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Review Article

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Molecular Insight of *Mangiferin* in Cancer Chemoprevention: A Review Article

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ABSTRACT

Cancer is a public health problem causing one in six deaths globally. Fighting cancer has always been challenging, leading to an evolution in cancer therapies. *Mangiferin*, a bioactive component found in honeybush tea and mangoes, is a chemotherapeutic and chemopreventive drug against many cancers. This review addresses the critical need for alternative and cost-effective cancer treatments in developing countries, which bear 57% of new cancer cases and 65% of cancer-related deaths globally. A non-systematic search was conducted using research engines such as MEDLINE, Scopus, PMC, Embase, PubMed, Web of Science, and Google Scholar. More than 250 studies have been carried out on *Mangiferin* between 2001 and 2021, including clinical trials for cancer treatment. *Mangiferin* demonstrates significant anticancer activity by suppressing malignant proliferation across multiple cancer cell lines, including CCD-18Co, LNCaP, MCF-7, OVCAR3, HeLa, HepG2, MDA-MB-231, A549, and others. The compound targets diverse molecular pathways involved in proliferation, apoptosis evasion, metastasis, and angiogenesis, including NF-kB, MMPs, COX-2, FGF, VEGF, and ICAM. Additionally, Mangiferin exhibits chemopreventive properties and synergizes with conventional anticancer agents. However, its clinical translation is hindered by poor oral bioavailability (<2%), necessitating advanced drug delivery strategies due to its synergistic effect with other anticancer drugs. This review highlights the manifold anti-cancer benefits of Mangiferin and proposes a robust methodology for validating animal studies through quantitative and qualitative analyses. These findings offer valuable insights for researchers to investigate the diverse pharmacological properties of Mangiferin in cancer, paving the way for promising avenues in cancer chemoprevention.

INTRODUCTION

Mangiferin (MGN), a C-glucosyl xanthone (1,3,6,7-tetrahydroxyxanthone-C2-β-D-glucoside)[1], is a naturally occurring polyphenolic flavonoid compound [2]. It is found primarily in plants belonging to the family Anacardiaceae, commonly known as mangoes [3], one of the highly marketed fruits of the world, with global production of more than 26 million in 2004 [4]. *Mangifera indica* (*M. indica*) is cultivated in tropical, subtropical regions, and its parts are frequently used in traditional medicine as a remedial measure for various diseases [5]. In Southeast Asia and Africa, the use of mango stem bark and leaves has also been reported as traditional medicine, mostly in the form of infusions based on its pharmacological purposes [6]. Mango (*Mangifera indica*) is an abundant source of bioactive chemicals with potential pharmacological and nutritive uses [7]. Mango contains various vitamins, including C, A, E, D, K, and the B complex [8]. Phenolic compounds are also present in the mango pulp, seeds, and peel, which have therapeutic values [9]. It contains derivatives of hydroxybenzoic acid and hydroxycinnamic acid, two important phenolics. The most prevalent polyphenols in it are flavonoids, lignans, and stilbenes, with flavonoids accounting for 60% of dietary polyphenols [10]. A considerable reduction in cell migration and metastasis can be achieved with the use of an extract containing this chemical constituent [10].

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This review has shown that there exist significant gaps in the clinical translation of *Mangiferin* in the treatment of cancer. Although *Mangiferin* has strong preclinical data with many types of cancer cells and in animal models, there are no phase III clinical studies assessing the efficacy of *Mangiferin* in cancer patients and that constitutes a significant knowledge gap. The main issue here is that there is a huge disparity between the large amounts of in vitro and in vivo mechanistic information and virtually no human clinical trials that could be used to make evidence-based clinical suggestions. This study aims to address the critical need for alternative and cost-effective cancer treatments in developing countries, which bear 57% of new cancer cases and 65% of cancer-related deaths globally.

Half-life and Pharmacokinetics of *Mangiferin*

Within one hour of a single oral dose, rats' serum and urine often absorb MGN and its metabolites [11]. Sprague-Dawley rats given 120 mg/kg of pure MGN had a maximum availability of 24–25 g/ml in blood plasma and urine after 24 hours. It has been evaluated to possess the ability to cross the blood-brain barrier in gerbils [12] and the blood-retina barrier in rats [13]. However, another pharmacokinetic study reported that MGN possessed extremely low bioavailability (about 1.2%) [14], and its plasma concentration was 38.64 ± 6.75 ng/ml about 1 h after orally administering 0.9 g MGN, and the apparent half-life (t1/2) was 7.85 ± 1.72 h [15]. However, within 15 minutes of intragastric injection, MGN was found in the rats' urine and serum. In addition, oral MGN bioavailability in humans has been investigated and found to be comparable to that in rats [13]. *Mangiferin's* water solubility is just 0.111 mg/mL, according to research. Additionally, it has been shown that mangiferin's oral bioavailability is as low as 1.2% [16]. Modern pharmaceutical and medical technology has made it possible to overcome the aforementioned challenges by using encapsulation and nanotechnology solutions, as well as derivatives with better pharmacokinetic profiles. *Mangiferin* nanocrystals have the potential to improve this poorly soluble drug's solubility, stability, and bioavailability, as shown by prior studies [17].

Prevalence of Cancer Worldwide

Worldwide, among non-communicable diseases, cancer is the biggest cause of death. According to estimates from 2012, there were 8.2 million cancer deaths and over 14 million new cases. This rate is approximated to reach up to 13.1 million deaths in 2030 [18], along with a heavy burden in the form of both monetary and morbidity burdens for the health care system. With 57% new cases and 65% mortality, the burden of cancer is greater in underdeveloped nations, where there is a higher incidence of late detection and treatment errors because of inadequate chemotherapeutic medications and screening methods. Although cancer was traditionally thought to be a disease in more developed nations, the situation is now even worse in less developed nations due to the adoption of Western lifestyles like food, alcohol consumption, smoking habits, and decreasing physical activity [19].

Cancer Treatment with Natural Components

A variety of natural dietary fibers have an impact on malignant lesions, including liver cancer, which is the most prevalent digestive system cancer and has a high mortality rate. Several foods, including grapes, black currants, plums, pomegranates, cruciferous vegetables, tomatoes, asparagus, French beans, garlic, turmeric, soy, rice bran, ginger, and some edible macrofungi, are effective in both the prevention and treatment of liver cancer. [20].

Role of *Mangiferin* as Cancer Therapy/Chemopreventive Effects

Several human cancer cell lines were used to test *Mangiferin's* anticancer efficacy. Against all-examined cancer cell lines, mango leaf extract exhibits cytotoxic capability [21]. Studies were carried out in both in vivo and in-vitro to gauge the suppression of cancer cells. *Mangiferin*-treated animals displayed a marked reduction in tumor weight and volume. Analysis of molecular processes revealed that the expression of the proteins MMP2 and MMP9 associated with metastasis was downregulated by *Mangiferin* [22]. *Mangiferin* showed cytoprotective, antiproliferative, and antioxidant DNA damage inhibition due to the presence of phenolics and flavonoid compounds [23]. *Mangiferin* nanoparticles are used as a therapeutic agent against oxidative stress and related diseases due to the polyphenol compound [24]. Another study explored the mechanism of antitumor activity of *Mangiferin* against bacterial lipopolysaccharide (LPS) in non-small cell lung cancer (NSCLC) [25]. In vitro, study of *Mangifera indica* indicated cytoprotective and antioxidant potential against UV radiation-induced oxidative stress due to the polyphenol compounds [26]. *Mangifera indica* leaf, seed, fruit, and bark extracts were utilized to treat breast cancer because of their anticancer properties [27]. These results showed a significant effect due to the xanthonoid, phenolics, and gallotannins compounds, which possess antitumoral, cytotoxic, and antioxidant activity [28].

Different Extracts of *Mangiferin* Against Cancer

Using ethanol, methanol, chloroform, n-hexane, distilled water, and butanol, plants containing *Mangiferin* have been separated into several parts [29]. The methanolic extracts of mango peel and pulp have been used to control breast cancer in MCF-7 cells [30]. A study discovered that BT-474

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(luminal B: ER-/PR-/HER2-positive) cells were cytotoxic to ethanolic mango leaf extract (200 g/mL) [21]. Mango bark aqueous extract contains terpenoids, microelements, fatty acids, steroids, and polyphenols. The dose-dependent aqueous extract shows significant inhibition of the proliferation of MDA-MB-231 cells [31]. The viability of MCF-7 (luminal A: ER-positive, PR-positive, HER2-negative), MDA-MB-231, and MCF-10A (normal human mammary epithelial cell line) cells may be reduced by mango kernel ethanolic extract in a dose-dependent manner, according to a relevant study. Due to the polyphenolic components, the ethanolic extract of mango showed antioxidant activity [32]. The aqueous extract of mango bark used in vivo and in-vitro experiments revealed inhibition of TNFα and NO production. The aqueous extract of mango played a role in the inhibition of tumor growth, reactive oxygen species (ROS), and angiogenesis suppression[33].

In-vitro studies of *Mangiferin*: Apoptotic Property

To maintain organ and tissue homeostatic balance, apoptosis is known as the most fundamental life process in a multicellular organism. Apoptosis is a type of programmed cell death in which cells activate enzymes that dissolve their nuclear components, as well as various protein elements of the cytoplasm and nucleus. This involves the modulation of key protein families. Specifically, *Mangiferin* has been shown to downregulate anti-apoptotic proteins like Bcl-2, while concurrently activating the cascade of executioner caspases (e.g., caspase-3, -7, -8, 9). *Mangiferin* showed potent apoptotic properties against RD (rhabdomyosarcoma) cells by inducing oxidative stress. *Mangiferin*-induced nuclear condensation and cell shrinkage, combined with the occurrence of a late apoptotic event [34]. The diagram shows how *Mangiferin* triggers cytochrome c release from mitochondria, activating procaspase-9, while death receptor engagement activates procaspase-8. Both pathways converge on executioner caspases-3 and -7, leading to PARP cleavage and DNA fragmentation(Figure 1).

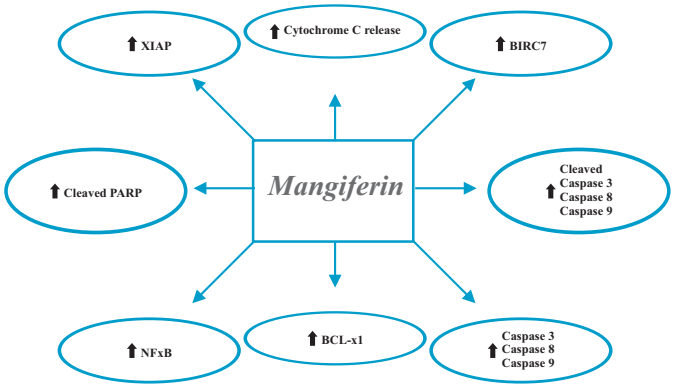

Figure 1: Effects of *Mangiferin* on Apoptotic Signaling Pathways

Suppression of Pro-inflammatory and Metastatic Pathways

Beyond direct apoptotic effects, *Mangiferin* demonstrates a potent capacity to suppress pathways crucial for tumor inflammation, survival, and metastasis. A central node in these processes is the transcription factor NF-kB, which regulates the expression of numerous genes involved in inflammation and cell survival(Figure 2).

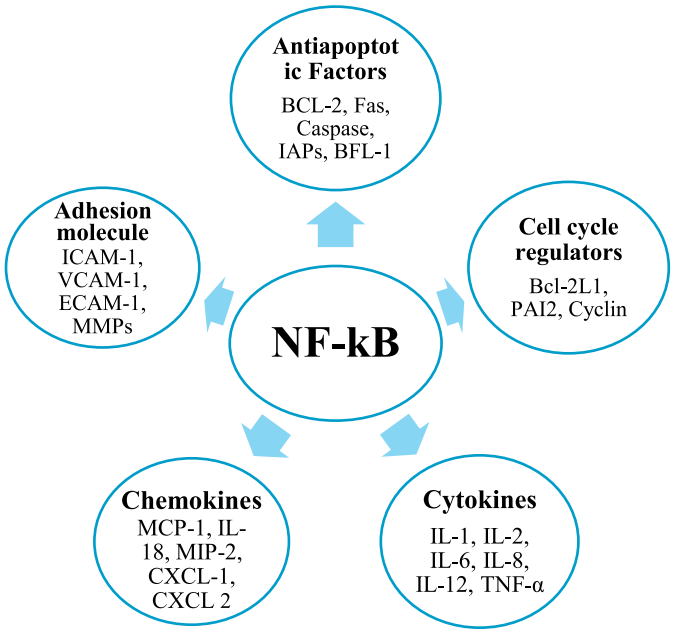

Figure 2: NF-kB Targets Genes Involved in the Onset and Progression of Inflammation

NF-kB activation leads to transcription of genes controlling inflammatory cytokines (TNF-α, IL-1, IL-6), anti-apoptotic proteins (Bcl-xL, XIAP), cell cycle regulators (cyclin D1), adhesion molecules (ICAM-1), and angiogenic factors (VEGF, COX-2). Furthermore, *Mangiferin* directly inhibits several downstream effectors of these pathways. This includes the suppression of Matrix Metalloproteinases (MMPs), which play a significant role when it comes to remodeling related to pathological processes such as cirrhosis, arthritis, and cancer, as well as physiological

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processes such as morphogenesis, angiogenesis, and tissue repair [35]. *M. indica* (*Mangiferin*) has been shown to inhibit the MMP-2, -7, and -9 expression and regulate apoptosis and proliferation in glioma cells [36]. In addition, *Mangifera indica* peels and leaves have been shown to inhibit the Cyclooxygenase-2 (COX-2) [37]. *Mangiferin* reduces the expression of COX-2and the synthesis of prostaglandin E2 by inhibiting Fibroblast Growth Factor (FGF), a key promoter of angiogenesis [38]. The role of FGF in both the early and late phases of tumor angiogenesis is depicted, highlighting how its downregulation by *Mangiferin* can disrupt new blood vessel formation. FGF signal transduction contributes to both early and late-phase tumour angiogenesis. FGF signaling contributes to angiogenesis through direct stimulation of endothelial cell proliferation, induction of MMP production, synergistic interactions with VEGF, and recruitment of pericytes for vessel maturation (Figure 3).

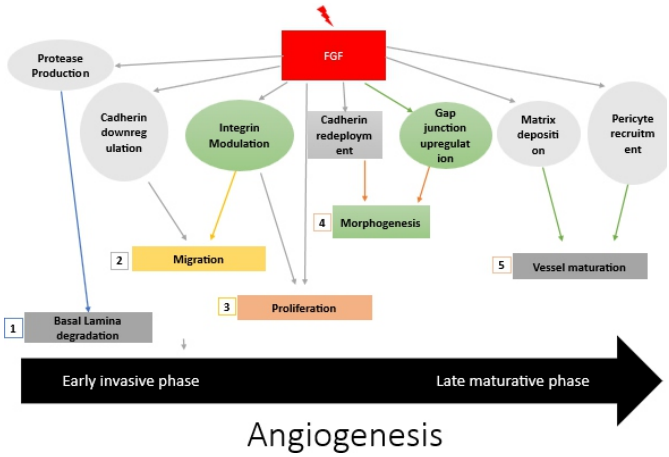

Figure 3: FGF Signal Transduction Contributes to Both Early and Late-Phase Tumour Angiogenesis

The results consolidate the in-vitro evidence for all the mechanisms discussed above: apoptosis, NF-kB suppression, MMP inhibition, and COX-2 downregulation, providing a detailed, study-by-study account of *Mangiferin's* multi-targeted activity (Table 1).

Table 1: Apoptotic Property, Suppression of Nf-kB, Suppression of MMP, COX2 Inhibition, FGF Down-Regulation Activities of *Mangifera ondica*

Plant Part	Mechanism of Action	Cancer Type (Cell Line)	Targeted Biomarker	References
Peel	Apoptotic activation	HeLa cancer cells	Downregulated anti-apoptotic Bcl-2 expression ↓ Activation of caspase-3, 7, 8, and 9	[39]
Mangiferin	Apoptosis	RD cells	Oxidative stress (Cell shrinkage and nuclear condensation)	[29]
Peel	Apoptosis	Colon cancer cells	Caspase activation and PARP1 fragmentation via ERK & JNK activation and ROS formation.	[40]
Mangiferin	Apoptosis	OVCAR3 cells	Caspase-3 and 9 Notch3	[22]
Bark	Apoptosis	MCF-7, MDA-MB-231, SKOV-3, MCF-10A cancer cell lines	Caspase 3 and 7	[41]
Leaves	Suppression of NF-kB	Peptidoglycan, LPS (Macrophages)	IRAK1 phosphorylation in NF-κB & MAPK pathways	[35]
Mangiferin	Suppression of NF-kB	HRGEC (Human renal glomerulus endothelial cells)	NF-kB, IL-6, IL-8, IkBa, and IKKa.	[42]
Mangiferin	Suppression of MMP	Breast cancer cells	MMP-7 and -9, β-catenin signalling pathway	[36]
Peel	COX-2 Inhibition	Sheep placental cotyledons	COX- (PGE2 production) and leukotrienes	[37]
Leaves	COX-2 Inhibition	cyclooxygenase-1 and -2	PGE2 production.	[38]
Mangiferin	COX-2 Inhibition	microglial cells	COX-2 transcript stability's	[39]

In-Vivo Studies of *Mangiferin*: Effects on Tumor Growth, Angiogenesis, and Metastasis

Building on the mechanistic insights from in-vitro work, in vivo studies in animal models provide a more complex picture of *Mangiferin's* anti-cancer effects within a living system [43]. These studies confirm its potential to inhibit tumor growth, angiogenesis, and metastasis [44]. The key mechanisms observed in vivo are summarized in the schematic figure 4, which integrates findings related to cell cycle arrest, suppression of survival signaling (mTOR), and inhibition of factors driving angiogenesis (VEGF) and metastasis (MMPs, ICAM). Schematic summary of *Mangiferin's* key anti-cancer mechanisms observed in in vivo studies. The diagram integrates the major pathways modulated by *Mangiferin* treatment in animal models (Figure 3).

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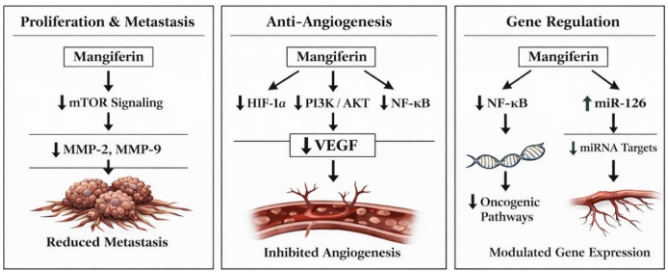

Figure 4: Major Pathways Modulated by *Mangiferin* Treatment in Animal Models

The anti-cancer properties of *Mangifera indica* in in vivo studies are summarized. It provides a detailed account of the plant part used, the observed in vivo mechanism, the cancer model employed, and the specific biomarkers that were modulated. Cell cycle arrest, Proliferation, metastasis, VEGF downregulation, ICAM suppression, Suppression of anti-apoptotic protein, Transcription factor, Anti-angiogenic properties of *Mangifera indica* in vivo and their mechanism of action (Table 2).

Table 2: Cell Cycle Arrest, Proliferation, Metastasis, VEGF Downregulation, ICAM Suppression, Suppression of Anti-Apoptotic Protein, Anti-Angiogenic Properties of *Mangifera Indica* In Vivo

Plant Part	Mechanism of Action	Cancer Type (Cell Line)	Targeted Biomarker	References
Seed Kernel	Proliferation and metastasis	B16F10 murine melanoma cells	VEGF, MMP-9, and MMP- 2 expression levels.	[43]
Mango Polyphenols	VEGF downregulation	BT474 breast cancer cells & xenografts in mice.	VEGF protein, pAKT, pPI3K, NF- kB (p65), mTOR and HIF-1α levels	[43]
Mango Polyphenols	Transcription factor	Human colon HT-29 adenocarcinoma cell and CCD-18Co myo-fibroblastic cell lines	miRNA-126, PI3K, AKT, mTOR signaling axis in rats	[45]
Mango	Transcription factor	miRNAs sequence (8496)	miRNA (min-miR5658, min-miR8577, min-miR6482)	[46]
Mangiferin	Anti-angiogenic properties	chick embryo.	proangiogenic factors	[47]
Seed (AuNps)	Anti-angiogenic	Chick embryo.	Ang-1/Tie2 pathway.	[32]

Clinical Trials of *Mangiferin*

Despite robust preclinical evidence, clinical investigation of *Mangiferin* in cancer patients remains remarkably limited. To date, only two clinical trials have evaluated *Mangiferin*-containing preparations in human subjects, none of which were phase III efficacy trials. *Gilberto L.* 2006 studied the effect of *Mangifera* indica against serum oxidative stress in elderly humans and showed positive results. Furthermore, it is used in treating patients with inflammatory bowel disease, showing anti-inflammatory properties, which have demonstrated its effectiveness in human clinical trials [48]. There is currently no comprehensive in-depth clinical trial investigation on the anticancer efficacy of *M. indica* isolated chemicals or crude extracts; more research in this regard is needed to open a window of opportunity for affordable cancer treatment.

Chemotherapeutic Synergism

One of the key issues in the development of cancer cell resistance to treatment is the multidrug resistance phenotype. Meanwhile, combination therapy is gaining popularity in cancer treatment due to its anti-cancer synergy [49]. A recent study has shown that some natural chemicals (such as *Mangiferin*) derived from medicinal plants have promising anti-cancer properties in drug-resistant cancer cells. Moreover, in cancer cell lines, a combination of oxaliplatin and *Mangiferin* causes increased apoptosis and NF-kB downregulation. In addition, *Mangiferin* in combination with etoposide, paclitaxel, doxorubicin, Adriamycin, vincristine, and cisplatin has been demonstrated to have more positive effects on preventing acquired resistance in cancer cells [1]. Among the promising findings, there are glycosylated derivative drugs (like cisplatin) that contribute to enhanced solubility and cytotoxicity profiles by themselves [50]. The utilization of presently existing anticancer medicines in combination with *M. indica* plant extracts may be a novel cancer therapy approach. Recent studies also validate and strengthen the traditional usage of *M. indica* plant extracts for cancer treatment and management.

Cytoprotective effects of *Mangiferin*

Cytoprotective drugs have the potential to decrease anticancer therapy-related toxicity while maintaining effectiveness. Extract of the peel of *Mangifera indica* also protects rat erythrocytes against hydrogen peroxide-induced oxidative damage [51]. In another research, the cytoprotective effect of mango extracts on oxidative damage produced by H2O2 has been evaluated, and the underlying mechanism has also been investigated in a human hepatoma cell line, HepG2. Another study also reported that *Mangiferin* aglycone protects human intestinal epithelial cells from radiation-induced damage/injury. In a different investigation, the effects of *Mangifera* stem bark extract (MSBE) and *Mangiferin* on DNA damage and protection in lymphoblastoid cells and primary human lymphocytes revealed that MSBE can either protect or damage DNA and can behave as an antioxidant or pro-oxidant product [52]. Additionally, research is being done on the antigenotoxic properties of *Mangiferin* against cadmium chloride-induced toxicity in HepG2 cells. MGN demonstrates a potent cytoprotective and antigenotoxic effect in the HepG2 cell line against toxicity caused by CdCl2, which may be caused by a decrease in the levels

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of oxidative stress and reactive oxygen species produced by CdCl2 [53]. The cytoprotective properties of *Mangifera indica*, along with their mechanism of action, are presented in table 3, highlighting the plant part, mechanism of action, cancer cell line, targeted biomarker, and relevant study references.

Table 3: Cytoprotective properties of *Mangifera* and their mechanism of action

Plant Part	Mechanism of Action	Cancer Type (Cell Line)	Targeted Biomarker	References
Leaves	Cytoprotective	PBMC cells	UV radiation-induced oxidative damage (H2O2 & intra-cellular ROS)	[43]
Peel	Cytoprotective	HepG2 human hepatoma cell line	oxidative stress → DNA damage	[43]
Stem bark	Protection from radiation	Lymphoblastoid cells and primary human lymphocytes	DNA damage	[52]
Mangiferin	Cytoprotective	HepG2 cells	P-gp, ROS	[53]

In vivo studies showed that *Mangiferin* decreased tumor volume to a comparable level to cisplatin. *Mangiferin* has been shown to synergize with pro-apoptotic chemotherapy drugs such as oxaliplatin and cisplatin. This is particularly intriguing given *Mangiferin's* low toxicity and broad oral safety margin in comparison to other drugs with comparable action. However, *Mangiferin's* bioavailability and administration need further review and analysis in clinical trials.

Limitation and Future Recommadations

Poor oral bioavailability and water solubility are two limitations that currently restrict clinical usage, but more research efforts targeting optimal delivery mechanisms are needed to increase clinical effectiveness. Clinical studies in humans may significantly advance our knowledge about the macroscopic effects of *Mangiferin.*

CONCLUSIONS

Mangiferin is a rare natural gift that we did not know about for a long time, since its qualities were only explored in the past few decades. Much research has emphasized *Mangiferin's* biological properties, including its anti-cancer mechanisms. The association between *Mangiferin* and the alteration of numerous molecular pathways to prevent cancer is well established. *Mangiferin* has been linked to reducing inflammation, proliferation, metastasis, and increased apoptosis in malignant cells, and protects against oxidative stress and DNA damage. NF-kB, MMP, COX2, FGF, VEGF, ICAM, and other transcription factors have all been demonstrated to target *Mangiferin*. Cancer cell lines tested included LNCaP, OVCAR3, HepG2, MCF-7, MDA-MB-231, SKOV-3, MCF-10A, A549, HRGEC, HT-29, CCD-18Co, U87 glioma, and MCF-7. *Mangiferin* inhibited malignant cell development in cancer cell lines. Its therapeutic and chemopreventive characteristics may help slow the development of cancer.

Authors' Contribution

Conceptualization: SAZ
Methodology: SAZ, AR
Formal analysis: AR
Writing and Drafting: MA, MSN, AR, UH
Review and Editing: MA, MSN, SAZ, AR, UH

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

The authors declare no conflict of interest.

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