romanian journal of preventive medicine

MDPI

Review

Effect of *Manilkara zapota* (L.) P. Royen in Cancer and Inflammation

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Abstract

As of 2020, liver cancer has emerged as the fifth most common cancer and the third leading cause of cancer death worldwide, following lung and colorectal cancers. The most prevalent type is hepatocellular carcinoma (HCC), originating from hepatocytes. Despite advancements, liver cancer treatment outcomes remain poor due to metastasis and recurrence. Existing anticancer drugs often exhibit narrow therapeutic windows and limited selectivity for cancer cells. *Manilkara zapota* (L.) P. Royen has attracted significant scientific attention because of its diverse bioactive constituents and potential therapeutic properties. Of particular interest in this review, we explored the molecular connectivity of oxidative stress-induced liver cancer. We discussed the underlying mechanisms of *Manilkara zapota* (L.) P. Royen involved in cancer and inflammation. The phytochemical constituents were also highlighted in this study. The phytochemicals reported from *Manilkara zapota* (L.) P. Royen included flavonoids, tannins, saponins, and phenolic compounds. These compounds demonstrated potential anticancer activities through mechanisms such as induction of apoptosis, inhibition of cell proliferation, modulation of oxidative stress, and regulation of PI3K/Akt and NF-κB signaling pathways. Further investigations are required to clarify the benefit–risk profile of *Manilkara zapota* (L.) P. Royen through large-scale clinical trials. Collectively, the current evidence suggests that this plant may offer a promising strategy for cancer management, provided that such interventions are optimized to minimize adverse effects.

Keywords: antioxidant; hepatocellular carcinoma; inflammation; liver cancer; oxidative stress; sapodilla

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Academic Editor: Dimitrios Stagos

Received: 11 July 2026
Revised: 5 September 2026
Accepted: 10 September 2026
Published: 11 September 2026

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1. Introduction

Liver cancer is the fifth most frequently diagnosed malignancy and the third leading cause of cancer-related mortality worldwide, following lung and colorectal cancers [1]. In 2020, it accounted for approximately 830,180 deaths, representing 8.3% of all cancer deaths across both sexes and all age groups [1]. The predominant histological subtype is hepatocellular carcinoma (HCC), which arises from hepatocytes, the principal liver cell type. Prognosis varies considerably depending on disease stage, patient age, overall health status, and treatment efficacy. Survival statistics indicate that patients diagnosed at an early stage have a 5-year relative survival rate of approximately 36%. However, this rate declines

to 13% when the disease has spread to adjacent tissues, organs, or regional lymph nodes and further decreases to 3% in cases with distant metastasis [2].

Despite considerable advances in therapeutic strategies for liver cancer in recent years, clinical outcomes remain unsatisfactory [3]. Metastasis and recurrence frequently occur following treatment, underscoring the limitations of current approaches. Moreover, many conventional anticancer agents exhibit narrow therapeutic efficacy and limited selectivity toward malignant cells [4]. The effectiveness of systemic chemotherapy is further compromised by both intrinsic and extrinsic mechanisms of chemoresistance in liver cancer cells [5]. Consequently, there has been growing scientific interest in the identification of novel anticancer compounds derived from natural products. Among these, *Manilkara zapota* (L.) P. Royen has emerged as a promising candidate, attracting increasing attention for its potential therapeutic applications.

Manilkara zapota (L.) P. Royen, a member of the family *Sapotaceae*, is a lowland rainforest species commonly known as sapodilla and locally referred to as *ciku*. It is a tropical evergreen tree native to Mexico, Central America, and the Caribbean region. It is now widely cultivated across the tropical and subtropical regions worldwide, including Southeast Asia and across the Indian subcontinent, including Bangladesh [6]. Traditionally, the fruit is consumed as a snack, the wood is utilized for furniture production, and the latex is harvested for gum and glove manufacturing. Beyond these uses, various plant parts, such as seeds and leaves, have long been employed in traditional medicine. For example, preparations from the plant have been used to treat diarrhea and alleviate pulmonary infections. In India, crushed seeds are administered for diuretic-induced edema and kidney stones, while leaf decoctions are applied in the treatment of fever, hemorrhage, wounds, and ulcers. A previous study found that aqueous extracts of *Manilkara zapota* leaves possess antioxidant properties, highlighting their potential for both medicinal and nutritional applications [7].

Emerging research has demonstrated that *Manilkara zapota* (L.) P. Royen contains a variety of polyphenolic compounds, particularly concentrated in the fruit peel. These bioactive constituents include flavonoids, tannins, and phenolic acids, which are associated with significant health-promoting properties [7]. Optimization of extraction techniques has been shown to enhance the recovery of these compounds, thereby increasing their potential therapeutic value. Extracts of *Manilkara zapota* have attracted attention as complementary agents in cancer therapy, especially for liver cancer. Experimental evidence indicates that *Manilkara zapota* extracts exert inhibitory effects on liver cancer progression in murine models and exhibit cytotoxic activity against human hepatocellular carcinoma cells [8]. Importantly, in vitro studies have reported that methanolic leaf extracts of *Manilkara zapota* are non-cytotoxic to BALB/c 3T3 normal cells, suggesting a favorable safety profile [9]. Although several studies have summarized the traditional uses, phytochemical composition, and broad pharmacological activities of *Manilkara zapota*, including its antioxidant, anti-inflammatory, and general anticancer properties, the precise biological mechanisms underlying liver cancer remain to be fully elucidated. Given the involvement of oxidative stress, chronic inflammation, dysregulated apoptosis, and aberrant signaling pathways in hepatocarcinogenesis, understanding how *Manilkara zapota* and its bioactive constituents influence these mechanisms is of considerable scientific and therapeutic interest. Therefore, this review aims to explore the current evidence regarding the anti-liver cancer potential of *Manilkara zapota*, with particular emphasis on the molecular mechanisms associated with oxidative stress regulation, apoptosis induction, inflammatory modulation, and signaling pathways implicated in liver cancer progression.

2. Methods

The literature included in this review was identified through electronic scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search covered studies from January 2003 to January 2026 were retrieved using combinations of keywords such as "*Manilkara zapota*", "sapodilla", "hepatocellular carcinoma", "liver cancer", "anticancer activity", "phytochemicals", "antioxidant", "anti-inflammatory", and "mechanism of action". Boolean operators (AND, OR) were applied to refine the search strategy. Additional articles were identified through manual screening of reference lists from selected articles. Studies were included if they investigated the phytochemical composition, biological activities, molecular mechanisms, or therapeutic potential of *Manilkara zapota*, particularly in relation to oxidative stress, inflammation, cancer, and hepatocellular carcinoma. Original research articles and review articles published in English were considered. Articles lacking sufficient methodological information, duplicate publications, and studies unrelated to the scope of *Manilkara zapota* were excluded.

3. Liver Cancer

Liver cancer is a malignancy that originates in the liver and is classified as primary liver cancer when the tumor arises within the liver itself rather than metastasizing from another organ [10]. HCC is the most common form of primary liver cancer and represents a major global health burden. The disease is often associated with chronic liver disorders and remains a leading cause of cancer-related mortality worldwide [11]. The development of HCC is strongly linked to chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, which can promote liver cirrhosis and subsequent malignant transformation [12]. In addition, metabolic and lifestyle-related factors, including obesity and diabetes, have emerged as important contributors to hepatocarcinogenesis [13]. The global incidence of liver cancer continues to increase, with approximately 860,000 new cases reported annually, highlighting its significant public health impact [14].

Despite advances in disease management, liver cancer remains highly lethal, primarily because many patients are diagnosed at advanced stages when curative treatment options are limited [15]. Consequently, HCC continues to be associated with poor clinical outcomes and substantial mortality worldwide [16]. Prognosis is influenced by factors such as disease stage, patient characteristics, and response to therapy [17,18]. Although current therapeutic approaches, including surgical resection and systemic treatments, have been widely recognized, several challenges such as recurrence, treatment resistance, and adverse effects limit its effectiveness [19]. These limitations have prompted increasing interest in identifying novel therapeutic agents, particularly those derived from natural products, for the prevention and treatment of HCC.

4. Conventional Treatment

Conventional treatment strategies for liver cancer include surgery, chemotherapy, and radiotherapy, but they are limited by significant drawbacks such as cytotoxicity to healthy tissues, adverse effects, and suboptimal efficacy [20–24]. Despite these challenges, ongoing advances in therapeutic techniques have improved clinical outcomes. For example, drug-eluting bead transarterial chemoembolization has enhanced the management of unresectable liver cancer, while supportive clinical interventions have contributed to improved patient quality of life and survival [25,26].

4.1. Chemotherapy

Chemotherapy remains an important systemic treatment option for liver cancer, particularly in patients with advanced or unresectable disease. Its therapeutic efficacy is

achieved through the disruption of cellular processes essential for tumor growth and survival. Sorafenib, one of the most widely used first-line agents for advanced HCC, exerts its anticancer activity through inhibition of multiple kinases involved in tumor angiogenesis and proliferation, including vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), and the RAF/MEK/ERK signaling pathway [27]. In addition to suppressing tumor growth, sorafenib has been shown to induce apoptosis through caspase-independent mechanisms in HCC cells [28]. Doxorubicin, another commonly used chemotherapeutic agent, acts by intercalating into DNA, inhibiting topoisomerase II activity, generating reactive oxygen species, and triggering apoptosis in rapidly proliferating cancer cells [29].

Despite its therapeutic benefits, chemotherapy is frequently associated with significant limitations. Adverse effects such as fatigue, nausea, myelosuppression, and dose-dependent cardiotoxicity can compromise treatment tolerability and quality of life [30]. Furthermore, the molecular heterogeneity of liver tumors and the development of chemoresistance through alterations in drug transport, apoptosis pathways, and cellular survival signaling often limit long-term efficacy [31]. Nevertheless, ongoing efforts to combine chemotherapy with targeted therapies, immunotherapy, and locoregional interventions have demonstrated promise in improving treatment responses and clinical outcomes in patients with liver cancer [32].

4.2. Surgery

Surgical intervention remains the most effective curative option for selected patients with liver cancer. Hepatic resection involves the complete removal of tumor-bearing liver tissue while preserving sufficient functional hepatic reserve, thereby providing the potential for long-term disease control in patients with localized tumors [33]. Liver transplantation offers an alternative curative strategy, particularly for patients with early-stage HCC, as it simultaneously eliminates both the tumor and the underlying diseased liver that may predispose to recurrence [34]. Recent advances in minimally invasive approaches, including laparoscopic and robotic-assisted liver surgery, have further improved surgical precision while reducing postoperative morbidity and accelerating recovery [35].

However, the success of surgical treatment is highly dependent on tumor characteristics and patient condition. Factors such as tumor size, vascular invasion, anatomical location, and underlying liver dysfunction may limit eligibility for surgical intervention [36]. Moreover, postoperative complications, including hemorrhage, infection, liver failure, and tumor recurrence, continue to present significant clinical challenges. Consequently, careful patient selection and multidisciplinary management are essential to maximize the therapeutic benefits of surgery while minimizing associated risks.

4.3. Radiation Therapy

Radiation therapy is an important treatment modality for liver cancer, particularly for patients who are unsuitable candidates for surgical resection or other locoregional interventions. Conventional radiation approaches include external beam radiation therapy (EBRT) and brachytherapy, both of which exert anticancer effects through the induction of DNA damage, generation of reactive oxygen species, cell cycle arrest, and apoptosis of malignant cells [37,38]. Advances in radiation delivery have substantially improved treatment precision and reduced damage to surrounding healthy tissues. In particular, intensity-modulated radiation therapy (IMRT) enables highly conformal dose distribution by modulating radiation intensity according to tumor geometry, thereby enhancing tumor targeting while minimizing exposure to adjacent organs and normal liver tissue [39]. Furthermore, clinical evidence has demonstrated the superiority of IMRT over three-

dimensional conformal radiation therapy (3DCRT) in achieving improved dose conformity and organ preservation in patients with HCC [40].

Appropriate radiation treatment planning requires careful consideration of tumor size, anatomical location, and baseline liver function to maximize therapeutic efficacy while preserving hepatic reserve [41]. In addition to IMRT, stereotactic body radiation therapy (SBRT) has emerged as an effective non-invasive approach for both primary liver tumors and liver metastases [42]. SBRT delivers highly focused ablative radiation doses with steep dose gradients, allowing for precise tumor targeting over a limited number of treatment fractions while minimizing irradiation of surrounding tissues [43,44]. Despite these advances, radiation therapy remains constrained by the risk of radiation-induced liver disease (RILD) and other treatment-related toxicities [38].

5. Molecular Connectivity of Oxidative Stress-Induced Liver Cancer

Pre-clinical research, encompassing both in vitro and in vivo studies, provides a critical foundation for elucidating the molecular mechanisms underlying disease progression. In the context of liver cancer, extensive experimental investigations have yielded important insights into the signaling pathways driving hepatocarcinogenesis. The Wnt/β-catenin signaling cascade has emerged as a central regulator. Dysregulation of this pathway has been strongly implicated in HCC, the most prevalent form of liver cancer [45]. Experimental evidence demonstrates aberrant activation of Wnt/β-catenin signaling in HCC cells, promoting uncontrolled proliferation and tumor progression [46]. These findings highlight the therapeutic potential of targeting the Wnt/β-catenin pathway as a promising strategy for the management of liver cancer.

AKT serine/threonine kinase 1 (Akt1), a pivotal component of the PI3K/Akt/mTOR signaling axis, has been extensively investigated in HCC. Accumulating evidence demonstrates its critical role in hepatocarcinogenesis and disease progression [47]. In particular, the mTORC2–Akt1 cascade has been identified as a central driver of c-Myc–induced HCC [48]. Aberrant Akt1 expression in HCC cells has been closely linked to diverse cellular processes, including proliferation, survival, metabolic regulation, and tumorigenesis [49]. Moreover, Akt1-mediated modulation of the PI3K/Akt/mTOR pathway contributes to key pathological features of HCC, such as enhanced proliferation, invasion, and resistance to chemotherapy [50]. Beyond liver cancer, Akt1 has also been implicated in the growth of nasopharyngeal carcinoma cells through acetylation-dependent mechanisms, indicating its multifaceted role across malignancies [51].

In vitro studies have further demonstrated that activation of the PI3K/Akt/mTOR pathway promotes cell survival, proliferation, and resistance to apoptosis in liver cancer models [52]. Conversely, inhibition of the PI3K/Akt/mTOR pathway has yielded promising anti-tumor effects [53]. Complementing these findings, in vivo investigations have provided a broader perspective on the molecular complexity of liver cancer. Notably, the Hippo signaling pathway has emerged as a critical regulator of organ size and cell fate, and its disruption is frequently observed in HCC [54]. In mouse models, Hippo pathway activation exerts tumor-suppressive effects by inhibiting cell proliferation and inducing apoptosis in liver cancer cells [55]. These pre-clinical findings imply the therapeutic promise of targeting both the PI3K/Akt/mTOR and Hippo pathways in the management of liver cancer. Among the signaling pathways implicated, Notch signaling, an essential mediator of cell-to-cell communication, has been shown to promote tumor growth and metastasis in mouse models of liver cancer [56]. Importantly, experimental inhibition of the Notch pathway in vivo has demonstrated promising effects in suppressing tumor progression and limiting metastatic spread.

The integration of in vitro and in vivo findings is essential for advancing comprehensive strategies in liver cancer research. This translational crosstalk has attracted considerable attention, offering deeper insights into the molecular mechanisms that govern neoplastic progression, particularly within gastrointestinal tissues [57]. Notably, the interplay between the Wnt/β-catenin and Hippo pathways has been observed across both experimental settings, suggesting the complexity of interconnected signaling networks in hepatocarcinogenesis [58]. Patient-derived xenograft (PDX) models, in which human tumor tissues are engrafted into immunodeficient mice, have proven invaluable for investigating individualized responses to targeted therapies [59]. PDX models provide a robust platform for evaluating therapeutic efficacy and resistance mechanisms.

Epidermal growth factor receptor (EGFR), a pivotal regulator of oncogenic signaling, has been extensively investigated in HCC. Overexpression of EGFR has been observed in HCC and is strongly associated with early tumor recurrence [60]. EGFR contributes to HCC development by orchestrating fundamental cellular processes, including proliferation, survival, and invasion, thereby driving tumor progression [61]. Mechanistically, EGFR activation promotes HCC aggressiveness through multiple downstream pathways, such as the EGFR/HER2–ERK1/2 axis [62]. Therapeutically, EGFR inhibition has demonstrated promising anti-tumor activity, positioning EGFR as a compelling target for HCC treatment [63]. Beyond its role in signaling, EGFR has also been implicated in metabolic reprogramming, particularly by enhancing tumor glycolysis [64].

Hypoxia-inducible factor 1-alpha (HIF1A) has been implicated in a wide range of cellular processes essential for tumor development, including angiogenesis, glucose metabolism, cell growth, metastasis, and apoptosis [65]. In HCC, HIF1A has been shown to drive tumor progression, chemoresistance, migration, invasion, autophagy, and epithelial–mesenchymal transition (EMT), which indicates its pivotal role in promoting aggressive phenotypes and metastatic potential [66]. The multifaceted regulatory functions of HIF1A highlight its promise as a therapeutic target in HCC [28]. Beyond liver cancer, HIF1A has also been associated with the proliferation of cholesteatoma keratinocytes via regulation of endothelin-converting enzyme 1 expression [67]. In HCC, HIF1A further contributes to fibroblast migration and proliferation under hypoxic conditions through the BNIP3–autophagy pathway [68]. Given its involvement in angiogenesis, tumor growth, and therapy resistance, targeting HIF1A has been proposed as a promising strategy for HCC management [69]. Moreover, its association with invasion and metastasis further demonstrates its potential as a critical target for inhibiting HCC dissemination [70]. Taken together, these findings suggest that HIF1A is a central mediator of hypoxia-driven tumor biology and a compelling candidate for therapeutic intervention in liver cancer.

Heat shock protein 90 alpha family class A member 1 (HSP90AA1), a molecular chaperone, has attracted considerable attention in HCC due to its role in tumor progression and therapeutic resistance. Recent studies have highlighted its critical involvement in HCC pathobiology, particularly in mediating chemoresistance [71]. HSP90AA1 upregulation has been shown to enhance c-MYC protein expression, suggesting a functional interaction between HSP90AA1 and oncogenic drivers in HCC [72]. Elevation of HSP90AA1 expression correlates with poorer disease-free survival and increased risk of recurrence, positioning it as a potential prognostic biomarker [73]. Furthermore, transcriptomic analyses have identified HSP90AA1 as one of the commonly upregulated genes in both liver and esophageal cancers, implicating its role in cell cycle regulation and DNA replication [74].

Interleukin-6 (IL-6) has emerged as a critical mediator in the pathogenesis of HCC, with recent studies highlighting its diverse roles in tumor progression. Primarily secreted by inflammatory and stromal cells within the tumor microenvironment, IL-6 binds to the IL-6 receptor complex and activates Janus kinase (JAK)–signal transducer and activator

of transcription 3 (STAT3) signaling. This cascade regulates oncogenic gene expression, thereby promoting cell proliferation and inhibiting apoptosis [75]. Elevated IL-6 levels have been consistently associated with poor prognosis and increased risk of recurrence in HCC patients [76]. Importantly, the IL-6/STAT3 axis has been identified as a key driver of HCC metastasis, reinforcing its potential as a therapeutic target [76]. Beyond its role in metastasis, IL-6 exerts multifunctional effects on HCC progression, with heightened expression correlating strongly with disease occurrence and adverse clinical outcomes.

Nuclear factor-kappa B (NF-κB) is a pivotal transcription factor with profound implications in HCC progression. NF-κB regulates key biological processes, including inflammation, immunity, cell proliferation, differentiation, and survival [77]. In HCC, aberrant NF-κB activation has been linked to oncogenic functions, notably the induction of inflammatory cytokines such as IL-6, thereby contributing to tumor pathogenesis [78]. Beyond its role in inflammation, NF-κB orchestrates essential cellular functions related to growth, survival, and immune regulation [79]. Importantly, inhibition of NF-κB has been shown to selectively target cancer stem cell populations, suggesting a promising therapeutic approach for patients with poor prognosis [80]. NF-κB activation has also been associated with enhanced tumor growth and chemoresistance [81]. Another study has additionally revealed crosstalk between regulatory non-coding RNAs and NF-κB signaling, highlighting its central role in hepatocarcinogenesis and disease progression [82].

6. *Manilkara zapota* (L.) P. Royen

Manilkara zapota (L.) P. Royen, commonly known as *ciku* or sapodilla, is a tropical evergreen tree belonging to the *Sapotaceae* family, widely cultivated in Malaysia and other tropical regions. Originally native to Central America, the species has successfully spread to diverse tropical environments, thriving in countries such as Mexico, India, and the Philippines [83]. The plant is highly valued not only for its sweet, grainy fruit, which is consumed as a refreshing delicacy, but also for its durable wood used in furniture production and its latex historically harvested for chewing gum and glove manufacturing. Beyond its culinary and industrial applications, *Manilkara zapota* holds broader significance, with emerging research highlighting its potential pharmacological and therapeutic properties, thereby extending its relevance well beyond traditional uses.

Manilkara zapota is a tropical evergreen tree native to the Yucatán Peninsula in Mexico, which has successfully acclimatized to diverse climates and is now widely cultivated across tropical and subtropical regions. The genus *Manilkara* comprises several ecologically and economically significant species, including Manilkara zapota, and exhibits considerable genetic diversity across different species such as *Manilkara hexandra*, *Manilkara kauki*, and *Manilkara littoralis* [84].

Sapodilla fruits are valued for their distinctive sweet, malty flavor and nutritional richness. Beyond their culinary appeal, *Manilkara zapota* has a long history of use in traditional medicine, with various plant parts including bark and leaves, employed for their purported therapeutic properties. Ethnomedical practices have utilized sapodilla extracts to manage ailments such as diarrhea, dysentery, and respiratory disorders. Ripe fruits are energy-dense and contain significant amounts of sugars, organic acids, proteins, phenolic compounds, carotenoids, and ascorbic acid, contributing to their notable antioxidant capacity [85].

6.1. Phytochemical Constituents in Manilkara zapota (L.) P. Royen

Recent studies on the phytochemical profile of *Manilkara zapota* have identified a broad range of bioactive compounds, including tannins, saponins, flavonoids, and alkaloids [86]. These metabolites are considered to play a pivotal role in the plant's therapeutic potential.

Flavonoids, a prominent class of polyphenolic compounds, are widely recognized for their diverse biological activities that contribute to human health. In *Manilkara zapota*, flavonoids play a crucial role in promoting well-being, particularly through their antioxidant and anti-inflammatory properties. Studies have demonstrated that these compounds effectively neutralize reactive oxygen species, thereby mitigating oxidative stress, a pathological process implicated in numerous chronic conditions, and enhancing cellular protection [87,88]. Moreover, flavonoids in *Manilkara zapota* exhibit significant anti-inflammatory activity, which demonstrate their potential in the prevention and management of inflammation-associated diseases [89]. Organic sulfur compounds in *Manilkara zapota* have been associated with multiple biological activities, including antioxidant, antimicrobial, and anti-inflammatory effects [90]. Emerging evidence further suggests potential roles in anti-diabetic, anticancer, and cardioprotective applications [91].

In addition, the diverse medicinal attributes of *Manilkara zapota* highlight its value as a natural resource, with different plant components contributing distinct health benefits. For example, sapodilla leaves are rich in bioactive compounds and have been shown to possess anti-inflammatory and antioxidant properties, supporting their potential in mitigating oxidative stress and inflammation-related disorders [92]. Complementing these findings, the bark of *Manilkara zapota* has been investigated for its pharmacological relevance, revealing hypoglycemic activity and anti-diabetic potential, which are attributed to its bioactive constituents [93]. Together, these studies emphasize the therapeutic promise of both leaves and bark in traditional and modern medicinal potentials.

Moreover, the fruits of *Manilkara zapota* are characterized by their sweet, grainy texture and nutritional profile. They contain vitamins, minerals, and dietary fiber, sapodilla fruits may contribute to digestive health and overall well-being, while their antioxidant constituents have been associated with free radical-scavenging activity and protecting cellular integrity [94]. Beyond the fruit, other plant components also demonstrate therapeutic potential. The seeds, often discarded, exhibit anti-inflammatory and analgesic properties, suggesting possible applications in the management of pain and inflammatory disorders [95]. In addition, the latex extracted from the sapodilla tree, known as chicle, has been reported to possess antibacterial activity, indicates potential benefits for oral health alongside its historical use in the chewing gum industry [96]. While the phytochemical profile of *Manilkara zapota* has been extensively described in previous studies, the relevance of these constituents to cancer-related pathways has not been discussed. Therefore, the following sections focus specifically on mechanistic evidence linking *Manilkara zapota*-derived bioactive compounds involved in hepatocarcinogenesis.

6.2. The Role of Manilkara zapota (L.) P. Royen in Cancer

Manilkara zapota is recognized as a rich source of bioactive compounds, among which polyphenols are particularly notable. Polyphenols are well known for their antioxidant properties, playing a critical role in neutralizing free radicals and reducing oxidative stress [97]. Recent studies have demonstrated significant antioxidant activity in *Manilkara zapota* extracts, highlighting their potential in mitigating oxidative damage associated with various diseases, including cancer [92].

Beyond its antioxidant effectiveness, *Manilkara zapota* has also demonstrated anti-inflammatory properties attributed to its diverse bioactive compounds. Since inflammation is a central factor in the pathogenesis of many chronic diseases, extracts of *Manilkara zapota* showing anti-inflammatory activity suggest therapeutic potential in conditions such as arthritis and cardiovascular disorders [91]. The combined antioxidant and anti-inflammatory effects of *Manilkara zapota* have attracted considerable attention in clinical and

preclinical research, where studies report encouraging outcomes on markers of oxidative stress and inflammation [98].

Recent investigations have further expanded its relevance to cancer prevention. Extracts of *Manilkara zapota* have exhibited cytotoxicity against colorectal cancer cells, inhibiting proliferation and inducing apoptosis, thereby highlighting its potential role in colorectal cancer management [86]. Similarly, studies on breast cancer suggest that phytochemicals in *Manilkara zapota* interfere with molecular pathways involved in tumor growth and progression [99].

The anticancer potential of *Manilkara zapota* also extends to HCC, a major global health concern. Evidence indicates that its extracts exert hepatoprotective effects, likely mediated through antioxidant and anti-inflammatory mechanisms that mitigate factors contributing to liver carcinogenesis [8]. In addition, anticancer activity has been observed against gastric cancer cells, where polyphenol-rich extracts inhibit proliferation and promote apoptosis, suggesting possible applications in gastric cancer prevention [92].

7. Molecular Pathways Mediated by *Manilkara zapota* (L.) P. Royen

Recent scientific investigations have explored the molecular pathways associated with *Manilkara zapota*, revealing its potential influence on diverse physiological processes and disease mechanisms [9]. Chronic inflammation, a critical driver in the development and progression of cancer, cardiovascular disorders, and metabolic syndromes, has been a particular focus [100]. In this context, *Manilkara zapota* has been examined for its anti-inflammatory properties, offering valuable insights into the modulation of key molecular pathways involved in inflammatory responses [101]. Table 1 summarizes different extracts of *Manilkara zapota* in in vitro and in vivo models.

Table 1. Effect of *Manilkara zapota* extracts in in vitro and in vivo models.

Experimental Model	Plant Part	Extraction Type	Concentration and Duration	Findings	Reference
albino Wistar rats	Leaf	Crude ethanolic and ethyl acetate extract	300 mg/kg	Inhibition of paw edema	[101]
Human cervical cancer (HeLa) cells	Leaf	Methanol	12, 24, and 48 µg/mL for 72 h	Decreased viability of HeLa cells via induction of apoptosis and reduction in *EGFR* and NF-κB transcriptional activities	[9]
Human Hepatocellular Carcinoma (HepG2) Cells	Leaf	Water	24, 48, and 96 µg/mL for 72 h	Increase percentage of early apoptotic cells, induce the formation of ROS, upregulate *JNK1* and *iNOS*, and reduce *Akt1* and *VEGFA* transcriptional activities	[8]
Human colorectal cancer (HT-29) cells	Leaf	Water	21, 42, and 84 µg/mL for 72 h	Increase total apoptotic HT-29 cells and triggered both caspase-3 and -8 activities	[87]
Alloxan-induced diabetes in Wistar rats	Stem bark	70% ethanolic	250 mg kg^{-1}	Improved glycemic control and ameliorated diabetic complications	[93]
In vitro	Leaf	Aqueous, ethanolic, and hydroalcoholic	100–1000 µg/mL	Inhibit α-amylase and α-glucosidase	[98]
Human gastric cancer (HGT-1) cell line	Leaf	70% Ethanol	21, 42, and 84 µg/mL for 72 h	Suppressed proliferation of HGT-1 cells, activate *HO-1* and *Nrf2*, and inhibit *NF-κB* and *iNOS* mRNA levels	[92]

Abbreviations: EGFR = epidermal growth factor receptor, HO-1 = heme oxygenase-1, iNOS = inducible nitric oxide synthase, JNK1 = c-Jun N-terminal kinase 1, NF-κB = nuclear factor-kappa B, Nrf2 = nuclear factor E2-related factor 2, VEGFA = vascular endothelial growth factor A.

7.1. Inflammation Pathway

The presence of inflammatory cells and mediators within the tumor microenvironment has been well documented, indicating the intricate link between inflammation and cancer development [102]. Similarly, insights into arterial inflammation progressing to atherosclerosis highlight the broader significance of understanding inflammatory mechanisms in disease pathogenesis [103]. Liver cancer, particularly HCC, represents a major global health challenge due to its rising incidence and high mortality rates [104]. Inflammation plays a pivotal role in the initiation and progression of HCC, with pathways such as toll-like receptors, IL-6, NF-κB, and signal transducer and activator of transcription 3 (STAT3) implicated in liver tumorigenesis [105]. Chronic infections, including hepatitis C, schistosomiasis, and *Helicobacter pylori*, further contribute to elevated risk of liver carcinoma [106].

Within this context, extracts of *Manilkara zapota* have demonstrated anti-inflammatory activity through the inhibition of proinflammatory cytokines and mediators. Notably, leaf extracts reduced the production of tumor necrosis factor-alpha (TNF-α) and IL-6 in vitro (Figure 1), with evidence suggesting modulation of NF-κB signaling in HeLa cells [9]. This ability to influence NF-κB activity highlights the plant's potential in regulating inflammatory processes and associated disease outcomes. Beyond direct inhibition of inflammatory mediators, *Manilkara zapota* extracts exhibit immunomodulatory properties, contributing to balanced immune responses. Such immunomodulation may enhance the overall anti-inflammatory effects of the species, positioning it as a promising candidate for therapeutic interventions targeting inflammation-related disorders [9].

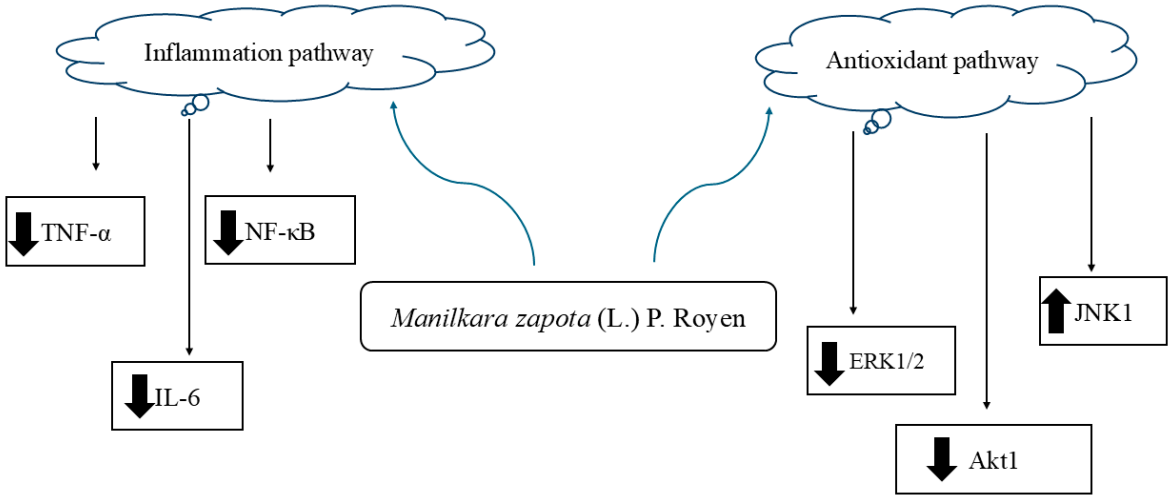


Figure 1. Molecular pathways underlying *Manilkara zapota* (L.) P. Royen in mediating human hepatocellular carcinoma (HepG2) and human cervical cancer (HeLa) cells.

7.2. Antioxidant Pathway

The antioxidant pathway is essential for protecting cells against oxidative stress, a process closely linked to aging and the onset of various diseases, including cancer. In liver cancer, both development and progression have been associated with oxidative stress and impaired antioxidant defenses [107]. Mechanistic studies have shown that resistance to oxidative stress mediated through the MK2/heat shock protein 27 (Hsp27) pathway contributes to liver cancer progression [108]. Likewise, the Nrf2-ARE signaling pathway, a key regulator of antioxidant responses, has been implicated in liver diseases, including HCC [109]. Several natural antioxidants, such as astaxanthin, punicalagin, and watercress, have demonstrated hepatoprotective effects by attenuating oxidative stress and liver damage [110]. Within this context, *Manilkara zapota* has attracted attention for its potent antioxidant properties, largely attributed to its polyphenolic compounds. Notably,

extracts of *Manilkara zapota* have been shown to induce apoptosis in human hepatocellular carcinoma (HepG2) cells via ERK1/2, Akt1, and JNK1 signaling pathways (Figure 1), suggesting its potential role in liver cancer prevention and therapy [8].

8. Conclusions and Future Perspectives

This review provides evidence supporting the potential of *Manilkara zapota* (L.) P. Royen as a source of bioactive compounds with antioxidant, anti-inflammatory, and anticancer properties. The leaves, fruit, stem bark, and other plant parts contain diverse phytochemicals, including flavonoids, phenolic acids, tannins, and related polyphenolic compounds that have been associated with various biological activities. In addition to studies reporting the anticancer effects of *Manilkara zapota* against hepatocellular carcinoma, previous studies have demonstrated antidiabetic, anti-inflammatory, antioxidant, and ethnopharmacological significance of *Manilkara zapota* (L.) P. Royen, collectively supporting its broader therapeutic potential. However, the current evidence regarding the anticancer activity of *Manilkara zapota* (L.) P. Royen remains limited and is derived predominantly from in vitro studies. Furthermore, a substantial proportion of the mechanistic evidence describing the anti-HCC activity of *Manilkara zapota* (L.) P. Royen has been derived from a limited number of studies, several of which were conducted by the same research group. Therefore, the reported mechanisms and therapeutic effects require independent validation by other researchers and across different experiments to strengthen their reproducibility and generalizability. To date, there is also a lack of studies evaluating its efficacy and mechanisms in animal models and clinical studies. Consequently, the translational relevance of the existing findings and therapeutic potential require further elucidation in long-term clinical studies. The current understanding of the molecular mechanisms underlying the anti-liver cancer activity of *Manilkara zapota* remains incomplete. Future studies should focus on the isolation and characterization of active compounds, pharmacokinetic and toxicological evaluations, mechanistic validation in preclinical models and in vivo models, and well-designed clinical trials to establish efficacy and safety of *Manilkara zapota* in the management of HCC.

Author Contributions: B.L.T., design and conception of the manuscript, writing—review and editing. M.E.N., writing—review and editing. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by MSU Seed Grant (SG-005-02023-FHLS).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

EBRT	External beam radiation therapy
EGFR	Epidermal growth factor receptor
HCC	Hepatocellular carcinoma
HepG2	Human hepatocellular carcinoma
HIF1A	Hypoxia-inducible factor 1-alpha
Hsp27	Heat shock protein 27
HSP90AA1	Heat shock protein 90 alpha family class A member 1

IL-6	Interleukin-6
IMRT	Intensity-modulated radiation therapy
NF-κB	Nuclear factor-kappa B
PDX	Patient-derived xenograft
RILD	Radiation-induced liver disease
SBRT	Stereotactic body radiation therapy
STAT3	Signal transducer and activator of transcription 3
TNF-α	Tumor necrosis factor-alpha
3DCRT	Three-dimensional conformal radiotherapy

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