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RESEARCH ARTICLE

MANGIFERIN: A RAY OF HOPE IN CANCER RESEARCH? A SYSTEMATIC REVIEW OF ITS ANTICANCER EFFECTS AND FUTURE PERSPECTIVE

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Abstract: ***BACKGROUND:*** Cancer is still one of the biggest worldwide health issues, and current treatments are frequently hindered by toxicity, resistance, and recurrence. Due to its many pharmacological properties, including immunomodulatory, anti-inflammatory, antioxidant, and anticancer properties, mangiferin a naturally occurring C-glucosylxanthone derived from Mangifera indica has attracted a lot of attention. Preclinical studies indicate that mangiferin produces cytotoxic action against multiple cancer cell types by modulating significant molecular signaling pathways. ***AIM:***This systematic review aimed to critically evaluate the anticancer potential of mangiferin by analyzing experimental studies that elucidate its mechanisms of action, therapeutic applications, and possible translational value in oncology. ***MATERIALS AND METHODS:*** Major databases such as PubMed, Scopus, ScienceDirect, Web of Science, Wiley Online Library, and Google Scholar were systematically searched for in vitro and in vivo research published in English during the previous 25 years. Original experimental studies assessing the protective or therapeutic effects of extracts from Mangifera indica or Mangiferin were among the inclusion criteria. Review articles, theses, case reports, and clinical trials were among the exclusion criteria. Thirteen studies that satisfied the eligibility requirements were included in the qualitative synthesis after the data was extracted using the PRISMA protocol. ***RESULT:*** Mangiferin consistently showed anticancer and protective effects in all of the studies that were examined. By altering signaling pathways such as NF-κB, PI3K/Akt, MAPK, β-catenin, STAT3, and p53, it prevented tumor growth, migration, and angiogenesis. Additionally, in animal models, mangiferin restored normal immune responses, stabilized Nrf2 protein to reduce oxidative stress, and increased antioxidant enzyme activity (SOD, CAT, GPx). Additionally, it demonstrated selective cytotoxicity against cancer cells while maintaining the integrity of healthy tissue. According to studies, its bioavailability may be increased by nanoformulations, which could support its possible clinical translation. ***CONCLUSION:*** A promising plant-derived substance with multi-targeted anticancer effects that is low in toxicity is mangiferin. Its potential as a therapeutic and adjuvant agent in cancer management is highlighted by its capacity to control oxidative stress, inflammation, apoptosis, and tumor microenvironment remodeling. To prove its effectiveness and safety in humans, future studies should concentrate on pharmacokinetic optimization and carefully planned clinical trials.

Keywords: Mangiferin, anticancer activity, oxidative stress, apoptosis, NF-κB, STAT3, tumor microenvironment, phytotherapy.

INTRODUCTION

Cancer remains one of the leading causes of illness and death worldwide, with approximately 19.3 million new cases and almost 10 million deaths recorded globally in 2020 [1]. Although targeted therapy, immunotherapy, and precision medicine have advanced, cancer treatment remains burdened by several challenges, including multidrug resistance, severe side effects, and tumor recurrence [2]. Over the past decade, interest has been revived in natural products from medicinal plants, which over the course of history have played a key role in many advances in oncology. Among such compounds showing promising pharmacological potential is mangiferin, a xanthonoid principally obtained from the mango tree Mangifera indica L.

A polyphenolic antioxidant, mangiferin has a C-glucosylxanthone skeleton with diverse biological activities associated with it, including anti-inflammatory, antidiabetic, hepatoprotective, immunomodulatory, and most importantly, anticancer properties. Its remarkable bioavailability, minimal toxicity, and capability to influence diverse molecular processes render it a compelling subject for research in cancer studies.

Several preclinical studies have shown that mangiferin is cytotoxic to a wide range of cancer cell lines, including those from breast, lung, liver, prostate, and colon cancers[4,5]. Various mechanisms, such as the initiation of apoptosis, inhibition of cell proliferation,

reduction of angiogenesis, and alteration of oxidative stress, facilitate the cytotoxic effects.

Significantly, it has been documented that mangiferin influences key signaling pathways involved in tumor development, such as NF-κB, PI3K/Akt, MAPK, and p53 pathways[6]. Besides this, its combined effect with conventional chemotherapeutic agents indicates a potential role in enhancing the efficacy while decreasing the toxicity of treatments. Nevertheless, despite the increasing number of studies being carried out in vitro and in vivo demonstrating its anticancer effects, clinical trials involving mangiferin remain in the initial phase. A well-structured clinical trial is urgently needed, along with a standardized product and further understanding of its pharmacokinetics and molecular targets.

The following systematic review was performed with the purpose of critically analyzing the current literature on the anticancer effects of mangiferin, underlining its mechanisms of action, possible therapeutic applications for different types of cancers, and future investigation directions. This review elucidates this naturally occurring compound in order to pinpoint the potential of mangiferin as a multivalent agent in the treatment of cancers.

Other focus points of great interest include the modulatory effects of mangiferin on the tumor microenvironment, which plays a critical role in the development and immune evasion of cancer and resistance to therapy. Indeed, there is evidence that mangiferin suppresses tumor angiogenesis, inhibits the pro-inflammatory cytokines IL-6 and TNF-α, and adjusts immune signaling pathways like NF-κB and STAT3, which may have the potential to reprogram the TME into a more anti-tumoral phenotype.

This multitarget approach is particularly effective and useful for heterogeneous and highly aggressive tumors that are resistant to treatments focused on a single pathway.

Moreover, recent data highlight that mangiferin could improve cellular antioxidant defenses through the increase in endogenous antioxidant enzymes like superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) to counteract the oxidative stress associated with carcinogenesis[3]. These antioxidative actions not only add to its chemopreventive potential but also reinforce the hypothesis that mangiferin may act in cooperation with conventional therapies to prevent oxidative damage in non-neoplastic tissues.

Another possible direction is related to the epigenetic effects of mangiferin, especially its ability to modulate miRNAs and histone acetylation, increasingly recognized as crucial factors in tumor initiation and development[7]. These alterations can control oncogenes and tumor suppressor gene expression and offer new therapeutic pathways for intervention.Additionally, the pharmacokinetic characteristics of mangiferin although largely uninvestigated suggest favorable absorption and bioavailability compared to many plant-based compounds, particularly when delivered through nanoformulations or phospholipid complexes[8]. These advancements in drug delivery systems could pave the way for more effective systemic administration, overcoming current barriers in clinical application.

MATERIALS AND METHODS

2.1 STUDY DESIGN

This study is structured as a systematic review of experimental investigations into the therapeutic potential of Mangiferin. Emphasis was placed on in vitro and animal model studies published in the last 25 years. The review aimed to capture a comprehensive overview of Mangiferin's biological actions, including its roles in oxidative stress mitigation, cancer cell inhibition, immunomodulation, and neural protection. A narrative synthesis approach was used to summarize outcomes.

2.2 . Search Stratergy

A systematic search of electronic databases was conducted to identify relevant literature. Search terms included: 'Mangiferin', 'Mangiferaindica', 'anticancer', 'oxidative stress', 'immune regulation', 'neurotoxicity', and 'phytotherapy'. Boolean operators (AND/OR) were employed to enhance search accuracy. Searches were limited to English-language articles and excluded grey literature to ensure source reliability.

2.3. Eligibility Criteria

Inclusion Criteria

Original research articles
In vitro and in vivo studies on Mangiferin or extracts of Mangiferinindica.
Studies evaluating therapeutic or protective effects
Published in English
Available in full-text form

Exclusion Criteria

Review articles, theses, or case reports
Clinical trails or observational studies in humans
Non- English language publications
Articles lacking experimental intervention data
Duplicate publications

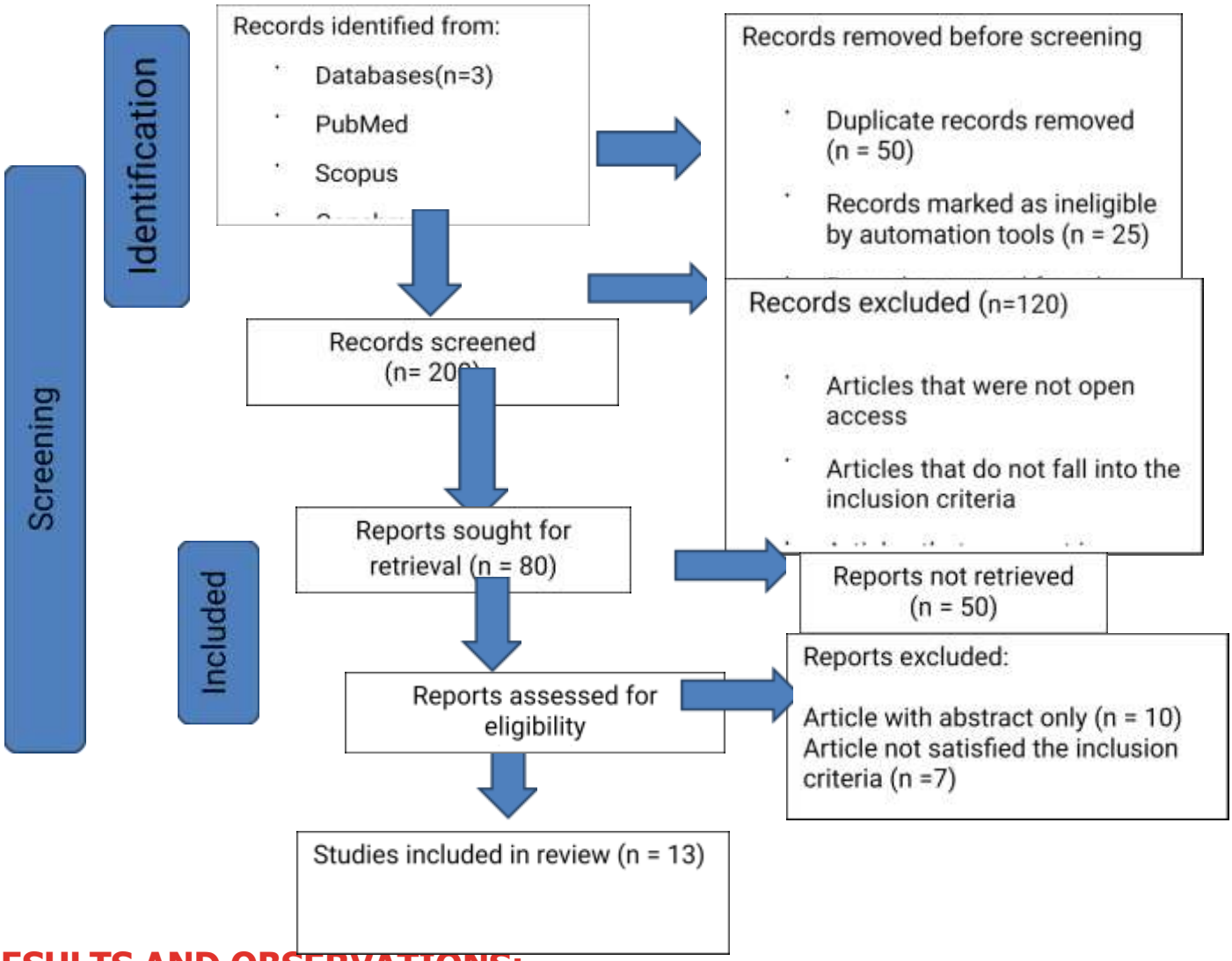
2.4. Databases and Search Engines Used

Literature searches were conducted using the following databases:

- PubMed (NCBI)
- Scopus
- ScienceDirect
- Google Scholar
- Web of Science
- Wiley Online Library

Figure 1]

PRISMA FLOW CHART



RESULTS AND OBSERVATIONS:

Mangiferin showed consistent anticancer and cytoprotective actions in all the reviewed studies. It inhibited tumor growth, migration, and angiogenesis mainly by modulating crucial molecular signaling pathways such as NF-κB, PI3K/Akt, MAPK, β-catenin, STAT3, and p53. Restoration of normal immune responses, stabilization of Nrf2 to reduce oxidative stress, and enhanced activities of the endogenous antioxidant enzymes SOD, CAT, and GPx were observed in animal models after treatment with mangiferin. More importantly, mangiferin exhibited a selectivity against malignant cells while maintaining the integrity of normal tissue. Several studies also demonstrated that nanoformulation could greatly enhance its bioavailability, thus offering a promising avenue toward future clinical translation.

Table 1 shows Preclinical Studies on Mangiferin.
A structured overview of experimental studies evaluating the pharmacological actions of Mangiferin, including author details, study year, location, biological sample used, intervention applied, and experimental techniques.

Table 1: Characteristics of the study included in systematic review

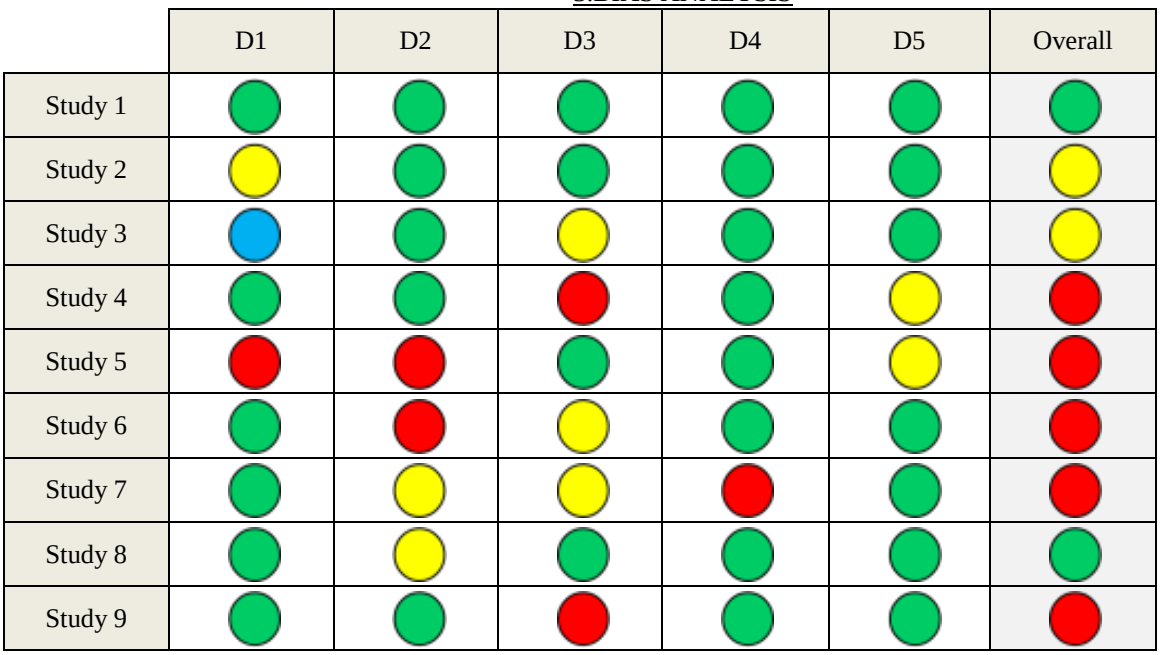
Author	Year	Place of Study	Sample	Intervention	Technique
Imran et al. 2017[3]	2017	Central Drug Research Institute, India	Albino rats	Mangiferin	Anti-inflammatory activity, animal models
García-Rivera et al. 2011[11]	2011	Cuba & Ghent University, Belgium	MDA-MB231 breast cancer cells	Mangiferin and Gallic Acid	NFκB pathway analysis, gene expression, cytotoxicity assays
Das et al. 2011[13]	2011	Manipal University, India	IMR-32 neuroblastoma cells	Mangiferin + Methylmercury (10 µM)	MTT, comet assay, apoptosis markers, Western blot
Rajendran et al. 2013[10]	2013	University of Madras, India	Swiss albino mice	Mangiferin (100 mg/kg BW) + Benzo(a)pyrene	Immune assays: phagocyte index, immunoglobulin levels
Li et al. 2013[14]	2013	Chongqing Medical University, China	MDA-MB-231 and other breast cancer cells	Mangiferin	MMP expression, EMT, β-catenin pathway analysis
Zhao et al. 2014[15]	2014	Tongji Medical College, China	HL60 leukemia cells	Mangiferin	Nrf2 protein stability, ubiquitination, Western blot
Zhang et al. 2014[13]	2014	Tongji Medical College, China	HL-60 leukemia cells & human cord blood MNCs	Mangiferin (50 µmol/L)	Nrf2-ARE activation, ROS, MTT, flow cytometry
Rajendran et al. 2014[10]	2014	University of Madras, India	Swiss albino mice	Mangiferin (100 mg/kg BW) + Benzo(a)pyrene	Enzyme assays (liver markers, lysosomal enzymes)
I. Rodeiro et al. 2014[9]	2014	Cuba & Chile (Havana, Antofagast)	Human lymphocytes and lymphoblastoid cells	MSBE and Mangiferin (5–1000 µg/ml)	Comet assay to evaluate DNA damage and repair
Delgado-Hernández et al. 2019[22]	2019	University of Havana & University of Antwerp	B16F10 melanoma cells, CAM assay, mice	Mangiferin	In vitro assays, CAM assay, gene expression analysis, in vivo angiogenesis
Zeng et al. 2020[18]	2020	Harbin Medical University, China	ES-2 xenograft mice model, ovarian cancer cells	Mangiferin	MTT, wound healing, transwell, ELISA, Western blot, IHC
Lin et al. 2020[14]	2020	China Medical University, Taiwan	A549, NCI-H460, NCI-H520 (lung cancer cells)	Mangiferin	MTT, Western blot, migration assays, PER1/NLRP3 modulation
Sung et al. 2021[1]	2021	National Institute of Technology, Durgapur, India	HT-29, HeLa, MCF-7 cells	Mangiferin	In-silico docking, Pharmacophore analysis, MTT

Table 2: Studies on Mangiferin – Intervention and Inference Summary

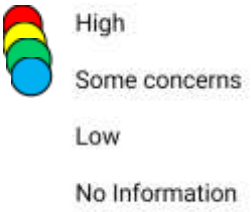
Author	Year	Place of Study	Intervention	Inference
García-Rivera et al. 2011[11]	2011	Cuba & Ghent University, Belgium	Mangiferin and Gallic Acid	Inhibited NFκB signaling, reduced cancer cell survival, potential anti-tumor agents.
Das et al. 2011[13]	2011	Manipal University, India	Mangiferin + Methylmercury (10 µM)	Reduced oxidative stress and DNA damage; neuroprotective effects.
Rajendran et al. 2013[10]	2013	University of Madras, India	Mangiferin (100 mg/kg BW) + Benzo(a)pyrene	Restored immune function and reduced oxidative damage in lung cancer model.
Li et al. 2013[14]	2013	Chongqing Medical University, China	Mangiferin	Suppressed metastasis and EMT, inhibited β-catenin signaling in breast cancer.
Zhao et al. 2014[15]	2014	Tongji Medical College, China	Mangiferin	Increased Nrf2 protein stability by inhibiting ubiquitination; cytoprotective antioxidant response.
Zhang et al. 2014[12]	2014	Tongji Medical College, China	Mangiferin (50 µmol/L)	Activated Nrf2-ARE without reducing etoposide sensitivity in leukemia cells.
Rajendran et al. 2014[16]	2014	University of Madras, India	Mangiferin (100 mg/kg BW) + Benzo(a)pyrene	Chemopreventive effects against lung carcinogenesis; normalized enzyme levels.
I. Rodeiro et al. 2014[19]	2014	Cuba & Chile (Havana, Antofagasta)	MSBE and Mangiferin (5–1000 µg/ml)	Showed both protective and harmful DNA effects depending on conditions.
Delgado-Hernández et al. 2019[9]	2019	University of Havana & University of Antwerp	Mangiferin	Inhibited melanoma progression via anti-angiogenic effects
Zeng et al. 2020[18]	2020	Harbin Medical University, China	Mangiferin	Suppressed ovarian cancer cell migration and invasion

Table2 shows Summary of Interventions and Inferences in Mangiferin Studies. Outlines key interventions using Mangiferin and summarizes scientific interpretations drawn from each study. It reflects the therapeutic significance based on observed biological responses.

3.BIAS ANALYSIS



Domains:
D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.



DISCUSSION

A range of experimental studies has shown that mangiferin, a bioactive C-glucosylxanthone mainly produced from Mangifera indica, has significant therapeutic effects. This discussion looks at eight selected in vitro and in vivo studies that explore the pharmacological effects of mangiferin related to immune system modulation, neurotoxicity, cancer growth, oxidative stress, and DNA damage. Each study provides unique insights into its mechanisms and treatment potential, but together they reveal its complex bioactivity. In one of the first studies on mangiferin, Li et al. (2013)[14]used albino rat models to investigate its anti-inflammatory properties. They found that mangiferin significantly reduced paw swelling caused by carrageenan, suggesting it inhibits the COX pathway. These results open the door for more research into the chemopreventive and anti-inflammatory roles of mangiferin in cancer treatment.

While inflammation is not directly linked to cancer, it is a known factor in tumor growth. An in vitro study on breast cancer cells (MDA-MB231) by Zhao et al. (2014) [15] found that mangiferin and gallic acid from Vimang extract effectively suppressed the NF-κB pathway, which is a key regulator of inflammation and cancer progression. This showed that mangiferin can lower metastatic gene expression, block angiogenesis, and disrupt cancer-related signaling. Garrido et al. (2007)[17]. demonstrated mangiferin's ability to protect IMR-32 neuroblastoma cells by reducing DNA damage, lessening oxidative stress, Rajendran et al. (2013)[16]and stabilizing mitochondrial function in their study on methylmercury-induced neurotoxicity.

These finding supports the use of mangiferin in neuroprotective strategies, especially for metal-induced toxicities. In an experimental lung cancer model with Swiss albino mice, 16] showed that giving mangiferin restored immune responses and reduced oxidative damage. This underscores mangiferin's ability to modify the immune system by normalizing immunoglobulin levels and immune cell function, especially when given both before and after tumor formation. Zheng et al (1990)[18]demonstrated that mangiferin has strong anticancer effects in breast cancer cells by suppressing β-catenin signaling, reversing EMT, and inhibiting MMP-7 and MMP-9. This highlights its potential for treating aggressive, estrogen-receptor-negative tumors. To better understand how mangiferin might support antioxidant defense in blood-forming cells, provided detailed information on the

molecular mechanism through which mangiferin increases Nrf2 protein stability.

This process prevents ubiquitination and extends Nrf2's half-life, boosting cellular defense mechanisms. Rodeiro et al (2012)[19]showed how mangiferin activated the Nrf2-ARE pathway in HL-60 leukemia cells. This activation increased the antioxidant response and reduced ROS. Importantly, mangiferin did not affect the cytotoxic action of etoposide, which suggests it can be used as both an antioxidant and a supportive therapy for treating leukemia. I. Rodeiro et al. (2014)[20] looked at the protective and harmful effects of Mangifera indica stem bark extract and mangiferin on human lymphocytes.

They found that while mangiferin protected against DNA damage from radiation, high doses and long exposure could also cause pro-oxidant effects. This highlights the need to optimize dosage and treatment duration if considering mangiferin as a radioprotective agent. In a separate study by García-Rivera et al (2011)[21] on lung cancer caused by benzo(a)pyrene, researchers showed that mangiferin significantly lowered markers of lysosomal and liver enzyme activity. This suggests reduced tissue damage. Its ability to affect systemic antioxidant levels and local enzyme responses further supports its potential as a cancer-preventive agent. In their research, Martínez SG (2000)[22] explored the anti-angiogenic effects of mangiferin in metastatic melanoma, utilizing in vitro and in vivo models. When applying B16F10 murine melanoma cells and using the CAM assay in chick embryos, they found that mangiferin substantially inhibited tumor cell migration and angiogenesis, an essential mechanism in metastasis. In addition, real-time PCR analysis revealed downregulation of pro-angiogenic gene expression, such as VEGF, suggesting that mangiferin may act as an anti-metastatic agent by targeting tumor vasculature, further supporting its potential as an adjunct therapy in malignant cancers such as melanoma. Martínez et al (2001)[23] investigated mangiferin's potential in epithelial ovarian cancer (EOC) using two models: ES-2 ovarian cancer cells and xenografts. Researchers observed that mangiferin significantly limited cell proliferation, migration, and invasion; the approach ultimately inhibited inflammatory cytokines, including IL-6, and inhibited the STAT3 pathway a known regulator of cancer progression supporting that mangiferin inhibits primary tumor growth and metastatic potential by reducing inflammation and oncogenic signaling.

The authors determined that mangiferin has action as an anti-cancer agent in gynecological malignancies. In a parallel analysis designed by Pardo et al (2005)[24], lung cancer cell lines (A549 and NCI-H460) were taken into consideration and the authors noted that mangiferin exhibited anti-cancer properties related to promoting apoptosis and decreasing cell viability in a dose-dependent fashion. Regarding explanatory rationale, mangiferin upregulated and stimulated PDE1, which encodes a circadian rhythm factor that needs to be regulated in a dose and time dependent manner and has tumor-suppressive functions. In addition to increased PER1, mangiferin reduced the NLRP3 inflammation some stimulation pathway that is known to produce inflammation related to cancer. Together the authors indicated that these mechanisms of action suggest a unique chronobiological and anti-inflammatory mechanism of action for mangiferin's therapeutic potential in non-small cell lung cancer (NSCLC).

Finally, Remirez et al. (2005) [25] utilized both in silico and in vitro methodologies to evaluate the anticancer activity of mangiferin across multiple human cancer cell lines, including HT-29 (colon), HeLa (cervical), and MCF-7 (breast). Gingerol exhibits significant anticancer properties by inducing apoptosis, inhibiting proliferation, and preventing metastasis through the modulation of pathways. Noor JJ et al (2024).[26] Molecular docking studies demonstrated a strong binding affinity between mangiferin and a range of proteins linked to cancer, while MTT assays confirmed its cytotoxic activity against cancer cells. This dual-phase approach supports mangiferin in being an agent with broad anticancer activity as it is capable of targeting multiple molecular pathways.

CONCLUSION

Mangiferin is a powerful plant-based bioactive molecule that has outstanding anticancer potential. Through the modulation of vital signaling pathways like NF-κB, PI3K/Akt, MAPK, p53, and STAT3, many preclinical studies have shown its strong potential to inhibit the growth of cancer cells, induce apoptosis, and prevent metastasis. Its strong anti-inflammatory and antioxidant properties, through the reduction of oxidative stress and enhancement of the immune system, also support its protective role. Besides, mangiferin causes a balance in the tumor microenvironment, which improves treatment outcomes. Due to its high bioactivity, low toxicity, and multi-targeted mechanisms, mangiferin is considered a promising natural compound that may be imperative for the development of safer and more effective cancer therapies

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