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Review Article

The Anti-Cancer Effect of Mangiferin Extract: A Mini Review

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Abstract

Mangifera Indica was used in traditional medicine due to its various medicinal effects. Many nutraceutical agents could be derived from Mangifera Indica. Mangiferin, one of the researched extracts, has shown promising therapeutic potential in different diseases. Mangiferin is also used in the treatment of several cancers, including breast, cervical, colon, gastric, pancreatic, and nasopharyngeal cancers. In this mini-review, we focused on recent in-vitro and in-vivo studies discussing the anti-cancer effect of Mangiferin, while highlighting its effect and mechanism of action. We hope that this mini-review can help to update our knowledge about the effects and mechanisms of extracts from this promising herb Mangifera Indica for ongoing studies and speed up its clinical application in the future.

Keywords: Mangiferin; Anti-Cancer; Herbal Therapy; Tongue Carcinoma

Background

Cancer represents a major issue affecting the worldwide health status, were its burden on the global health increased to be the second most leading cause of death after cardiovascular disease [1]. Owing to this burden, research in the field of cancer treatment has gained a significant importance. Traditional treatment options for cancer include surgery, radiotherapy, and chemotherapy as single treatments or in combination with each other [2]. However, these treatments showed many adverse effects, so continued research gave rise to other novel cancer therapies such as targeted therapy, nanoparticles, stem cell therapy, as well as gene therapy [3].

Another treatment option with a promising potential is the use of natural antioxidants. Natural antioxidants such as various vitamins, alkaloids, flavonoids, and polyphenols have proved their ability to successfully detoxify the adverse effects of the many cancerous effects of exogenous insults to which cells are subjected to on daily basis, such as ultraviolet rays, pollution, and tobacco smoke [3]. The accumulated effects of these insults alter the genomic DNA, induce and promote cancer growth [4].

Mangifera indica L., also known as mango, is a plant of the Anacardiaceous family that is generally found in tropical and sub-tropical areas of the world. This plant was found to be rich in many phytochemicals, such as polyphenols, flavonoids, carotenoids, organic acids, fatty acids as well as essential and non-essential amino acids [5]. Mangiferin (2-β-d-glucopyranosyl-1,3,6,7-tetrahydroxy-9H-xanthene-9-one) is a polyphenol found with high concentration in various parts of the mango tree, with the highest content in the plant young leaves, figure 1 [6].

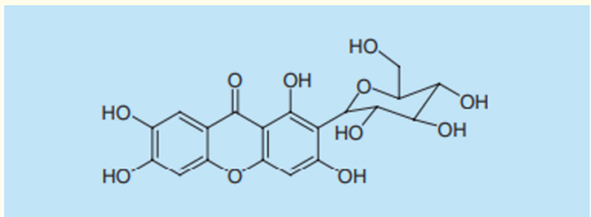

Figure 1: Chemical structure of Mangiferin.

Mangiferin extract was shown to have immense pharmacological properties, where various studies proved its anti-inflammatory, antidiabetic, immunomodulatory, anti-hypertensive, anti-viral and anti-bacterial properties [7]. Mangiferin was also searched for its

potential in the treatment and prevention of cancer as well as its interaction with various anti-cancer drugs and carriers [8]. The aim of this work is to critically analyze the available literature to provide an exhaustive overview of cancer preventive and therapeutic potential of Mangiferin with an emphasis on molecular mechanisms of action.

Mechanisms of action of Mangifera against cancer

Mangiferin exerts its anti-cancer potential through a myriad of molecular mechanisms. These mechanisms include reduction of reactive oxygen species, stimulation of apoptosis, cell cycle arrest, anti-inflammatory activity, loss of mitochondrial potential, anti-angiogenesis, inhibition of lipid peroxidation as well as metastasis prevention, a summary shown in figure 2 [9].

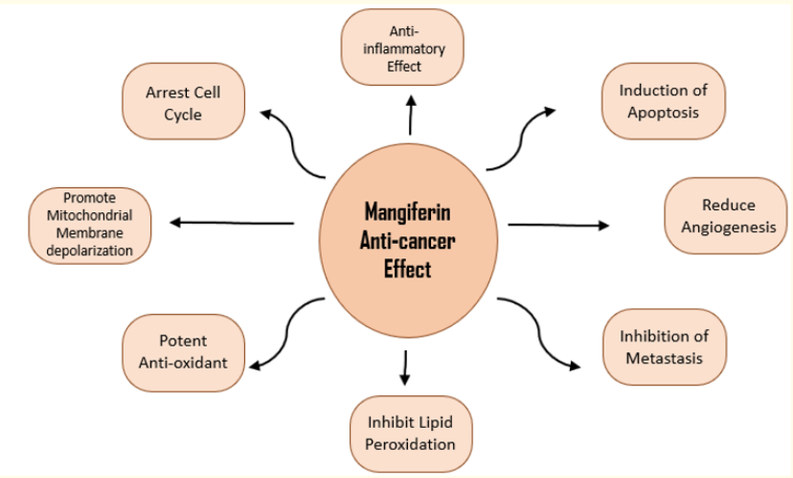

Figure 2: Diverse mechanisms for potential activity of Mangiferin.

- **Potent antioxidant:** Mangiferin was found to possess a potent free radical-scavenging activity, owing to its xanthonoid structure with C-glucosyl linkage together with the presence of multiple polyhydroxy -OH groups, thus increasing its chelating capacity. This structure is also essential for its antioxidant potential. It also enhances the levels of endogenous antioxidants such as glutathione. It is also known to inhibit xanthine oxidase, one of the enzymes responsible for oxidation [10].
- **Inhibition of metastasis:** β-catenin is a transcriptional factor that is associated with proliferation and metastasis and is often observed to have aberrant activation in cancer. Mangiferin is thought to reduce cell proliferation and metastasis through modulation of β-catenin pathway and consequently the reduction of matrix metalloproteinase-7 (MMP-7), MMP-9, and epithelial to mesenchymal transition. Mangiferin could also reduce metastasis through downregulation of nuclear factor kappa beta (NF-κB), vascular endothelial growth factor (VEGF) and cyclooxygenase-2 (COX-2) [11].
- **Inhibit lipid peroxidation:** Mangiferin was found to inhibit the onset of lipid peroxidation in human peripheral blood lymphocytes in a dose-dependent manner due to its antioxidant activity. Mangiferin was also found to have an iron-complexing ability, thus providing protection from lipid peroxidation induced by Fe^{2+}-citrate in rat liver mitochondria [7].
- **Reduce Angiogenesis:** Mangiferin acts as an anti-angiogenic agent by its ability to suppress NF-κB which consequently suppresses VEGF that codes for essential growth factor for vascular endothelial cells. Mangiferin also acts to reduce Heme oxygenase 1 (HMOX1), transforming growth factor beta 3 (TGFB3), thus reducing trans-differentiation of mesenchymal stem cells into endothelial cells [12,13].
- **Promote mitochondrial membrane depolarization:** [14] found that Mangiferin doesn't cause pro-oxidant activity on organelles under normal conditions. However, in cases of enhanced reactive oxygen species (ROS) production, the accumulation of ROS could increase the oxidized products of Mangiferin, which are capable of interacting with mitochondrial membrane thiol groups, resulting in mitochondrial permeability transition onset and finally cell damage.
- **Anti-inflammatory effect:** Cancer-related inflammation plays a crucial role in the occurrence and progression of cancer by providing growth factors, chemokines, and cytokines that participate in the tumor microenvironment. Mangiferin exhibits strong anti-inflammatory effects through its ability to suppress NF-κB which in turn down-regulated the expression of a variety of NF-κB target genes such as MMP-19, interleulin-6 (IL-6), tumor necrosis factor (TNF) and interferon gamma (INF-γ). Mangiferin also inhibits COX-2, IL-1β, IL-8, and enhances microRNA expression [8].
- **Arrest cell cycle:** [15] Observed that Mangiferin showed its ability to inhibit cell cycle progression at G2/M phase through the stress response DNA damage pathway, or the ATR-Chk1-

cdc25c and cdc2/cyclin B pathway in HL-60 leukemia cells. [16] also observed that in A549 human lung carcinoma cells, Mangiferin triggered G_2/M phase cell cycle arrest via downregulating the (cdc2)-cyclin B1 signaling pathway.

- **Induction of apoptosis:** Through the various research in many cell lines, it could be concluded that Mangiferin has the ability to induce apoptosis via multiple targets. This was suggested to occur through activation of caspase-3 and -9, release of cytochrome *c* into the cytoplasm, reduction of mitochondrial membrane potential, upregulation of proapoptotic Bax, downregulation of anti-apoptotic Bcl-2 and Bcl-X_L, and cleavage of Poly (ADP-ribose) polymerase (PARP), which are characteristics of caspase- and mitochondrial-dependent apoptosis [11,16].

Pharmaceutical use of Mangiferin as an anticancer drug

- **Mangiferin against Nasopharyngeal carcinoma**: In 2014, an *in-vitro* study was performed to investigate the effect of Mangiferin on nasopharyngeal carcinoma cell line. This study concluded that Mangiferin stimulates apoptosis through down-regulation of B cell lymphoma- 2 (Bcl-2) messenger RNA (mRNA) level and up-regulation of Bcl-2 associated X protein (Bax) mRNA level in Mangiferin-treated cells compared with control. Mangiferin was also found to inhibit nasopharyngeal carcinoma cells proliferation via cell cycle arrest at the G2/M checkpoint [17].
- **Mangiferin against cervical cancer:** [18]. studied the effect of various concentrations of mangiferin on human cervical carcinoma HeLa cells. The study concluded that mangiferin caused apoptosis of HeLa cells through downregulation of anti-apoptotic Bcl-2 expression, resulting in the proteolytic activation of caspase-3, 7, 8, and 9 as well as the degradation of PARP protein.
- **Mangiferin against Colo-rectal carcinoma:** In [19] used Molecular docking of Mangiferin with various colon cancer target proteins, using the colon cancer (HT29) cell line to determine its mode of action. The docking analysis revealed that Mangiferin can target multiple enzymes/proteins involved in the progression colo-rectal cancer, mainly through blocking the overexpression of COX-2 in colorectal carcinomas. It also showed that Mangiferin can block the activity of Bcl-2 and Bcl-xL proteins increasing the rate of cancer cells' apoptosis. This study also proved that Mangiferin toxicity was targeted to cancer cells compared to normal cells, indicating that it could be a promising candidate for the site-directed target in the future for the treatment of colorectal cancer.
- Another study by [20] treated both human colon adenocarcinoma cell line (HT29) and mouse model of murine CT26 colon carcinoma with serial concentrations of Mangiferin for 24, 48, and 72 hours. The murine models treated with Mangiferin showed dose dependent tumor regression, comparable to the models treated with Cisplatin. Mangiferin was also found to inhibit invasion, angiogenesis, and vasculogenesis of cancer cells thus proving to have the potential value to be used as adjuvant phyto-therapeutic treatment against colo-rectal carcinoma to reduce adverse toxicity and to mitigate outcome of colon cancer treatment.
- **Mangiferin against Prostate cancer:** [21] Investigated the anticancer effects of Mangiferin on human prostate cancer cells PC3 as well as the underlying potential mechanisms. This study proved the ability of Mangiferin in reducing PC3 cells proliferation in a time-dose dependent manner. Mangiferin was found to promote caspase-3 activity as well as enhance microRNA-182 (miR-182) expression and reduce Bcl-2 expression, the overall effect leading to inhibiting proliferation and inducing apoptosis of PC3 cells.
- **Mangiferin and Gastric carcinoma:** [22] Observed the antiproliferative effect of Mangiferin on gastric carcinoma cell lines, were it was found that Mangiferin caused a significant decrease in Bcl-2, Bcl-xL and myeloid cell leukemia-1 (Mcl-1) expression levels as well as a significant increase in Bax, Bad and cleaved caspase-3 and caspase-9 expression, thus effectively inhibiting cell growth and inducing apoptosis of gastric cancer cells, making it a promising research direction as a novel chemotherapeutic agent against gastric cancer.
- **Mangiferin against Pancreatic carcinoma:** [23] Examined the anticancer effects of Mangiferin against the gemcitabine-resistant human pancreatic cancer cells (Mia-PaCa 2) in comparison to normal pancreatic cells, the results showed that Mangiferin exerted its anticancer effect through the production of the significant amounts of ROS which is associated with decline in mitochondrial membrane potential as well as enhanced Bax/Bcl-2 ratio and triggering G2/M phase arrest, collectively leading to apoptosis in Mia-PaCa 2 with little toxic effects on the normal cells.
- **Mangiferin against Breast carcinoma:** In [24] searched new approaches in breast cancer therapy through *in-vitro*, pre-clinical murine and pilot human clinical investigations using Mangiferin conjugated gold nanoparticles known as 'Nano Swarna Bhasma' (NSB) drug. The in-vitro study proved NSB to be selectively toxic to tumor cells with minimal or no toxicity against the normal cells.

In the murine group, animals were treated with either 3 or 7 mg drug/30 gm mouse orally twice per week for 60 days, and it was found that it was able to control or reduce the tumor volumes by over 80% during 60 days of treatment as compared to the control groups.

For the clinical trial group, seven female patients with pathologically confirmed invasive breast carcinoma stage IIIA or IIIB were divided into test and control groups. The test group patients received two capsules of NSB three times per day after food as an adjuvant to their standard chemotherapy protocol of treatment for a period of 12 weeks in the form of four cycles. Patients showed ei-

ther partial response to treatment or a stabilized condition with no disease progression. This study concluded that NSB can be safely used as a valuable adjuvant therapeutic agent to reduce the adverse effects of routine chemotherapeutic agents while providing measurable therapeutic efficacy in treating breast cancers [24].

Table 1 summarizes the most important in-vitro and vivo studies which investigated the anticancer effect of Mangiferin on different cancer cell lines.

Type of cancer	Molecular target/effect	Model	Dose/Regimen	References
Nasopharyngeal carcinoma	Anti-proliferative effect via cell cycle arrest at G2/M. Apoptotic induction through upregulation of Bax and downregulation of Bcl-2 levels of gene expression.	Nasopharyngeal carcinoma cell line (CNE2)	12.5, 25, 50, 100, 150 and 200 µM	[17]
Cervical cancer	Induction of apoptosis through: Downregulation of the BH3 and Bcl 2 expression & degradation of PARP. Activation of caspase-3, -7, -8 and -9 as well as activation of NF-κB pathway.	Human cervical carcinoma cell line (HeLa)	23.7 µM	[18]
Colo-rectal cancer	Molecular docking analysis of Mangiferin with various cancer target proteins showed it can: Inhibit the inflammatory pathway (5-LOX and COX-2 pathway) involved in colon cancer progression. Promote apoptosis through blocking the activity of Bcl-2 and Bcl-xL proteins. Mangiferin toxicity selectively targets cancer cells.	Colon cancer cell line (HT29)	12, 23.7, 35.5, and 71 µM	[19]
	Mangiferin plays its cytotoxic effect through inhibition of tumor cell invasion, angiogenesis, and vasculogenesis. Mangiferin induces dose dependent CT26 tumor regression in vivo with results comparable to cisplatin treatment.	Human colon adenocarcinoma cell line (HT29) Mice models implanted with murine colon adenocarcinoma (CT26).	10-400 µM for 24, 48, and 72 h. 10, 50, 100 mg/ kg	[20]
Prostate cancer	Inhibition of proliferation in a time-dose dependent manner. Induction of apoptosis through downregulation of Bcl-2 and upregulation of miR-182 and caspase-3.	Human prostate cancer cells (PC3)	(10, 20 and 40 µM) for 0, 24, 48 and 72 h.	[21]
Gastric carcinoma	Induction of apoptosis by: Increasing Bax, Bad, cleaved caspase-3 and caspase-9 expression. Decreasing Bcl-2, Bcl-xL and myeloid cell leukemia-1 (Mcl-1) expression. Growth inhibition of gastric cancer cells by deactivating the PI3K/Akt signal pathway.	Gastric carcinoma cell lines BGC-823 and SGC-7901		[22]
Pancreatic carcinoma	Induction of apoptosis by: increasing Bax and Bad decreasing Bcl-2 increased Reactive oxygen species decrease in the mitochondrial membrane potential levels Inhibition of proliferation through triggering G2/M phase arrest	Human pancreatic cancer cell line (Mia-PaCa 2)	0-320 µM	[23]

Breast carcinoma	*In-vitro* study: drug cytotoxic to cancer cells with minimal or no toxicity on normal cells *In-vivo* murine group: Reduce the tumor volumes by over 80% compared to controls. Clinical trial group: Patients showed either partial response to treatment or a stabilized condition with no disease progression, thus this drug could be safely used as a valuable adjuvant therapeutic agent to reduce the adverse effects of routine chemotherapeutic agents	MDA-MB-231 tumor breast cell line Immunodeficient female mice Pilot clinical trial investigation in pathologically confirmed invasive breast carcinoma stage IIIA or IIIB female patients Immunodeficient female mice Pilot clinical trial investigation in pathologically confirmed invasive breast carcinoma stage IIIA or IIIB female patients	Mangiferin conjugated gold nanoparticles: *In-vitro* cell line group: serial dilution (0-473.6) *In-vivo* murine group: 3 or 7 mg drug/30 gm mouse orally twice/week for 60 days. Clinical trial: 3 times/day as adjuvant to chemotherapy protocol for 12 weeks.	[24A]
N.B: All concentrations were transferred into their approximate equivalent in micromolar unit μM)				

Table 1: Examples of research on anti-cancer effect of Mangifera.

Concluding Remarks

Mangiferin displayed strong anticancer activities, including inhibition of metastasis, arrest of cell cycle progression, anti-angiogenesis, and induction of apoptosis. This review provides up-to-date information about anticancer activities and the action mechanism of Mangiferin in different types of cancer in in-vitro and in recent in-vivo studies. These studies would shed light on its potential anti-cancer mechanisms and encourage the development of natural product-based drugs using novel technologies that could be applied to the therapy of various cancers in the future.

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