Anticancer Activity of *Mangifera indica* Through the Caspase Activation: A Short Review

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Abstract: Cancer is one of the major global health concerns. Although several treatment processes are available for cancer, they have many side effects. Several natural plants, like *Mangifera indica*, have gained attention for cancer treatment due to their fewer side effects. This paper aims to review the anticancer effects of *M. indica* by analyzing its role in activating caspase. A literature review was carried out using databases like PubMed, Science Direct, and Google Scholar directly, with a focus on *in vitro* and *in vivo* investigations to demonstrate caspase activation in cancer treatment. Our findings revealed that *M. indica* extracts significantly enhance caspase-3, -8, and -9 activity, which induces apoptosis in breast, cervical, and colon cancer cells. This plant extract fights against cancer by stopping the spread of cancer cells and their growth. *M. indica* exhibited significant anti-cancer activity via caspase activation, proving its potential as a natural anti -cancer therapy.

Keywords: Cancer; Caspase activation; *Mangifera indica*; Natural sources

1. Introduction

A condition known as cancer occurs when some body cells proliferate out of control and spread to other bodily organs. Cancer arises from the unchecked growth of altered cells that are subject to natural selection-driven evolution (Brown et al., 2023; Akter et al., 2024; Eity et al., 2024). An estimated 9.7 million people died from cancer and 20 million new cases were reported in 2022. It was projected that 53.5 million people survived five years after receiving a cancer diagnosis. One in five people will get cancer at some point in their lives, and one in nine men and one in twelve women will pass away from it (https://www.who.int/news/item/01-02-2024-global-cancer-burden-growing--amidst-mounting-need-for-services).

While important advancements are being made recently, such as stem cell therapy, targeted therapy, nanoparticles, natural antioxidants, radionics, and chemodynamic therapy, traditional treatment approaches like surgery, chemotherapy, and radiotherapy have yet to be replaced (Debela et al., 2021; Chowdhury et al., 2024; Al Hasan et al., 2024). Numerous cancers can be cured using radiation therapy, but the biophysical effects of radiation therapy are not unique to tumor cells and can cause damage if other organs and tissues are exposed (Wang & Tepper, 2021; Jahan Oni et al., 2024; Bhuia et al., 2023). The efficiency and accessibility of immunotherapy in the treatment of cancer are limited by issues like resistance mechanisms, side effects, and high prices (Gupta & Shukla, 2022; Bhuia et al., 2024; Mizan et al., 2025).

For over fifty years, natural compounds with a wide range of chemical compositions have been thoroughly studied for their ability to treat cancer (Huang et al., 2021; Bhuia et al., 2025). Mango bark (*Mangifera Indica L.*) is the source of the standardized extract known as "vimang," which is frequently used as a phytomedicine with anti-inflammatory properties and has recently been utilized to help cancer patients get cancer treatments (García -Rivera et al., 2011). The xanthone mangiferin (MGF), which comes from *M. indica L.*, was first used as a nutraceutical but is currently being thoroughly investigated for its ability to treat cancer. By blocking lipid peroxidation and NF-κB activation, it effectively combats a number of malignancies, including glioblastoma, breast, liver, and prostate cancer (Sarfraz et al., 2023). Despite not causing cytotoxicity in non-cancer cells within the same concentration range, mango polyphenols decreased cancer cell proliferation by up to 90%. It decreases inflammation and increases miR-126 in MCF-12A cells while also inhibiting ROS production in MDA-MB231 and MCF-12A cells (Arbizu-Berrocal et al., 2019).

This short review aims to assess the future perspective to use anticancer medication through several *M. indica* extracts by the caspase activation pathway, which increases apoptosis in various cancer cells. The study will give a future direction and study for its therapeutic qualities for safer and more efficient cancer therapies.

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2. Methodology

2.1. Literature search strategy

A comprehensive search was conducted in significant scientific databases, including PubMed, Science Direct, PubMed, and Google Scholar, using the keywords *Mangifera indica,* cancer, and effect/ activity.

2.2. Data inclusion period

The literature search covered studies published from 2000 to 2025. This timeframe ensured the inclusion of the most recent and relevant data related to the anticancer properties of *M. indica*.

2.3. Inclusion and exclusion criteria

The inclusion criteria for this research include studies investigating anticancer properties from multiple sources. It includes research conducted *in vitro* and *in vivo*, with or without the use of experimental animals. Additionally, studies may be considered regardless of whether they explore the mechanism of action. The exclusion criteria for the article included duplicate data, as well as titles and abstracts that did not meet the inclusion requirements. Additionally, studies focusing on the other pharmacological activities of *M. indica* were excluded.

3. Results and discussion

3.1. Key chemicals and their structures

M. *indica* contains several major important compounds, including mangiferin, isomangiferin, gallic acid, quercetin, kaempferol, catechins, ellagic acid (Ribeiro & Schieber, 2010). It also contains glutamic acid, palmitic acid, stearic acid, linoleic acid, arachidic acid, tyrosine, arginine, and vitamin A (Maldonado-Celis et al., 2019). The 2-dimentional structures of key chemicals of *M. indica* are given in **Fig.1**.

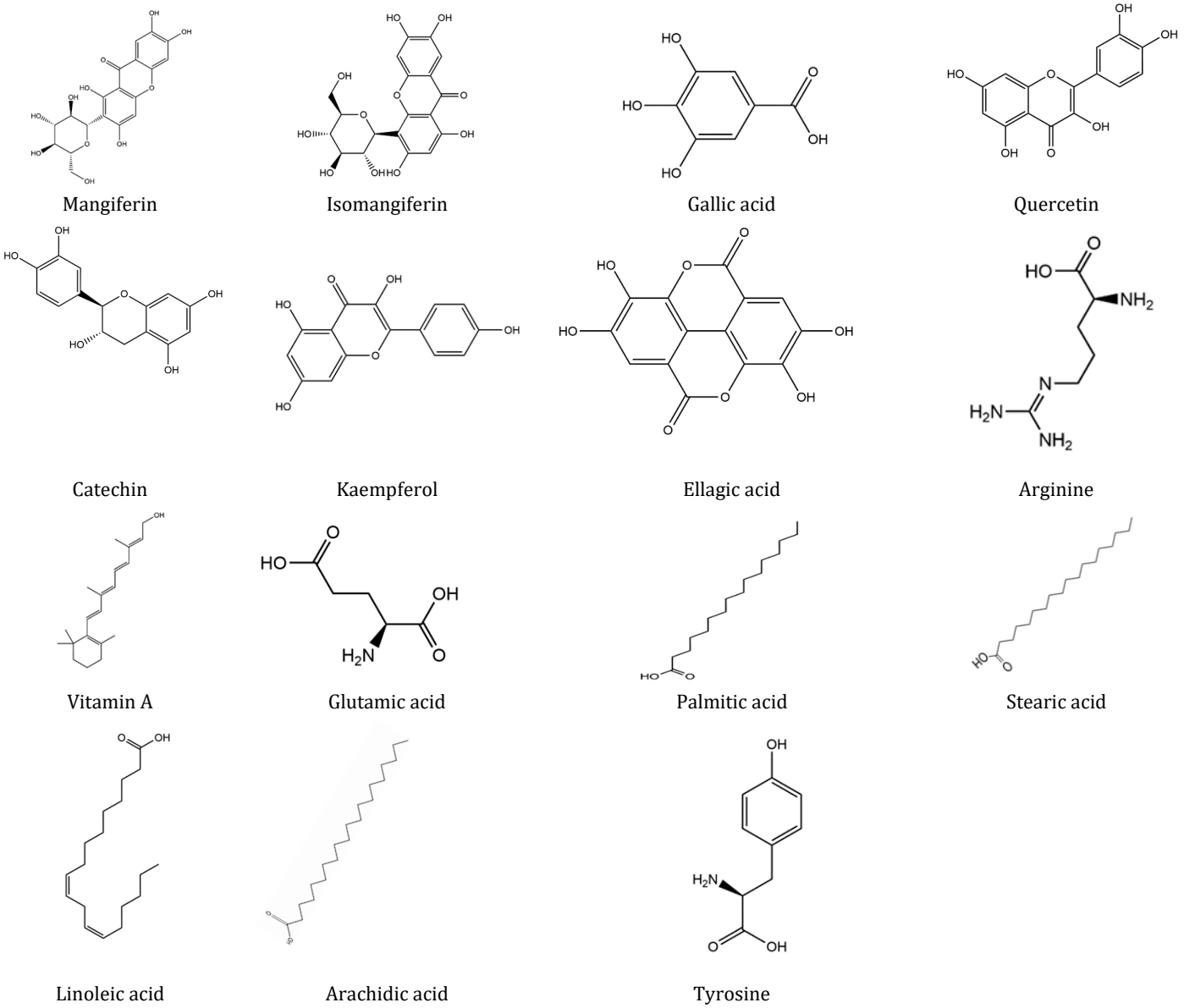

Fig. 1. The 2-dimentional structures of key chemicals of *Mangifera indica*.

3.2. Activities on caspase pathway

Caspase activators play a crucial role in cancer treatment (Wen et al., 2012). Caspase-targeted treatments have received a lot of interest because of their ability to carry out programmed cell death, which is an important strategy for removing cancer cells (Philchenkov et al., 2004). Caspases are essential proteases that mediate apoptosis by activating the cleavage of cellular components, resulting in programmed cell death (D'arcy, 2019). Small-molecule activators like PAC-1 chelate inhibitory zinc ions, allowing procaspase-3 to convert into active caspase-3, leading to apoptosis in cancer cells, with preclinical studies showing its efficacy (Peterson et al., 2009). Cancer cells often produce high levels of IAPs like XIAP, which block caspase activity and prevent cell death. Smac-mimicking compounds (LCL161, birinapant, xevinapant) disable IAPs, allowing caspases to trigger apoptosis and kill cancer cells (Fulda & Vucic, 2012).

3.3. Cellular and molecular anticancer mechanisms of *M. indica*

The present study evaluated the anticancer potential of *M. indica* extract by analyzing its effects on caspase activation in cancer cells. The results demonstrated a significant induction of apoptosis, as indicated by increased caspase activity in the treated MDA-MB231 breast cancer cell line (Arbizu-Berrocal et al., 2019; Abdullah et al., 2015). An *in vivo* study using female Sprague–Dawley rats demonstrated that *M. indica* peel and seed kernel extracts enhanced caspase-3 activity in breast cancer (Shaban et al., 2023). Additionally, the ethanol extract of *M. indica* significantly elevated caspase-9 activity in HeLa cervical cancer cells (Timsina et al., 2015). The Fozli peel (FP) extract was tested *in vitro* on the HeLa cell line at concentrations ranging from 12.5 to 200 µg/mL, resulting in the upregulation of caspase-3, caspase-8, and caspase-9 (Ali et al., 2012). The seed kernel extract of *M. indica* was found to increase caspase-3, caspase-8, and caspase-9 expression in colon cancer cell lines Colo 320DM and SW480, while ethanolic peel extracts decreased pro-caspase-3 and pro-caspase-9 levels, indicating apoptotic pathway activation (Wu et al., 2015; Lauricella et al., 2019). Furthermore, aqueous extracts of *M. indica* were tested on B lymphocyte cells using an MTT assay, revealing significant caspase-3 activation at concentrations ranging from 50 to 2000 µg/mL, supporting its potential role in apoptotic induction in chronic lymphocytic leukemia (Ayatollahi et al., 2019).

Our overall findings indicate that *M. indica* extracts, including peel, seed kernel, polyphenolic, and ethanolic extracts, effectively upregulated caspase activation across various cancer cell lines, indicating both intrinsic and extrinsic apoptotic pathways anticancer potential against breast, cervical, colon, and leukemia cancer. *In vitro* studies of *M. indica* extracts (0–2000 µg/mL) demonstrated significant caspase activation, including caspase-3, -8, and -9, indicating their potential to induce apoptosis in cancer cells. Our study also revealed that only one *in vivo* study has been conducted using female Sprague Dawley rats, highlighting the need for more *in vivo* research to thoroughly assess the safety, efficacy, and potential toxicity of *M. indica* extracts. However, all the data are shown in **Table 1.** Additionally, **Fig. 2** showed the possible mechanism of *M. indica* against several cancers through caspase activation, which activates the apoptotic pathway.

Table 1. Mechanism of caspase activation in anticancer activity of *Mangifera indica*.

Parts/ types of extract	Cancer types	Experimental model/ cell lines	Doses/ tested concentrations, (R/A)	IC_{50}	Mechanisms/ results	References
Peel and seed kernel	Breast cancer	Female Sprague–Dawley rats, *in vivo*	80 mg/kg (Orally)	-	↑Caspase-3	Shaban et al., 2023
Polyphenolic extract		MDA-MB231, *in vitro*	0 – 10 mg GAE/L	-	↑Caspase-3	Arbizu-Berrocal et al., 2019
Ethanolic mango seed extract		MDA-MB-231 cell line, *in vitro*	5–50 µg/mL	-	↑Caspase-3, caspase-8, caspase-9	Abdullah et al., 2015
Ethanolic extract	Cervical cancer	HeLa, CHO cell lines, *in vitro*	5 – 40 µg/mL	<10 µg/mL	↑Caspase-9	Timsina et al., 2015
Fozli peel (FP) extract		HeLa cell line, *in vitro*	12.5 – 200 µg/mL	-	↑Caspase-3, Caspase-8, Caspase-9	Ali et al., 2012
Seed kernel extract	Colon Cancer	Colo 320DM and SW480 cells line, *in vitro*	12.5 – 50 µg/mL		↑Caspase-3, caspase-8, caspase-9	Wu et al., 2015
Ethanolic peel extracts		HT29, Caco-2 and HCT116 colon cancer cells lines, *in vitro*	0 – 600 µg/mL	-	↓Pro-caspase-3, and 9	Lauricella et al., 2019
Aqueous extracts	Chronic lymphocytic leukemia	B lymphocytes cells, MTT assay, *in vitro*	50 –2000 µg/mL	-	↑Caspase-3	Ayatollahi et al., 2019

↑: Increase/ Activation; ↓: Decrease/ Deactivation; MTT Assay: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay; BrdU Assay: Bromodeoxyuridine assay;

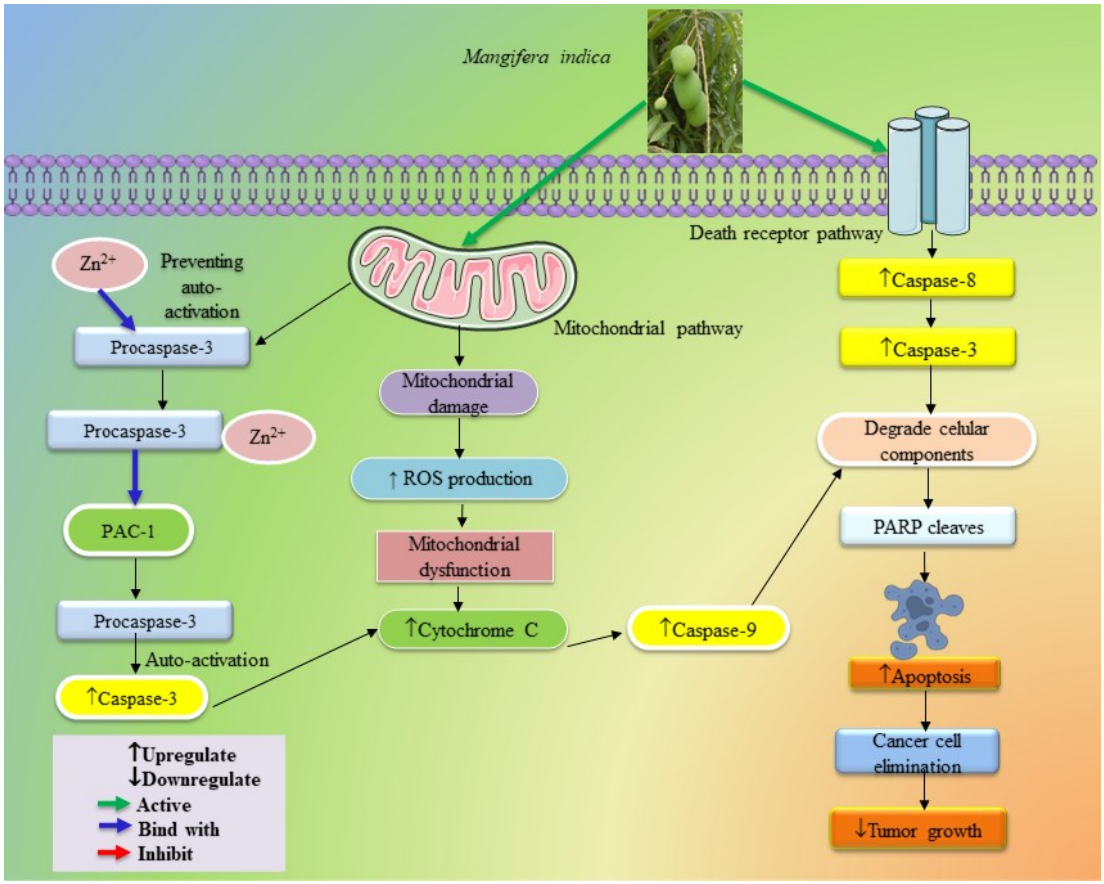

Fig. 2. Anticancer mechanism of *Mangifera indica* based on different preclinical studies through caspase activation.

4. Clinical importance of *M. indica* on cancer

M. indica (mango) has potential anticancer effects, mainly due to its high polyphenolic content including mangiferin (Noratto et al., 2010). Studies have demonstrated that extracts from various parts of the mango, such as the kernel and peel, can induce cytotoxic effects in human breast cancer cell lines and other cancer models (Abdullah et al., 2014). It is also proved by many researchers that, mango extracts inhibit cancer cell growth and induce apoptosis by affecting survival and death signaling pathways (Lauricella et al., 2019). Several clinical trials have demonstrated that polyphenolic compounds exhibit potential as anticancer agents by targeting various cancer pathways (Honari et al., 2019). So that further clinical studies are necessary to fully establish its efficacy and safety in cancer therapy.

5. Conclusion

In conclusion, cancer continues to be a leading cause of death worldwide, claiming numerous lives annually, despite significant progress in treatment options. Numerous experimental studies have shown that the plant extract of *M. indica* significantly lowers the risk of several cancers including cervical, breast, colon, and leukemia cancer, by activating caspase, which is essential for programmed cell death. Future research should focus on massive *in vivo* studies and well-designed clinical trials to validate *M. indica's* anticancer properties. Exploring its molecular processes and long-term safety may pave the way for its use in cancer treatments.

Conflict of interest

The authors declared no conflict

Data availability

Data will be made available on request.

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Author's contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas, that is, revising or critically reviewing the article; giving final approval of the version to be published; agreeing on the journal to which the article has been submitted; and confirming to be accountable for all aspects of the work. All authors have read and agreed to the published version of the manuscript.

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