SYSTEMATIC REVIEW

A Systematic Review of Potential Anticancer Activities of *Muntingia calabura* L. with a Focus on Cellular and Molecular Mechanisms

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ABSTRACT

Introduction: Medicinal plants have been extensively explored for their chemopreventive and antiproliferative properties. *Muntingia calabura* has emerged as a promising candidate due to its ability to modulate various signaling pathways involved in cancer progression and suppression. This includes interactions with multiple cell signaling molecules that regulate cancer formation and development. Purpose: This review aims to critically evaluate the anticancer properties of *M. calabura* across different cancer types. **Materials and methods:** A systematic literature search was performed across major scientific databases, including ScienceDirect, PubMed, and Scopus. Studies were selected based on predefined inclusion criteria using the keywords "*Muntingia calabura*", "*M. calabura*", "anticancer," and "cancer." A total of 14 studies met the eligibility criteria and were analyzed for this review. **Results:** Evidence from the reviewed studies highlights the anticancer effects of *M. calabura* extracts, which include inhibition of inflammatory and apoptotic pathways. The modulation of dysregulated signaling cascades, such as the LOX, XO, and RAF1 pathways, was shown to contribute significantly to its anticancer activity. **Conclusion:** The findings support the potential application of *M. calabura* and its phytochemical constituents in cancer prevention and therapy. However, further in-depth studies are necessary to identify its bioactive compounds and elucidate the mechanisms underlying its anticancer effects for clinical translation.
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INTRODUCTION

Medicinal plants have long been recognised as an important source of therapeutic aid for various human disorders, including cancer [1]. Among the many pharmacological properties of medicinal plants, anticancer activity has received a lot of interest. Several clinically available anticancer drugs are derived from plants, such as Vincristine, Vinblastine, and Paclitaxel, highlighting the value of medicinal plants in oncology [2].

Current cancer therapy faces challenges in developing agents that can selectively target cancer cells while decreasing the toxicity side effects on healthy cells and minimizing drug resistance [3]. In this context, a growing interest in plant-based treatment with anticancer and chemopreventive properties has gained attention as an alternative and complementary strategy [4]. Natural compounds typically have multi-targeted effects on a variety of molecular targets, such as adhesion molecules, growth factor receptors, cytokines, chemokines, transcription factors, and inflammatory enzymes, among others [5].

One such plant with promising medicinal potential is *Muntingia calabura* L. (Elaeocarpaceae), commonly known as Jamaican cherry. *M. calabura* is the sole species in the genus Muntingiaceae, Elaeocarpaceae family. It is a fast-growing flowering plant, broadly cultivated in India and Southeast Asia, such as Malaysia, Indonesia, and the Philippines [6]. In Malaysia, *M. calabura*, locally known as "Kerkup siam", is commonly cultivated as a roadside tree [7]. The tree typically grows between 7.5 and 12 metres in height, with toothed, hairy leaves and

small white flowers [8, 9]. Its round green fruits ripen to red (Figure 1).

Various parts of *M. calabura*, including its leaves, stems, fruits, and roots, have been used traditionally for multiple ailments such as headache, fever, liver infection, stomach ache, and pain [10]. Pharmacological studies have confirmed its broad therapeutic activities, including antioxidant, anti-inflammatory, antinociceptive, antimicrobial, gastroprotective, and hepatoprotective effects [11]. Recent studies have extended these findings to explore their potential anticancer mechanisms. Notably, extracts and compounds from *M. calabura* have demonstrated the ability to modulate multiple cellular signalling pathways associated with oxidation and inflammation, which are key hallmarks of cancer development [12-15]. For example, *M. calabura* reduces prostaglandin production through the inhibition of COX-2 activity or modulating reactive oxygen species (ROS), which affects oxidation and inflammation [16-18]. According to another study, the extracts from *M. calabura* fruits modulate the inflammatory processes by activating nuclear factor erythroid-2-related factor 2 (Nrf2), which has an anti-inflammatory effect, and inactivating nuclear factor-κB (NF-κB), mitogen-activated protein kinases (MAPKs) p38 and c-Jun NH2-terminal kinase 1/2 (JNK1/2), and Janus kinase 2 (JAK2)/ signal transducers and activators of transcription 1/3 (STAT1/3) [19].

Although there are a few published reviews on the pharmacological activities of *M. calabura*, none of them examined the potential of *M. calabura* for cancer therapy. Consequently, there has not been a thorough, comprehensive, systematic assessment of the anticancer capabilities of *M. calabura* and its related phytochemicals. Therefore, this review aims to present an up-to-date, systematic examination of the anticancer potential of *M. calabura*.

Figure 1: The various parts of *M. calabura*. (a) The *M. calabura* tree. (b) The leaves of *M. calabura*. (c) The flower of *M. calabura*. (d) The fruit of *M. calabura* (Adapted from NParks, 2024).

M. calabura: Sources, Chemistry, and Pharmacology

M. Calabura, also known as the Jamaican cherry, is a member of the Elaeocarpaceae family and native to tropical America [20]. This compact tree has spread across Southeast Asia and other parts of the world, where its various parts are valued for their nutritional and medicinal properties [21]. Historically, different parts of the plant have been used in traditional medicine across cultures, particularly in Malaysia, Indonesia, and the Philippines. Its leaves, roots, bark, and fruits have been used to treat conditions such as headaches, liver diseases, fevers, and cold symptoms, as well as anti-hysteric, anti-dyspeptic, diaphoretic, and antispasmodic use [22]. Despite its long history of medicinal use, records of *M. calabura* being used traditionally for cancer treatment are lacking.

M. calabura contains essential macronutrients like carbohydrates, proteins, and lipids, and important micronutrients such as calcium, iron, and phosphorus, further highlighting its nutritional value [23]. It is also rich in bioactive compounds, especially flavonoids (e.g., quercetin, kaempferol), phenolic acids (e.g., gallic acid, ferulic acid), tannins (e.g., ellagic acid), and triterpenoids (e.g., ursolic acid, oleanolic acid) [24-29]. These compounds are most concentrated in the leaves [30] and are known for their potent antioxidants, anti-inflammatory, antimicrobial, gastroprotective, hepatoprotective, anti-ulcer, and anticancer activities [31, 32].

Flavonoids and phenolic acids act as free radical scavengers, reducing oxidative stress, while tannins and triterpenoids provide anti-inflammatory and anticancer benefits by inhibiting enzymes like COX-2 and downregulating pro-inflammatory cytokines [33]. These antioxidant and anti-inflammatory properties are crucial for preventing chronic diseases such as cancer by protecting cells from oxidative damage and inflammation [34].

The pharmacological properties of *M. calabura* are attributed to its capacity to modulate multiple cellular pathways. Flavonoids in the plant can inhibit NF-κB, a major transcription factor that drives inflammation, while phenolic acids neutralise reactive oxygen species, protecting cells from oxidative damage [35]. Ursolic acid, a key triterpenoid, has demonstrated anticancer effects by inducing apoptosis through mitochondrial pathways and inhibiting cancer-promoting enzymes [36]. These mechanisms underscore the therapeutic potential of *M. calabura* in managing inflammation, oxidative stress, and cancer.

Pharmacokinetics and Toxicity of *M. calabura*

M. calabura has been the subject of extensive investigation for its pharmacological attributes. Multiple research endeavors have been undertaken to evaluate the plant's safety profile through *in vivo* investigations. Comprehensive toxicity assessments encompassing acute, subacute, and sub-chronic studies have been conducted employing *M. calabura* extract on rat models, consistently yielding plant safety indications.

Multiple studies have addressed the acute toxicity of *M. calabura*'s methanol and ethanol extracts from the leaves and fruits [37]. The outcomes of these investigations establish that oral administration of *M. calabura* extract to rats was well-tolerated, demonstrating safety at doses up to 5000 mg/kg. Additionally, it was observed that rats treated with ethanol and crude extracts at doses of 2000 mg/kg and 15000 mg/kg, respectively, exhibited no toxic manifestations or mortalities during acute toxicity assessments [38]. These findings substantiate the safety of *M. calabura*, with an estimated lethal dose surpassing 15000 mg/kg.

Further reinforcing this safety profile, a 90-day sub-chronic toxicity study utilizing *M. calabura* methanol extract in rats revealed no discernible clinical signs of weakness or abnormalities at doses of 50, 250, and 500 mg/kg [39]. The corroborative evidence from histopathological, haematological, and serum biochemical analyses underscored the capacity of the extracts to not disrupt physiological equilibrium and overall well-being in rats.

MATERIALS AND METHODS

The current systematic review was carried out according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) criteria [40]. Studies were selected from various electronic databases (PubMed, Scopus, Science Direct, Google Scholar, and EBSCO) up to February 2025. The search strategy employed the keywords: '*Muntingia calabura*' AND '*M. calabura*' AND 'cancer' AND 'anticancer' AND '*in vivo*' AND '*in vitro*'.

Inclusion criteria focused on experimental research (*in vivo* and *in vitro*) assessing the anticancer efficacy of *M. calabura* in any animal model and/or cancer cell line. Unrelated papers were excluded based on titles and abstracts, with two independent researchers conducting the review to minimise bias. We removed review papers, meta-analyses, novels, book chapters, conference abstracts, clinical trials, and non-English language materials. In total, 183 reports were excluded due to duplicate findings, 549 due to article type, and 82 for being review articles, leaving 139 studies. From these, 26 were eliminated for focusing on other pharmacological effects of *M. calabura*. Ultimately, 14 research papers were included, as depicted in the flowchart (Figure 2).

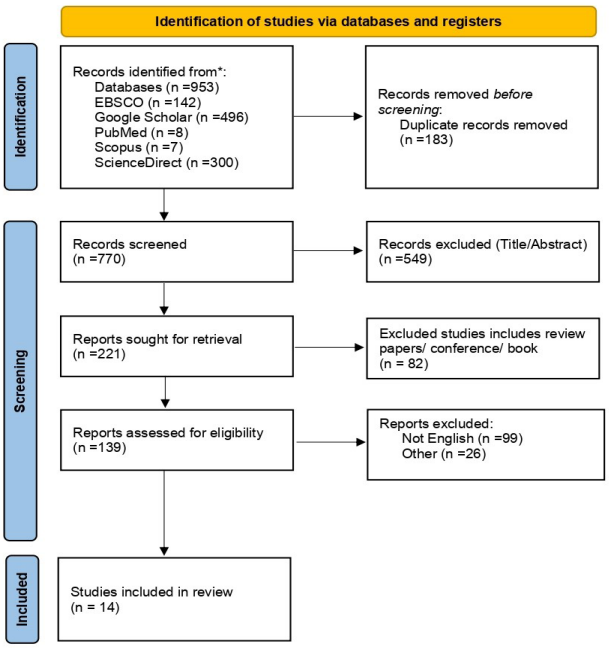

Figure 2: The flow chart of the PRISMA selection procedure for the included studies.

RESULTS

Out of the final 14 articles, 11 focused on *in vitro* studies using cancer cell lines, while the remaining three utilised *in vivo* animal models. The following section will explore the anticancer potential of *M. calabura* and the underlying mechanisms, as summarised in Tables I and II. This investigation comprehensively explored the potential anticancer properties of *M. calabura* extracts, fractions, and compounds through various *in vitro* and *in vivo* studies.

Cytotoxic and Antiproliferative Effects

Approximately 70% of the included studies (11/14) explored the cytotoxicity and antiproliferative activity of *M. calabura* extracts, fractions, and isolated compounds. The earliest study, conducted in 1991, evaluated twelve new flavonoids isolated from the methanol extract of *M. calabura* roots. These compounds were tested against eight cancer lines: BC1, HT-1080, Lul, Me12, Col2, KB, KB-V, and P-388. Among them, flavans (compounds 1-7) showed stronger cytotoxic activity than falavones (compounds 8, 10, 12), with an ED50 value ranging between 2-16.7 µg/mL [41]. Notably, compounds 2 and 5 demonstrated enhanced activity against KB-V cells, while compounds 3, 9, and 11 showed broad

cytotoxicity but lacked specificity. Selective cytotoxicity was also observed for certain compounds against BC-1, HT-1080, Lu1, and CO-12 cell lines.

A follow-up study reinforced these findings by identifying 2',4'-dihydroxychalcone and chrysin as potent cytotoxic agents, with ED50 values ranging between 0.7-20 µg/mL across nearly all tested cancer cell lines [42]. Moreover, flavonoids from the leaves also demonstrated chemopreventive activity in mouse Hepa 1c1c7 cells by inducing quinone reductase, with an IC_{50} value exceeding 20 µg/mL [43].

Subsequently, the cytotoxicity studies of bioactive compounds (flavonoids) isolated from *M. calabura* were extended and tested against P-388, A549, and HT-29. Among the 15 compounds isolated, only compounds 8-hydroxy-7,3′,4′,5′-tetramethoxyflavone (1), 8,4′-dihydroxy-7,3′,5′-trimethoxyflavone (2), 3,5-Dihydroxy-6,7-dimethoxyflavone (5), (2S)-5′-Hydroxy-7,8,3′,4′-tetramethoxyflavan (6), Syringic acid (10), Vanillic acid (11), and 3-hydroxy-1-(3,5-dimethoxy-4-hydroxyphenyl)propan-1 (12), exhibited cytotoxic activity against P-388 cells with an ED50 values of 3.56, 3.71, 9.39, 6.28, 10.72, 15.62, and 3.27 µg/mL, respectively [44]. Interestingly, only one compound (compound 6) displayed notable cytotoxicity against colorectal (HT-29) and lung (A549) cancer cell lines with an ED50 of 16.81 and 20.60 µg/mL, respectively. Another study rreported that out of the 20 isolates, four isolates ((2S)-5′-hydroxy-7,3′,4′-trimethoxyflavanone, 4′-hydroxy-7-methoxyflavanone, 2′,4′-dihydroxychalcone, and 2′,4′-dihydroxy-3′-methoxychalcone) displayed notable cytotoxic effects against P-388 and/or HT-29 cell lines, with IC_{50} values <4 µg/mL [45].

To further assess the antiproliferative activity of *M. calabura*, the methanol, aqueous, and chloroform extracts were tested using the MTT assay against 5 cancer cell lines (MCF-7, HeLa, HL-60, K-562, MDA-MB-231) and 3T3 normal cell lines. All three extracts showed no cytotoxicity toward the 3T3 cells, indicating selective toxicity. However, they significantly inhibited proliferation of cancer cells, especially MCF-7 (IC_{50}: 18–98 µg/mL), HeLa (IC_{50}: 22–52 µg/mL), K-562 (IC_{50}: 18–42 µg/mL), and HL-60 (chloroform and methanol: 29 and 7 µg/mL, respectively) [46]. The methanol extract displayed the highest antiproliferative activity. In another study, the cytotoxicity of *M. calabura* methanolic (MeOH) extract and its partitions (petroleum ether (PEE), ethyl acetate (EAE), and aqueous (AE)) against various cell lines, including MCF-7, HL-60, HCT116, and WRL68, was evaluated. It was found that MeOH displayed moderate cytotoxicity against HL-60 and HCT-116, with IC_{50} values of 30.90 and 61.29 µg/mL, respectively [47]. In comparison, its partitions PEE and EAE showed similar activity with IC_{50} values of 29.46 and 58.44 µg/mL, but none of the partitions presented substantial cytotoxicity against MCF-7. As for the AE, it was found to possess no cytotoxicity against all normal and cancer cell lines (IC_{50} >100 µg/mL in all extracts).

Moreover, the EAE was considered active and selective according to the National Cancer Institute-Selective Index (NCI-SI) guidelines and was further fractioned into 7 fractions (F1-F7). Fraction 5 was found to be the most active with an IC_{50} of 3.98, 34.85, and 32.29 µg/mL against HL60, MCF7, and WRL68. Therefore, the active chemical constituent of the F5 fraction was identified and isolated. Four bioactive compounds were isolated, of which compounds 1 and 3 are novel isolates. These four compounds are (5, 7-dihydroxy-3, 8-dimethoxyflavone (1), 20, 40-dihydroxychal-cone (2), 5-hydroxy-3, 7-dimethoxyflavone (3), and 3, 5, 7-trihydroxy-8-methoxyflavone (4)). Compounds 2 and 4 have been reported previously to possess various biological activities such as antimicrobial, cytotoxicity, antioxidant, and anti-inflammatory activity. Similarly, the antiproliferative properties of ethyl acetate partitions derived from the methanol extract of *M. calabura* leaves against colon cancer cells (HT-29) were studied. The ethyl acetate partition (EAP) showed the most potent antiproliferative activity against HT-29 with an IC_{50} of 58 µg/mL, while demonstrating selectivity toward 3T3 [48].

Furthermore, the fruit ethanolic extract of *M. calabura* (MFEE) demonstrated notable anticancer effects by inhibiting the expression of vascular endothelial growth factor (VEGF) in nickel-stimulated HepG2 hepatocellular carcinoma cells. Treatment with MFEE at concentrations of 25, 50, and 100 µg/mL resulted in a significant, dose-dependent reduction in VEGF production, closely mirroring the effect of the positive control, gallic acid (25 µg/mL) [49]. Similarly, the ethanolic leaf extract of *M. calabura* showed anticancer activity against CT26 colorectal cancer cells, exhibiting mild cytotoxicity with an IC_{50} value of 70.81 µg/mL [50].

In parallel, gold nanoparticles synthesised using *M. calabura* extract (MC-AuNPs) offered an innovative anticancer strategy, displaying selective cytotoxicity against laryngeal carcinoma (Hep2) cells with an IC_{50} value of 63.23 µg/mL, while sparing normal cells. This finding highlights the potential of *M. calabura*-based nanomedicine as a targeted cancer therapy [51].

In summary, over 60% of studies reported selective toxicity against cancer cells while sparing normal cells such as 3T3 and WRL-68 [41-49]. Flavonoids isolated from *M. calabura* roots, stems, and leaves were commonly tested against cancer cell lines. Compounds such as chrysin, 2',4′-dihydroxychalcone, and (2S)-5′-hydroxy-7,8,3′,4′-tetramethoxyflavan showed potent cytotoxicity with IC_{50} or ED_{50} values ranging between 0.7–20 µg/mL [46–50]. Methanolic and ethyl acetate extracts exhibited IC_{50} values of 18–46 µg/mL against

HT-29, MCF-7, and HL-60 cells, suggesting moderate activity and high selectivity [49-51].

Inhibition of Inflammatory and Oxidation Pathways

Anti-inflammatory mechanisms were reported in approximately 36% of the studies (5/14). *M. calabura* ethyl acetate partition extract exhibited a high anti-inflammatory activity, with over 95% inhibition of lipoxygenase (LOX) and more than 70% inhibition of xanthine oxidase (XO), supressing petroleum ether and aqueous partitions [48]. In *in vivo* models, the ethyl acetate extract reduced the expression of pro-inflammatory genes, including COX-2, TNF-α, and IL-6 [53-54]. These genes are pro-inflammatory and pro-cancer genes that are released through a reactive oxygen species (ROS)-dependent NF-κB pathway [55]. ROS are elevated in models induced with DMH without treatment. Methanol *M. calabura* extract treatment reduces ROS levels by increasing antioxidant enzymes activity such as superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH), while decreasing malondialdehyde (MDA) level, a maker of oxidative stress [52]. The methanol and ethyl acetate antioxidant and anti-inflammatory activity is attributed to the suppression of NF-κB signaling [52-54].

Induction of Apoptosis and Regulation of Apoptotic Genes

Induction of apoptosis and modulation of related genes were evident in around 43% of studies (6/14). *M. calabura* ethyl acetate (EFMC) extracts enhanced the expression of pro-apoptotic genes (Caspase-3, Caspase-9, p53) and downregulated anti-apoptotic markers in colorectal cancer models [53-54]. These results were further validated by western blot analysis, which confirmed that EFMC treatment reduced COX-2 and NF-κB protein levels, in contrast to their elevated expression in untreated DMH-induced colon cancer models.

Similarly, the ethanolic leaf extract of *M. calabura* demonstrated anticancer activity against CT26 colorectal cancer cells by modulating the WNT/β-catenin signaling pathway [50]. Phytochemical analysis revealed the presence of rutin (0.727 mg/mL), a flavonoid with known anticancer effects. Molecular docking and qRT-PCR confirmed a significant reduction in the β-catenin gene expression in treated cells, indicating that rutin may help suppress WNT-mediated cancer cell proliferation.

MC-AuNPs extract induced apoptosis in Hep2 cells via cell membrane disruption, nuclear changes, and G2 phase cell cycle arrest, demonstrating the potential of *M. calabura*-mediated nanoparticles as an emerging tool in cancer therapy [51].

Modulation of Dysregulated Signalling Pathways

Around 21% of studies (3/14) highlighted the modulation of critical cancer-related pathways. *M. calabura* extracts were shown to modulate PI3K/Akt/mTOR, RAF/MEK/ERK, JAK/STAT3, WNT/β-catenin, and HIF-1α signalling pathways [49, 50]. Notably, treatment with *M. calabura* fruit extract reduced VEGF expression and suppressed angiogenesis in HepG2 cells via downregulation of RAF1, PI3K, and STAT3 [49]. In colorectal cancer cells, WNT/β-catenin pathway suppression was observed through rutin's interaction with β-catenin [50]. In colorectal cancer models, EFMC extract was found to significantly downregulate NF-κB, COX-2, TNF-α, and IL-6, as shown by RT-PCR and western blot analysis [53, 54]. These findings support the anti-angiogenic and anticancer potential of *M. calabura* by targeting signaling pathways involved in tumor growth, blood vessel formation, and cell proliferation.

***In vivo* Anticancer and Chemopreventive Activity**

In vivo investigations (3/14 papers) confirmed the chemopreventive activity of *M. calabura* in colon cancer models. Treatment with methanolic or ethyl acetate leaf extracts reduced aberrant crypt foci (ACF) formation and restored antioxidant enzyme levels such as SOD, CAT, and GSH while lowering MDA [44–46]. The HPLC analysis of methanol extract identified various phenolic compounds, including gallic acid, catechin, epicatechin, ferulic acid, and pinocembrin, which are known to possess antioxidant, anti-inflammatory, and anticancer properties. To summarize, the proposed antiproliferative and cytotoxic activity of *M. calabura* extracts, compounds, and partitions against various cancer cells may be attributed to the presence of different phytochemical constituents. According to the cited studies, *M. calabura* contains several bioactive compounds such as phenolic acids (gallic acid, gentisic acid, p-hydroxybenzoic acid, vanillic acid, p-coumaric acid, ferulic acid, sinapic acid, syringic acid, p-anisic acid, and rosmarinic acid), and flavonoids (epicatechin, rutin, diosmin, quercetin, chrysin, and luteolin) which likely work synergistically to produce the anticancer effects seen in various cells lines. Additionally, *M. calabura* extracts can upregulate apoptotic genes and expression of antiproliferative proteins, providing control against colorectal cancer. However, further studies are required to fully understand their exact molecular mechanism(s) and their action against colorectal cancer.

DISCUSSION

M. calabura has long been used in traditional medicine across Southeast Asia, including Malaysia, where its leaves, fruits, and roots are commonly consumed for ailments related to inflammation, fever, pain, and metabolic disorders [10, 22]. Its medicinal relevance has been largely attributed to its rich content of flavonoids, phenolic acids, and other bioactive compounds known for strong antioxidant and anti-inflammatory properties [11, 24]. This systematic review synthesised current evidence from *in vitro* and *in vivo* studies and demonstrates that *M. calabura* consistently exhibits

anticancer activity through several well-established mechanisms.

Cytotoxicity and Antiproliferative Activity

Across the studies reviewed, cytotoxic and antiproliferative effects were the most frequently reported outcomes, with more than 70% of included studies describing significant inhibitory activity against various cancer cell lines [41–49]. Flavonoid-rich fractions and isolated compounds, such as chrysin, rutin, and 2',4′-dihydroxychalcone, repeatedly demonstrated potent cytotoxicity with IC_{50} or ED_{50} values typically below 20 µg/mL. These findings are consistent with the known pharmacological behaviour of flavonoids, which often exert selective toxicity by targeting cancer-specific metabolic vulnerabilities while sparing normal cells.

Several extracts, including methanolic and ethyl acetate partitions, showed selective inhibition of cancer cells such as MCF-7, HL-60, HCT-116, and HT-29 while maintaining minimal toxicity toward normal 3T3 and WRL-68 cells [46–49]. This selectivity strengthens the therapeutic potential of *M. calabura*, particularly in chemopreventive applications where safety is crucial.

Anti-Inflammatory and Antioxidant Effects

Around 36% of the reviewed studies reported anti-inflammatory activity, largely mediated via suppression of COX-2, TNF-α, IL-6, and NF-κB-related signalling pathways [48, 52–54]. These pathways are central to tumor initiation and progression, especially in inflammation-driven cancers such as colorectal cancer. *In vivo* studies showed that extracts of *M. calabura* reduced oxidative stress by elevating antioxidant enzymes (SOD, CAT, GSH) and decreasing MDA levels—changes consistent with a reduction in reactive oxygen species [52–54].

The combined antioxidant and anti-inflammatory actions likely contribute to reduced DNA damage, improved cellular homeostasis, and suppressed tumor microenvironment activation.

Apoptosis Induction

Approximately 43% of studies demonstrated apoptosis-inducing effects, particularly with ethyl acetate fractions and rutin-containing extracts [50, 53–54]. Upregulation of pro-apoptotic markers (p53, Caspase-3, Caspase-9) and suppression of anti-apoptotic proteins suggest that *M. calabura* activates intrinsic apoptotic pathways. In colorectal cancer models, these effects corresponded with reduced aberrant crypt foci and improved histopathological outcomes.

Rutin-mediated inhibition of the WNT/β-catenin pathway is especially relevant to colorectal cancer, where this signalling axis plays a major role in uncontrolled proliferation [50]. Although this evidence is promising, only a small number of studies specifically targeted colorectal models, indicating a need for dedicated research in this area.

Modulation of Cancer-Related Pathways

A smaller subset of studies (21%) explored deeper mechanistic pathways, demonstrating modulation of PI3K/Akt/mTOR, RAF/MEK/ERK, JAK/STAT3, and HIF-1α pathways [49–50]. These pathways govern survival, angiogenesis, and proliferation in most cancers. Notably, inhibition of VEGF in HepG2 cells indicates a strong anti-angiogenic potential, supported by reductions in RAF1, PI3K, and STAT3 expression.

Together, these findings highlight the multi-target nature of *M. calabura*, which aligns with the behaviour of plant-derived polyphenols that typically exert broad regulatory effects rather than single-target inhibition.

***In vivo* Chemopreventive Evidence**

The *in vivo* studies reviewed confirmed the chemopreventive activity of *M. calabura* in colorectal cancer models, showing reductions in aberrant crypt foci and restoration of antioxidant systems [52–54]. HPLC profiling identified phenolic acids such as gallic acid, catechin, syringic acid, and ferulic acid, all of which have independently recognized anticancer properties. These compounds may work synergistically with flavonoids to enhance the observed chemopreventive effects.

CONCLUSION

In conclusion, the combined findings of *in vitro* and *in vivo* studies present a promising outlook for *Muntingia calabura*'s potential as a source of novel anticancer agents. This systematic review highlights its cytotoxic effects on various cancer cell lines and chemopreventive properties in animal models. Due to its inexpensive cost, long history of use, wide availability, and diverse pharmacological activities, *M. calabura* is a promising anticancer and chemopreventive agent. *In vitro* investigations involving *M. calabura* extracts have been shown to impact various cancers such as the breast, colon, larynx, lung, prostate, hepatocellular carcinoma, melanoma, and leukemia. Future studies may not limit the list to only these cancer types.

The selective cytotoxicity towards cancer cells observed, coupled with modulation of essential cellular pathways such as NF-κB/IL-6/STAT3, IKK/NF-κB, PI3K/Akt/mTOR, ERK, Bcl-2, and VEGF, hints at the powerful potential of *M. calabura* in the development of future anticancer strategies. However, as most of the evidence-based results for *M. calabura* anticancer activity were obtained from *in vitro* models, with only limited results from *in vivo* or randomised clinical studies, more *in vivo* models are necessary to fully understand its role in combating cancer. Therefore, to unlock the full therapeutic potential of these compounds in cancer treatment and

prevention, further insights into mechanistic and clinical investigations are essential.

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