ERBB2, EGFR, MET, RET, and VEGFR, which convert extracellular inputs into intracellular signals and activate RAS. PI3K-110α initiates the AKT/mTOR pathway by converting its lipid substrate, phosphatidylinositol-4,5-bisphosphate (PIP2), to phosphatidylinositol-3,4,5-bisphosphate (PIP3) after stimulation [9].

Changes in the mTOR Gene: Encoded by the mTOR gene, the mTOR protein is a member of the serine-threonine kinase family that regulates tumor development, survival, and physiological signaling in addition to controlling cell responses to stresses including growth hormones, food deprivation, and DNA damage. Mutations that activate mTOR increase its kinase activity, which causes downstream pro-proliferative pathways to become overactivated. Malignant tumors, including melanoma, esophagogastric adenocarcinoma, colorectal adenocarcinoma, renal cell carcinoma, bladder cancer, and endometrial carcinoma, frequently have MTOR mutations [10].

Genetic mutation in the AKT Gene: As members of the AGC kinase family, AKT1, AKT2, and AKT3 are downstream effectors of the PI3K signaling pathway and serine/threonine protein kinases. Cytosolic AKT1 is taken to the membrane after PI3K activation, where it interacts with PIP3 (PtdIns3,4,5-P3) to cause AKT1 phosphorylation and activation. Numerous downstream effectors, such as GSK3, FOXO, and mTORC1, are activated by AKT1 and are essential for cell growth, survival, and

metabolism. Because PI3K is inhibited by PTEN phosphatase activity, AKT1 may be adversely regulated. In addition, AKT1 activity in malignancies may result from PTEN inactivation or PI3K pathway activation. AKT1 activation is independent of phosphoinositide thanks to AKT1 stimulation mutations and AKT1 rare amplification [11]. AKT oncogenic activation is caused by the activating mutations of AKT2 and AKT3, which disrupt intramolecular pleckstrin homology domain (PH) and kinase domain (KD) interactions. In the MSK-IMPACT Clinical Sequencing Cohort, abnormalities in AKT1, AKT2, and AKT3 were found in 1.8% (183/10336), 1.6% (163/10336), and 1.4% (149/10336) of patients, respectively. In the China Pan-cancer Cohort, abnormalities in AKT1, AKT2, and AKT3 were found in 1.4% (138/10194), 2% (206/10194), and 1.2% (122/10194) of patients, respectively (OrigiMed2020). The most common AKT1 mutation in breast cancer, AKT1 E17K is a hotspot mutation that is also highly recurrent in many other forms of cancer. 6.3% (N=619) of patients with breast cancer had the AKT1 E17K mutation, which is linked to a higher death rate [12]. Many malignant cancers include amplifications or overexpressions of the oncogene AKT2, which promotes tumor growth and metastasis. Many malignancies, including ovarian epithelial tumors, breast cancer, endometrial cancer, melanoma, cholangiocarcinoma, and lung cancer that is not small cells, have been found to have more common amplification of the oncogene AKT3 [13].

Genetic changes in the PTEN Gene: Tumor suppressor PTEN is one of the most often mutated genes in cancer. It has the ability to adversely control the PI3K/AKT/mTOR pathway. On the cell membrane, PTEN performs the role of a phosphatase, changing phosphatidylinositol (3–5)-triphosphate (PIP3) into phosphatidylinositol (4, 5)-diphosphate (PIP2). When PTEN is dysfunctional, PIP3 accumulates and catabolic downstream AKT/mTOR signaling is activated, which promotes cell proliferation and survival. This can be triggered by inactivation alterations, homozygous modifications, a lack of heterozygosity (LOH), through epigenetic modifications. Furthermore, nuclear PTEN can control the expression of RAD51, a protein closely linked to double-strand breaks in DNA (DSBs) and homologous recombination (HR). Moreover, a deficit in PTEN may lead to a rise in instability in the genome, which opens the door for damaging mutations to accumulate [14]. When PTEN reaches high glucose levels, Nedd8 interacts with PTEN to cause PTEN Neddylation, which leads to PTEN nuclear import without compromising PTEN stability. Neddylated PTEN mostly forms aggregations in the nucleus where it dephosphorylates the enzyme fatty acid synthase (FASN), inhibits FASN ubiquitylation and disintegration by means of TRIM21, and ultimately promotes the production of fatty acids. Furthermore, PTEN neddylation has been directly linked to the growth of tumors and a less favorable outlook in cases of breast cancer. The cancer susceptibility syndrome Cowden, linked to a high frequency of thyroid and breast cancer occurrences, is related with 80% of individuals having germline PTEN mutations. One of the most common mutations in cancer is the PTEN mutation, which is commonly detected in prostate adenocarcinoma, glioblastoma, and endometrial carcinoma.

The Akt/mTOR/PI3K Pathway and Various Cellular Mechanisms in Cancer - Cell Proliferation, Autophagy, Apoptosis & Angiogenesis

The most frequently activated signaling pathway in human cancers is the PI3K/Akt/mTOR pathway, which is involved in cell survival, growth, and proliferation. One step in cancerogenesis is dysregulated mTOR activation, which is frequently observed in cancer. In addition to interacting with other proteins, mTOR is a part of two protein complexes called mTOR complex 1 and mTOR complex 2, which regulate different aspects of cellular activity. Subunits of mTORC1 and mTORC2 mediate distinct but overlapping activities. mTORC1 is induced by a number of foods and can be boosted by PI3K signaling. In contrast to mTORC2, which is an Akt downstream effector, mTORC1 is an upstream regulator [15]. In order to regulate cell growth and proliferation, mTORC1 controls the phosphorylation of downstream translation effectors such as eukaryotic initiation of translation factor 4E (eIF4E)-binding protein 1 (4E-BP1) and the ribosomal protein S6 kinase B1 (S6K1). Cell survival and proliferation are regulated by mTORC2, which phosphorylates Akt at Ser473. Small compounds can phosphorylate Akt, mTORC2, and mTORC1 through an Akt-dependent route. Examples of these molecules are growth factors and hormones. Through an Akt-independent phosphorylation pathway, nutrients can directly stimulate mTORC1 and activate Akt and mTORC2.

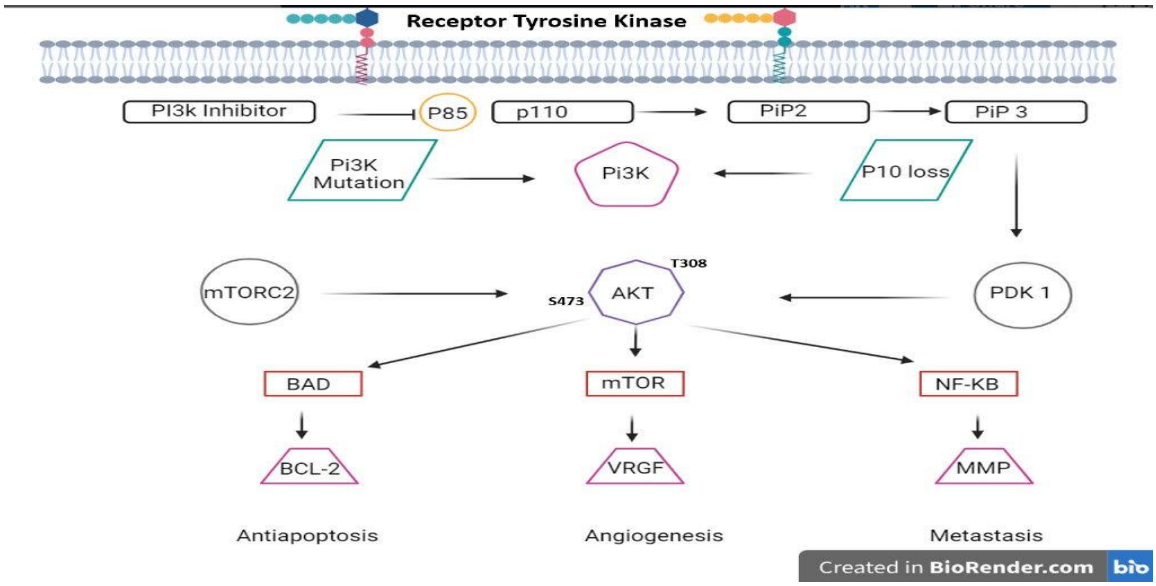

Figure 2: Akt/mTOR/PI3K signaling Pathway and Various Cellular Mechanisms in Cancer - Cell Proliferation, Autophagy, Apoptosis & Angiogenesis

Significant Akt substrate glycogen synthase kinase-3 beta (GSK3) is phosphorylated to cause its deactivation. By regulating the stability and synthesis of proteins involved in the G1/S cell cycle phase transition, such as cyclin D1, GSK3 encourages cell growth. Degradation of damaged or malfunctioning cellular proteins and organelles occurs during autophagy, a vital homeostatic cellular recycling process. Autophagy can be induced in cancers due to deregulation of the PI3K/Akt/mTOR pathway, which enables the cancers to grow and adapt to low-nutrient settings. Autophagy is inhibited by the regulator mTOR, whereas autophagy is promoted by anticancer medicines that interfere with the PI3K/Akt/mTOR pathway. By inhibiting autophagy and lysosome formation—two processes essential for lysosome-dependent macromolecule degradation—mTORC1 suppresses catabolism. By phosphorylating TFEB, a regulator of lysosomal gene expression, and ULK1, a crucial autophagy modulator, mTORC1 prevents autophagy and lysosomal breakdown [16]. Through the AMPK/TSC pathway, energy levels, nutritional status, and hypoxic environments can modify the activity of mTORC1, which impacts autophagy. Protein synthesis is regulated by p70S6 kinase and elongation factor 4E-BP1, two mTORC1 downstream effectors. In order to inhibit the downstream autophagy cascade, activated mTORC1 phosphorylates the autophagy-related protein complex (ULK1/2). AMPK that is activated by LKB1 or AMP can stimulate autophagy by phosphorylating TSC1/2, which inhibits mTORC1 activity. Essential amino acid transport inside cells may inhibit autophagy by activating mTORC1. Furthermore, ROS-dependent ERK activation increases autophagy and causes cell death, while MEK/ERK signaling supports starvation-induced autophagy [17]. By activating Akt and reducing the inhibitory effect of the TSC1/2 heterodimer on Rheb, PI3KCI may prevent autophagy and activate mTORC1. mTORC2 activates Akt, which further reduces autophagy. Furthermore, PTEN stimulates autophagy by inhibiting PIP3 synthesis, which initiates PI3K/Akt/mTOR signaling. GTP-Ras inhibits autophagy by RAF/MEK/ERK and PI3KCI activation. Through a mTORC1-dependent mechanism, the cyclin–CDK inhibitor CDKN1B, sometimes referred to as p27Kip1, increases starvation-induced autophagy. In amino acid-derived cells, a fraction of p27Kip1 is transferred to lysosomes where it interacts with LAMTOR1, a crucial part within the Ragulator complex, to activate mTORC1. Autophagy is aided by the inhibition of regulatory assemblies and mTORC1 activation caused by the binding of p27Kip1 to LAMTOR1 [18]. One kind of planned cell death that helps the body get rid of unwanted or aberrant cells in a systematic way is called apoptosis. As the initiators and executors of apoptosis, caspases play a crucial role in the apoptotic mechanism. The intrinsic endoplasmic reticulum pathway, the intrinsic mitochondrial pathway, and the extrinsic death receptor pathway can all trigger apoptosis. The binding of death ligands (TNF and FasL) to death receptors (TNFR1 and Fas) initiates the extrinsic death receptor pathway. The death-inducing signaling complex (DISC), a ligand-receptor-conjugating protein complex, is formed when the death ligand binds to the death receptor. This complex then facilitates the assembly and activation of caspase 8. Internal stimuli can also increase mitochondrial permeability and cause the cytoplasm to produce pro-apoptotic substances like cytochrome-c, which in turn stimulates the intrinsic mitochondrial pathway. These stimuli include genetic damage, hypoxia, high cytosolic Ca2+ concentrations, and severe oxidative stress. When cytochrome c is released from the cytoplasm, it forms an apoptosome complex with caspase 9, Apaf-1, and cytochrome c. This complex then activates caspase 3. Pro- and anti-apoptotic proteins make up the majority of the Bcl-2 family of proteins, which closely regulates the intrinsic mitochondrial pathway. Apoptosis is regulated by pro-apoptotic proteins like Bax, Bak, Bad, Bcl-XS, Bid, Bik, Bim, and Hrk, which increase the release of cytochrome c from mitochondria, and anti-apoptotic proteins like Bcl-2, Bcl-XL, Bcl-W, BFL-1, and McL-1, which prevent this release [19]. The process of angiogenesis, which results in the growth of new blood vessels, allows nutrients and oxygen to reach the body's tissues. Cancer needs the growth and metastasis of new blood vessels, which is why angiogenesis is essential to the disease's progress. Proteases, protease inhibitors, growth factors, cytokines, residual elements, cancer-causing genes, and endogenous modulators are the primary categories of endogenous angiogenesis regulators. Angiostatin, interferon, endostatin, platelet factor 4 (PF4), thrombospondin (TSP), and tissue inhibitors of metalloproteinases are examples of activators and inhibitors in this balance. Activators include vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), platelet-derived endothelial cell growth factor (PD-ECGF), tumor necrosis factor (TNF)-α, angiogenin, transforming growth factor (TGF)-α, TGF-β, granulocyte colony-stimulating factor (G-CSF), placental growth factor (PGF), hepatocyte growth factor (HGF), interleukin-8 (IL-8), and epidermal growth factor (EGF). Angiogenesis depends on mTOR, a fundamental switch that controls the anabolism and catabolism of endothelial cells. Tumor angiogenesis is facilitated by shear stress, coordinated interactions among endothelial growth factors (PDGF-B, VEGF, ANG1, ANG2, ephrin-B2, bFGF, and TGF-beta superfamily), intracellular signaling proteins (NOTCH1 and COUP-TFII), and intercellular interactions (VCAM1). These factors may activate the PI3K/Akt/mTOR pathway in cancer cells. Tumor cells begin producing more vascular endothelium growth factor (VEGF) when hypoxia stabilizes HIF-1α. By both independent and dependent mechanisms, activation of the pathway consisting of PI3K and AKT in cancer cells has the potential to increase VEGF synthesis [20].

Anticancer & antioxidant effect of *Moringa oleifera*

The species *Moringa oleifera* has long been a widespread plant across the world. It has an abundance of phenolic substances with a wide variety of biological functions. Its anticancer qualities can be used to develop new drugs to combat the progression of different cancers. Because they are less poisonous and have fewer adverse effects than synthetic medications, plants have long been believed to be employed as therapeutic agents. Moreover, phytochemical compounds support intricate physiological processes [21]. By 2020, cancer will be the primary cause of death worldwide, accounting for about 10 million fatalities, or nearly one in every six deaths. The most prevalent cancer kinds include lung, colon, prostate, breast, and rectum. Men are more prone than women to get cancers of the stomach, liver, prostate, lung, and colorectal; on the other hand, women are more likely to develop cancers of the breast, ovarian, colorectal cancer, lung, cervical, and thyroid [22]. Numerous other variables are also known to increase the risk of cancer, including certain disorders, dietary components, obesity, and environmental pollutants. These factors may combine to initiate or promote human carcinogenesis, making cancer the leading cause of mortality in the species. When it comes to cause-specific disability-adjusted life years (DALYs), cancer costs more clinically, socially, and financially than all other illnesses that affect humans. Between the ages of 0 and 74, the total risk of acquiring cancer is 20.2%; for males, it is 24.4%, and for women, it is 18.2% [23]. Cancer can be treated with a

variety of traditional methods, such as radiation, chemotherapy, and surgery, as well as more modern techniques involving hormonal therapy, immunotherapy, which is antiangiogenic stem cell therapies, and dendritic cellular-based immunotherapy. The kind of cancer, its location, and its severity are among the variables affecting the available treatments and its course [24]. Anticancer drugs and chemotherapy or chemoradiotherapy are beneficial treatments for many cancer patients. However, a variety of toxic side effects, including anorexia, nausea, vomiting, diarrhea, and oral mucositis, are brought on by these anticancer drugs. The toxic effects on cells or normal tissues are the root cause of all these adverse effects. Patients frequently have a worse quality of life as a result of these side events, which makes it difficult to keep on receiving chemotherapy or chemoradiotherapy [25]. In the modern era, herbal medicine is becoming more and more popular. Natural goods, particularly plant-based treatments, have been used to treat a wide range of ailments and disorders since ancient times and are part of folklore. Also, eighty percent of people globally still utilize traditional medicine. Natural products are a valuable resource for drug development in several therapeutic areas, most notably infectious disorders and cancer, due to their medicinal qualities, which have attracted researchers to identify their bioactive components [26]. Research has shown that a wide variety of medicinal plants can stop cancer from starting or spreading. *Moringa oleifera* Lam is one such plant [27]. For centuries, many cultures worldwide have used *Moringa oleifera,* also known as the miracle tree, as a traditional medicine to treat a wide range of conditions, including anemia, psoriasis, skin infections, anxiety, asthma, acne, blackheads, conjunctivitis, asthma, catarrh, cholera, wheeze, diarrhea, eye and infections of the ears, chest congestion, a high body temperature glandular tissues swelling, migraines, unusual blood pressure, hysteria, and joint pain. Additionally, the medical benefits of moringa oil have been retained by ancient societies. It is widely prized for its cosmetic qualities and may be used as a body and hair moisturizer and skin conditioner. Phytochemical components determine a medicinal plant's therapeutic effectiveness. Many phytochemical components, such as alkaloids, anthraquinone, saponins, tannins, steroids, terpenoids, phenolic compounds, anthocyanin, glucosinolates, flavonoids, or terpenes, and carotenoids, are present in Moringa oleifera's leaves, stems, bark, roots, seeds, pods, and oil.

For centuries, many cultures worldwide have used *Moringa oleifera*, also known as the miracle tree, as a traditional medicine to treat a wide range of conditions, including anemia, psoriasis, skin infections, anxiety, asthma, acne, blackheads, conjunctivitis, bronchitis, catarrh, cholera, conjunctiva cough, diarrhea, eye and infections of the ears, chest congestion, fever, glandular edema, migraines, abnormal blood pressure, hysteria, and joint pain. Additionally, the medical benefits of moringa oil have been retained by ancient societies. It is widely prized for its cosmetic qualities and may be used as a body and hair moisturizer and skin conditioner. Moringa oil ointments and skin treatments have been used in Egypt since ancient times. Several cancer types have been effectively treated with the right therapeutic approaches; nevertheless, toxicity and/or resistance need the development of novel, more effective treatments. Leaf and bark extracts of *Moringa oleifera* have been shown to effectively suppress the development of breast, pancreatic, and colorectal cancer cells [28]. According to gas chromatography–mass spectrometry (GC–MS), *M. oleifera* includes 12 distinct chemicals, three of which have anticancer qualities. A whole plant naturally contains glucosinolates, the precursor form of isothiocyanates that has been shown to be a potent anticancer agent. Isothiocyanates are the precursor form of glycosylates found naturally in *Moringa oleifera*, and they have been touted as potent anticancer chemicals. Myrosinase, an enzyme, mediates the hydrolysis of glucosinolates to produce isothiocyanate when the intact plant is disturbed. Isothiocyanates' anticancer properties have been well studied. Human prostate cancer cells that are androgen-dependent (LNCaP) and androgen-independent (PC-3) are inhibited by alyl isothiocyanates (AITC). AITC inhibited PC-3 cell development by causing gap2/mitosis (G2/M) cells to accumulate in addition to apoptosis. After treating PC-3 and LNCaP cells with AITC for 24 hours, a decrease in the amounts of cyclin-dependent kinase CDK1 (cyclin-dependent kinase 1), cell division cycle protein 25B (CDC25B), and CDC25C was seen. In mice implanted with BxPC-3 tumor xenografts, benzyl isothiocyanates (BITCs) exhibited a 43% reduction in tumor growth. Moreover, BITC treatment was found to decrease protein kinase B (AKT), mammalian target of rapamycin, forkhead box O3A, phosphorylation of phosphatidylinositide 3-kinase, FOXO1, and pyruvate dehydrogenase kinase. Phenyethyl isothiocyanates have been shown to slow the development of cancer via blocking AKT. Although moringa isothiocyanates have been thoroughly investigated in vitro, our first *in vitro* investigations and those involving other isothiocyanates indicate they could be valuable as cancer treatments [29].

Oxidative stress is a critical factor in linking environmental toxins to carcinogenesis in the multiple-stage process of carcinogenesis. Reactive oxygen species, also known as ROS, are produced in reaction to external and endogenous stimuli. Both *in vitro* and *in vivo* studies have demonstrated that environmental variables such as radiation, chlorinated compounds, and xenobiotics are significant inducers of cell death through ROS-mediated toxicity. Examples of naturally occurring endogenous enzymatic antioxidant defenses include glutathione peroxidase, catalase, and superoxide dismutase. These defenses may combat oxidative microenvironments by chelating superoxide and using different peroxides. Furthermore, the antioxidant enzyme coenzyme Q, glutathione, vitamins E and C, and the pigment b-carotene are examples of nonenzymatic endogenous antioxidants that can lower ROS activity [30]. Additionally, there is no proof that antioxidants interfere with chemotherapy mechanisms, although there is a possibility that antioxidants could improve tumor response or patient survival. Several studies show that antioxidant supplementation results in longer survival times, improved tumor response, or both, as well as fewer toxicities than controls [31]. One of the primary components needed for mutations in DNA in the development of cancer is free radicals, which subsequently starts the carcinogenesis stage of the disease. Exogenous antioxidants derived from natural sources can enhance the function of the body's endogenous antioxidants system, which protects against free radicals. It has been observed that the polyphenol content of extracts from *Moringa oleifera* has strong antioxidant properties. It has recently been shown that the water-based extract of the leaves from Moringa oleifera contains polyphenols and has the ability to scavenge DPPH radicals. Furthermore, according to certain studies, *Moringa oleifera* leaves have a high concentration of flavonoids and polyphenols and have antioxidant properties [32].

Impact on chemotherapy medications: Multidrug resistance is the main factor contributing to chemotherapy failure (MDR). Treatment effectiveness is frequently decreased and the risk of cancer recurrence is raised when chemotherapy medications develop multidrug resistance (MDR). Phytochemical substances have various benefits, including low toxicity, few adverse effects, multiple targets, poor tumor resistance, and the capacity to suppress tumor development and immune system function. In the battle against cancer, research into natural substances that have reversed MDR has taken center stage. Combining doxorubicin with extracts from the callus and leaves of Moringa oleifera results in a potent interaction that inhibits cell growth and is linked to inducing apoptosis. There aren't any chemopreventive drugs made from *Moringa oleifera* on the market right now. A possible cancer treatment strategy might involve using *Moringa oleifera* either by itself or in combination with the anticancer drugs that are now on the market [33,34].

Table 2: Ethnomedicinal utilization of *Moringa oleifera* in several dosage formulations and regions [34]

Country	Plant part used	Health benefits	Administration of the plant medicine
India	Root	Serves as a laxative, abortifacient, antilithic, rubefacient, vesicant, carminative, antifertility, anti-inflammatory, cardiac/circulatory tonic, treatment for rheumatism, articular aches, lower back or kidney discomfort, and stimulant in paralytic ailments.	Oral
	Leaves	Arthritis, treat hyperthyroidism, treat piles, fever, sore throat, bronchitis, eye and infections of the ear scurvy, and catarrh; also used as a purgative and to regulate blood pressure and reduce glucose levels.	Oral
	Seeds	antipyretic, larvicidal action against the mosquito that spreads dengue and yellow fever, antibacterial properties against bacteria and fungi, diuretic, antispasmodic, and anti-inflammatory	oral
North America	Leaves	Prostate cancer, radioprotective, antihypertensive, antiviral, antimicrobial, antimicrobial, antiviral, antiparasitic, antipathogenic, anti-tumor, diuretic, used in colitis, diarrhea, dysentery, ulcer/gastritis, hemorrhage anti-inflammatory in nature antirheumatic, the lactation period enhancer, antiseptic, used in catarrh, scurvy	Oral
	Flowers & Seeds	Diuretic, antihysteric, abortifacient, anti-inflammatory, anticancer, antimicrobial, antibacterial, anti-infective, antiviral, antirheumatic, and useful in ulcers and throat infections	Oral
Africa	Leaves powder	malnourishment, antihypertensive, antiseptic, antiasthmatic, diabetes mellitus, malaria/fever, syphilis and skin disease, bronchiasis, symptoms associated with the HIV/AIDS, external sores, colitis, gastritis, impotence, syphilis, flu, heartburn, bone setting, stress, and used as a deworming agent	oral

Table 3: *Moringa oleifera*'s purported anticancer properties stem from *in vitro* studies [34]

Dosage/extraction of plant sample	In vitro	Dose	Standard	Activity
Its leaves were separated into five parts using methanol extract: n-hexane, chloroform, ethyl acetate, butanol, and distilled water.	In 96-well plates using Hela cancer cell lines, the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide) reduction test is performed.	26, 52, 104, 208, and 416 µg/ml	-	Hela cancer cell viability is decreased, and the anticancer property
Leaves aqueous extract	Ehrlich ascites carcinoma (EAC) and human laryngeal carcinoma (Hep-2) cell culture Trypan blue dye exclusion assay MTT assay Lactate dehydrogenase (LDH) release assay Cell cycle assay	0.05, 0.1, 0.25, 0.5, and 1 mg/ml 0.05, 0.1, and 0.2 mg/Ml	Control (no treatment)	Anticancer Dose-dependent decrease in viable cells
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, Leaves and bark decrease

	Motility assay Clonogenic survival assay Cell viability assay Apoptosis assay Cell cycle assay	500 µg/ml		motility rate, Leaves and bark decrease colony formation, Leaves and bark decrease cell survival, Apoptotic cells increase from 27 to 46% in leaves and from 27 to 29% in bark, G2/M enrichment was observed in leaves and bark showing cell cycle arrest

CONCLUSION

Herbal remedies have been documented historically in countries like China and India. This medical trend offers necessary pharmaceuticals that have been recommended for many illnesses over the years. In industrialized countries, individuals seeking natural or alternative medicines have turned to nature for safe and extensive dietary therapies in order to avoid the side effects and high costs associated with chemotherapy. Numerous studies have looked into the possibility that some naturally generated botanical compounds agents, such as phenolic substances (such as alkaloids and flavonoids), particularly those consumed in diets of humans, can activate mechanisms that lead to the death of cancer cells and may be employed as potential chemo-preventive agents against specific types of cancerous cells. There are about 14 million new instances of cancer worldwide, and 8.2 million deaths from cancer-related reasons make it the leading cause of illness and mortality. Over the next 20 years, there will likely be a 70% increase in the number of new cases. Lung, prostate, colorectum, stomach, and liver cancer were the five most prevalent cancer locations among men. The five most prevalent cancer locations among women were stomach, cervix, lung, colorectum, and breast cancer. The most deadly gynecologic malignancy in North America and Europe is ovarian cancer. The cornerstone of management for this disease is effectively reduced with platinum-based chemotherapy because it usually presents at an advanced stage. Unfortunately, these tumors virtually always return after showing strong first responses to chemotherapy [35]. The molecular etiology of ovarian cancer has been greatly advanced due to recent large-scale molecular profiling investigations, such as the integrated genomic analysis carried out by the Cancer Genome Atlas (TCGA) network. The biology of ovarian cancer is briefly reviewed in this article, with an emphasis on the significance of the PI3K/Akt/mTOR signaling pathway and a discussion of the reasons behind focusing on this route in ovarian cancer. Additionally provided are preliminary data and the outcomes of current clinical trials. The need for prognostic markers, the problem of drug resistance, and methods for maximizing the development of innovative therapeutics targeting PI3K in ovarian cancer are some of the additional difficulties addressing the advancement of these inhibitors in this disease. In many cancers, including OC, the phosphatidylinositol 3 kinase (PI3K) pathway is disrupted. Mammalian target of rapamycin (mTOR) the initial inhibitors are currently licensed for the management of renal, pancreatic, the breasts, and some brain malignancies. They have shown promise in additional tumor types. Furthermore, other new drugs that target Akt or PI3K in addition to the second generation mTOR inhibitors are undergoing early-stage clinical studies [35]. Hence, inventing new improved drugs from herbal products is more beneficial.

Conflict of interest

There is no conflict of interest.

Funding

None declared.

ORCID ID

Mutthuraj D: https://orcid.org/0009-0003-1003-2372
Arjun K R: https://orcid.org/0009-0002-2600-9655
Sahana H D: https://orcid.org/0009-0002-7796-7351
Abhishek MK: https://orcid.org/0009-0002-5802-8877
Brunda M: https://orcid.org/0009-0008-2634-2582
Kanthesh M Basalingappa: https://orcid.org/0000-0002-6970-4546

REFERENCES

1. Senthilkumar A, Karuvantevida N, Rastrelli L, Kurup SS, Cheruth AJ. Traditional uses, pharmacological efficacy, and phytochemistry of Moringa peregrina (Forssk.) Fiori.—a review. Frontiers in pharmacology. 2018;9:465.
2. Solecki RS. Shanidar IV, a Neanderthal flower burial in northern Iraq. Science. 1975;190(4217):880-1.
3. Verpoorte R. Pharmacognosy in the new millennium: leadfinding and biotechnology. Journal of pharmacy and pharmacology. 2000;52(3):253-62.
4. Quattrocchi U. CRC world dictionary of grasses: common names, scientific names, eponyms, synonyms, and etymology-3 volume set. CRC Press; 2006.
5. Jahn SA. On the introduction of a tropical multipurpose tree to China: traditional and potential utilisation of Moringa oleifera Lamarck. Senckenb Biol. 1996;75:243–254.
6. The American Cancer Society; https://www.cancer.org/cancer/types/ovarian-cancer/about/key-statistics.html
7. Foster KG, Fingar DC. Mammalian target of rapamycin (mTOR): conducting the cellular signaling symphony. Journal of Biological Chemistry. 2010;285(19):14071-7.
8. Kim LC, Cook RS, Chen J. mTORC1 and mTORC2 in cancer and the tumor microenvironment. Oncogene. 2017;36(16):2191-201.
9. Bader AG, Kang S, Zhao L, Vogt PK. Oncogenic PI3K deregulates transcription and translation. Nature Reviews Cancer. 2005;5(12):921-9.
10. Murugan AK, Alzahrani A, Xing M. Mutations in critical domains confer the human mTOR gene strong

tumorigenicity. Journal of Biological Chemistry. 2013;288(9):6511-21.
11. Hoxhaj G, Manning BD. The PI3K–AKT network at the interface of oncogenic signalling and cancer metabolism. Nature Reviews Cancer. 2020;20(2):74-88.
12. Zehir A, Benayed R, Shah RH, Syed A, Middha S, Kim HR, Srinivasan P, Gao J, Chakravarty D, Devlin SM, Hellmann MD. Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients. Nature medicine. 2017;23(6):703-13.
13. Robinson DR, Wu YM, Lonigro RJ, Vats P, Cobain E, Everett J, Cao X, Rabban E, Kumar-Sinha C, Raymond V, Schuetze S. Integrative clinical genomics of metastatic cancer. Nature. 2017 Aug;548(7667):297-303.
14. Song MS, Salmena L, Pandolfi PP. The functions and regulation of the PTEN tumour suppressor. Nature reviews Molecular cell biology. 2012;13(5):283-96.
15. Tian T, Li X, Zhang J. mTOR signaling in cancer and mTOR inhibitors in solid tumor targeting therapy. International journal of molecular sciences. 2019;20(3):755.
16. Yoshida GJ. Therapeutic strategies of drug repositioning targeting autophagy to induce cancer cell death: from pathophysiology to treatment. Journal of hematology & oncology. 2017 Dec;10:1-4.
17. Al-Bari MA, Xu P. Molecular regulation of autophagy machinery by mTOR-dependent and-independent pathways. Annals of the New York Academy of Sciences. 2020;1467(1):3-20.
18. Janku F, McConkey DJ, Hong DS, Kurzrock R. Autophagy as a target for anticancer therapy. Nature reviews Clinical oncology. 2011;8(9):528-39.
19. Wong RS. Apoptosis in cancer: from pathogenesis to treatment. Journal of experimental & clinical cancer research. 2011;30:1-4.
20. Ji L, Wu M, Li Z. Rutacecarpine inhibits angiogenesis by targeting the VEGFR2 and VEGFR2-mediated Akt/mTOR/p70s6k signaling pathway. Molecules. 2018;23(8):2047.
21. Said-Al Ahl HA, Hikal WM, Mahmoud AA. Biological activity of Moringa peregrina: a review. American Journal of Food Science and Health. 2017;3(4):83-7.
22. Cancer. https://www.who.int/news-room/fact-sheets/detail/cancer (accessed July 07, 2024).
23. Mattiuzzi C, Lippi G. Current cancer epidemiology. Journal of epidemiology and global health. 2019;9(4):217-22.
24. Debela DT, Muzazu SG, Heraro KD, Ndalama MT, Mesele BW, Haile DC, Kitui SK, Manyazewal T. New approaches and procedures for cancer treatment: Current perspectives. SAGE open medicine. 2021;9:20503121211034366.
25. Akin S, Can G, Aydiner A, Ozdilli K, Durna Z. Quality of life, symptom experience and distress of lung cancer patients undergoing chemotherapy. European journal of oncology nursing. 2010;14(5):400-9.
26. Atanasov AG, Zotchev SB, Dirsch VM, Supuran CT. International natural product sciences taskforce. Nat. Rev. Drug Discov. 2021;20(3):200-16.
27. Aung TN, Qu Z, Kortschak RD, Adelson DL. Understanding the effectiveness of natural compound mixtures in cancer through their molecular mode of action. International journal of molecular sciences. 2017;18(3):656.
28. Mahmood KT, Mugal T, Haq IU. Moringa oleifera: a natural gift-A review. Journal of Pharmaceutical Sciences and Research. 2010;2(11):775.
29. Toma A, Deyno S. Phytochemistry and pharmacological activities of Moringa oleifera. International Journal of Pharmacognosy. 2014;1(4):222-31.
30. Fahey JW, Zalcmann AT, Talalay P. The chemical diversity and distribution of glucosinolates and isothiocyanates among plants. Phytochemistry. 2001;56(1):5-1.
31. Marnett LJ. Oxyradicals and DNA damage. carcinogenesis. 2000;21(3):361-70.
32. Block KI, Koch AC, Mead MN, Tothy PK, Newman RA, Gyllenhaal C. Impact of antioxidant supplementation on chemotherapeutic toxicity: a systematic review of the evidence from randomized controlled trials. International journal of cancer. 2008;123(6):1227-39.
33. Luqman S, Srivastava S, Kumar R, Maurya AK, Chanda D. Experimental assessment of Moringa oleifera leaf and fruit for its antistress, antioxidant, and scavenging potential using in vitro and in vivo assays. Evidence-Based Complementary and Alternative Medicine. 2012;2012(1):519084.
34. Singh J, Gautam DN, Sourav S, Sharma R. Role of Moringa oleifera Lam. in cancer: Phytochemistry and pharmacological insights. Food Frontiers. 2023;4(1):164-206.
35. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609-15.

HOW TO CITE THIS ARTICLE
Mutthuraj D, Arjun KR, Sahana HD, Abhishek MK, Brunda M, Basalingappa KM. Unveiling the Role of *Moringa oleifera* in Targeting the PI3K/AKT/mTOR Pathway in Ovarian Cancer. J Ayu Herb Med 2024;10(3):94-101. DOI: 10.31254/jahm.2024.10305