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Herbal-derived phytochemicals in hepatocellular carcinoma: A review of molecular targets and tumor microenvironment interventions

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ABSTRACT

Hepatocellular carcinoma (HCC) is a health concern and stands as the most common primary liver malignancy. HCC frequently arises from chronic liver damage caused by hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, prolonged alcohol consumption, and metabolic liver diseases, all of which contribute to the progressive accumulation of epigenetic and genetic alterations. These molecular changes drive uncontrolled proliferation, evasion of apoptosis, and immune resistance through the upregulation of programmed death ligand 1 (PD-L1) and remodeling of the tumor microenvironment (TME), together with enhanced angiogenesis, culminating in malignant transformation. Despite advancements in surgical and systemic interventions remain suboptimal, particularly in advanced stages where drug resistance and systemic toxicity pose significant limitations. In recent years, natural compounds derived from medicinal plants have garnered increasing interest due to their capacity to modulate multiple cancer-related pathways with comparatively lower toxicity. Alkaloids, flavonoids, saponins, and terpenoids exert anticancer effects by restricting tumor growth, inducing apoptosis and modulating Nrf2/Keap1 and VEGF/HIF-1α mediated pathways. Compounds such as curcumin, ginsenosides, withaferin A, and epigallocatechin gallate have demonstrated notable preclinical efficacy and enhanced the effectiveness of conventional therapies. This narrative review examines the molecular basis of HCC and the adjunctive potential of phytochemicals, emphasizing that extract variability, limited clinical evidence, and possible herb-drug interactions should be addressed to enable their safe and effective incorporation into standard therapy.

Implication for health policy/practice/research/medical education:
The study highlights the value of affordable, safe therapeutic alternatives for policy, supports the use of natural compounds in liver cancer, emphasizes the need for further research on bioactive molecules, and encourages inclusion of evidence-based traditional medicine in medical education for integrative healthcare.

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Introduction

Hepatocellular carcinoma (HCC) remains one of the most challenging cancers worldwide due to its complex pathogenesis and poor prognosis (1). The development and progression of HCC are driven by a multitude of molecular alterations that disrupt normal cellular functions such as proliferation, apoptosis, angiogenesis, and immune regulation (2). As illustrated in Figure 1, a multitude of etiological factors, including chronic viral infections, inherited metabolic disorders, fatty liver disease,

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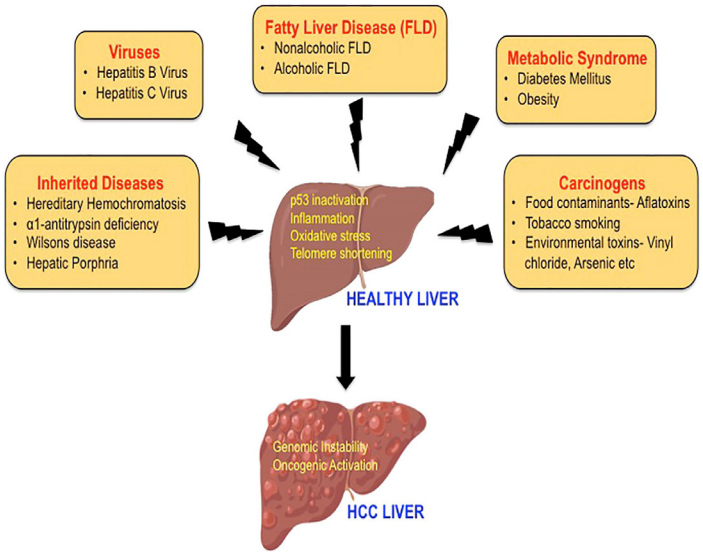

Figure 1. Schematic representation of the major etiological factors and molecular mechanisms involved in the pathogenesis of hepatocellular carcinoma (HCC). Reproduced from Suresh et al (4) under the terms of the Creative Commons Attribution License (CC BY).

metabolic syndrome, and exposure to environmental carcinogens, contribute to persistent hepatic damage. These pathological triggers initiate complex molecular events involving oxidative stress, inflammatory responses, telomere shortening, and suppression of the p53 regulatory pathway. The progressive accumulation of such cellular alterations fosters genomic instability and activates oncogenic signaling cascades, thereby driving the gradual transformation of normal hepatocytes into malignant cells characteristic of HCC (3,4).

HCC represents a dynamic network of malignant hepatocytes, stromal cells, immune infiltrates, and extracellular components (1). This environment accelerates tumor progression through unchecked proliferation, angiogenesis, and metastatic spread. Moreover, the tumor microenvironment (TME) enables immune escape and increases the risk of recurrence. Owing to its pivotal role, the TME is now recognized as both a reservoir of diagnostic biomarkers and a promising therapeutic target in HCC (3).

Current treatment options for HCC, including liver transplantation, surgical resection, and loco-regional therapies, often yield limited success, especially in advanced stages (4). Furthermore, the efficacy of systemic chemotherapies is frequently compromised by the presence of underlying liver dysfunction and intrinsic resistance mechanisms within tumor cells (5). Consequently, there is a growing emphasis on exploring novel therapeutic approaches that specifically target the aberrant molecular pathways involved in hepatocarcinogenesis (6).

In this context, natural products derived from medicinal plants have attracted significant interest due to their diverse bioactive compounds and ability to modulate multiple signaling cascades (7). Phytochemicals such as alkaloids, flavonoids, terpenoids, phenolic acids, and glycosides are known to exert antitumor effects by influencing critical molecular events, including the suppression of uncontrolled cell division, activation of programmed cell death, inhibition of new blood vessel formation, and enhancing immune surveillance against malignant cells (8,9).

Several plant-derived compounds have shown promising activity against HCC by targeting key molecular pathways. For instance, curcuminoids from *Curcuma longa* have been shown to regulate pathways related to oxidative stress, inflammation, and apoptosis thereby limiting tumor growth (10). Catechins found in green tea exhibit antioxidant properties and interfere with cancer cell proliferation and survival signaling (11). Withanolides from *Withania somnifera* and saponins present in ginseng also display potent anticancer effects by modulating cell cycle regulators and inducing apoptosis (12). Among these, phytochemicals such as alkaloids are particularly notable for their ability to interrupt tumor progression by targeting multiple signaling mechanisms and triggering both intrinsic and extrinsic apoptotic pathways (13). The aforementioned multitargeted mode of action not only inhibits tumor development but also helps to overcome the resistance often encountered with conventional chemotherapy (14).

Understanding how these natural compounds interact with the molecular machinery of HCC is crucial for harnessing their full therapeutic potential (15). Continued research into the pharmacological properties and mechanisms of action of herbal extracts may pave the way for the development of more effective, safer, and accessible treatment options (16). Integrating natural product-based therapies with existing practices holds promise for improving patient outcomes and raising public awareness about the role of herbal medicine in combating hepatic

cancer (17).

A thorough understanding of these genetic and molecular aberrations is crucial for developing early diagnostic tools and advancing precise, molecularly targeted therapies (18). Exploring the crucial pathways involved in HCC allows researchers to pinpoint biomarkers that support earlier diagnosis while also paving the way for therapies designed to block the core drivers of tumor growth, ultimately offering better prospects for patient care (19). This review aims to provide an integrated perspective on HCC, emphasizing the crucial role of the TME in disease progression and therapy resistance, while exploring the potential of phytochemicals to modulate multiple key molecular pathways.

Search methodology

A systematic search was performed in accordance with PRISMA 2020 recommendations to gather published evidence on phytochemicals with relevance to hepatocellular carcinoma (HCC). Four major scientific databases of PubMed, Scopus, Web of Science, and Google Scholar were searched for articles published in English from January 2000 to December 2025. The search was designed to identify studies evaluating isolated plant-derived compounds or standardized botanical extracts with documented activity against HCC or related molecular pathways.

Search terms

A combination of controlled vocabulary terms and text keywords was used. Search strings were adjusted for each database. Keywords included:

- Disease-related terms: "hepatocellular carcinoma", "HCC", "liver cancer", "primary liver tumor"
- Phytochemical and extract terms: "phytochemicals", "natural products", "plant derived compounds", "herbal extract", "standardized extract", "isolated phytoconstituent"
- Mechanistic terms: "molecular pathway", "signal transduction", "apoptosis", "autophagy", "oxidative stress", "anti-inflammatory", "anti-proliferative", "angiogenesis"

Boolean operators (AND, OR) were applied to refine the search and increase sensitivity.

Eligibility criteria

Studies were considered eligible if they:

1. Were original research articles published in peer-reviewed journals.
2. Were written in English between January 2000 and December 2025.
3. Investigated isolated phytochemicals or standardized plant extracts relevant to HCC.
4. Presented preclinical (in vitro or in vivo) or clinical findings.
5. Examined biological mechanisms, pathways, or pharmacological effects associated with HCC.

Exclusion criteria

The followings were excluded:

1. Non peer-reviewed material (conference abstracts, commentaries, dissertations, book chapters).
2. Studies not directly related to HCC or focusing on other cancers.
3. Reports using non standardized, crude or undefined plant preparations.
4. Articles without mechanistic, biological, or therapeutic data.
5. Publications not available in full text or not written in English.

Study screening and selection

The selection process adhered strictly to PRISMA guidelines. All retrieved records were exported to a reference management system, and duplicate entries were removed. Titles and abstracts were screened to remove clearly irrelevant studies. The full texts of potentially eligible articles were examined using predefined criteria. Any discrepancies in study eligibility were resolved through discussion and cross-checking of data. Reference lists of the finally included studies were screened manually to identify additional relevant publications that may not have been captured during the initial database search.

HCC pathogenesis: A molecular and cellular perspective

Hepatocarcinogenesis is driven by recurrent genetic alterations in critical genes, including telomerase reverse transcriptase (*TERT*), tumor protein p53 (*TP53*), catenin beta 1 (*CTNNB1*), axis inhibition protein 1 (*AXIN1*) and at-rich interactive domain containing protein 1A (*ARID1A*) (20,21), which impair telomere maintenance, DNA repair, cell cycle regulation, and transcriptional control (22,23). These disruptions enable uncontrolled cell proliferation, genomic instability, and resistance to apoptosis (24).

Chronic inflammatory signaling and oxidative stress promote genomic instability and epigenetic repression of tumor suppressor genes, while facilitating immune evasion through checkpoint pathways, such as the PD-1/PD-L1 axis, thereby accelerating hepatocarcinogenesis (25,26). Abnormal regulation of key oncogenic signaling pathways, including the Wnt/β-catenin, PI3K/AKT/mTOR, and MAPK/ERK pathways, plays a major role in accelerating tumor proliferation, new blood vessel formation, and metastatic spread (27,28). In addition, changes in epigenetic mechanisms, such as irregular DNA methylation, altered histone modification, and disrupted activity of non-coding RNAs, alter gene expression patterns, thereby supporting tumor growth and treatment resistance (29). Metabolic reprogramming also serves

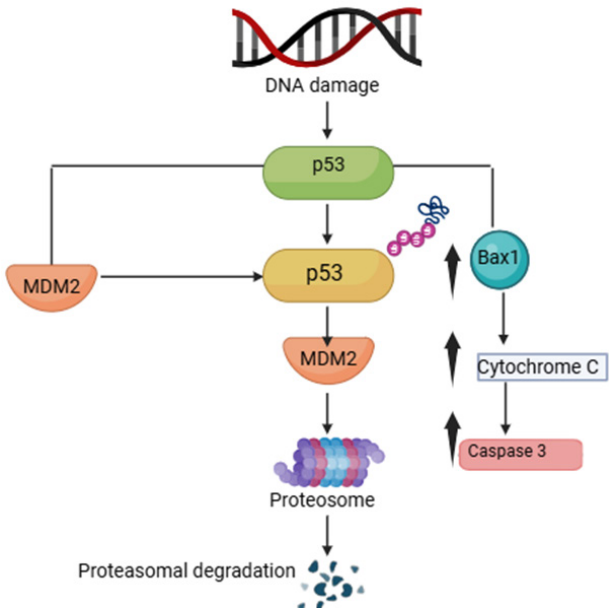

Figure 2. Regulation of p53 protein in hepatocellular carcinoma (HCC): The role of murine double minute 2 (MDM2) mediated ubiquitination.

as an essential adaptive process that ensures cancer cell survival. The Warburg effect, marked by enhanced aerobic glycolysis despite sufficient oxygen levels, enables tumor cells to meet the increased energy and biosynthetic demands necessary for rapid proliferation within the TME (30).

A hallmark of HCC progression is the synergy between impaired apoptosis and aberrant angiogenesis. Vascular endothelial growth factor (VEGF)-induced neovascularization ensures a steady supply of nutrients and oxygen, while enhancing the invasive capacity, whereas altered apoptotic regulation enables malignant cells to evade programmed cell death and persist (25,28). A comprehensive understanding of the molecular and cellular mechanisms driving HCC is vital for advancing early detection strategies and precision therapies. Current research has identified several genetic markers that contribute to HCC development, which have been extensively characterized and discussed (20).

Genetic drivers of HCC: An integrated perspective

HCC, the most common primary liver cancer, arises from early and frequent TERT promoter mutations along with other genetic and epigenetic changes that disrupt cellular regulation and promote malignancy (31). These promoter mutations, occurring in approximately 44% to 59% of HCC cases, increase the binding of the GA-binding protein (GABP) transcription factor, thereby enhancing *TERT* gene expression and telomerase enzyme activity (32). A key feature of cancer progression enables cells to maintain telomere length, avoid senescence, and continue to proliferate uncontrolled. Their early occurrence, particularly in cirrhotic livers, makes *TERT* promoter mutations significant diagnostic markers and therapeutic targets (31).

Another pivotal genetic alteration in HCC involves the *TP53* gene, which is mutated in approximately 35% to 50% of patients. The p53 protein functions as a critical tumor suppressor, regulating DNA repair, cell cycle arrest, programmed cell death, cellular aging, and metabolic balance (33). Most *TP53* mutations affect the DNA-binding domain, impairing p53's ability to regulate gene expression and allowing hepatocytes with abnormal chromosomal numbers to survive and proliferate (Figure 2). These mutations contribute to chromosomal instability and centrosome amplification, often correlating with poorly differentiated tumors and poorer outcomes (34).

The *CTNNB1* gene encodes β-catenin, a protein essential for cell-to-cell adhesion and for intracellular signaling through the Wnt/β-catenin pathway (30). Activating mutations of *CTNNB1* are found in 20% to 40% of HCC cases, leading to constitutive Wnt pathway signaling that drives tumor cell proliferation and impairs DNA repair fidelity (35). Moreover, Wnt/β-catenin pathway activation has been shown to increase *TERT* transcription and telomerase activity by linking these pathways in the progression of liver cancer. Notably, *CTNNB1* mutations rarely coincide with *TP53* mutations, suggesting distinct molecular subgroups within HCC (36).

AXIN1 plays an opposing role as a negative regulator of the Wnt/β-catenin pathway by promoting the degradation of β-catenin. Mutations in *AXIN1* present in approximately 5% to 10% of HCC cases lead to dysregulated Wnt signaling and tumor progression. Generally, *AXIN1* and *CTNNB1* mutations do not occur together, as they have antagonistic functions within the same signaling cascade (37).

The laminin subunit alpha 2 (LAMA2) gene, which encodes a key protein in the muscle basement membrane, is a potential tumor suppressor in liver cancer. Despite its frequent study in muscular diseases, LAMA2 mutations occur in 5% to 12% of HCC patients (35). The LAMA2 gene, which plays a crucial role in mediating cell adhesion and survival as a component of the basement membrane, is a potential tumor suppressor in liver cancer. However, its exact function in hepatocarcinogenesis requires further investigation (38).

ARID1A, which encodes a core subunit of the SWI/SNF chromatin remodeling BAF sub-complex, plays a critical role in controlling gene expression by repositioning nucleosomes. Its abnormalities, along with those of ARID2, are increasingly implicated in the pathogenesis of HCC. This complex controls gene expression by modulating nucleosome positioning and chromatin accessibility, thereby influencing transcription, DNA replication, and repair (39). Mutations in *ARID1A*, seen in about 20% of HCC cases, impair DNA mismatch repair and promote tumor aggressiveness and metastasis. Tumors deficient in *ARID1A* may respond to epigenetic therapies

and immune checkpoint inhibitors, making *ARID1A* a valuable biomarker for personalized treatment (40).

Similarly, *ARID2*, a component of the polybromo-associated BAF (PBAF) complex, is crucial for regulating interferon signaling and DNA damage. Inactivating mutations and deletions in *ARID2* occur in 5% to 10% of HCC cases, particularly those associated with chronic HCV infection (39). Loss of *ARID2* enhances epithelial-mesenchymal transition (EMT), facilitates immune escape, and increases metastatic potential (41). Furthermore, *ARID2* deficiency has been linked to resistance to immune checkpoint therapies, underscoring its role in modulating the tumor immune microenvironment (42). HCC arises through a complex network of genetic changes affecting telomere maintenance, tumor suppressor pathways, oncogenic signaling cascades, extracellular matrix components, and chromatin remodeling machinery. A comprehensive understanding of these molecular alterations is crucial for enhancing early detection and developing targeted, precision-based therapies for liver cancer management (43).

Phytochemicals with anticancer potential in hepatic cancer: Focus on alkaloids, flavonoids, saponins, and terpenoids

Natural compounds derived from medicinal plants have gained substantial attention in oncology due to their multi-targeted mechanisms and lower toxicity profiles compared to conventional chemotherapeutics (44). In HCC, the leading form of primary liver cancer, phytochemicals such as alkaloids, flavonoids, saponins, and terpenoids have emerged as key candidates due to their capacity to modulate diverse molecular targets. These agents interfere with cell proliferation, apoptosis, angiogenesis, metastasis, oxidative stress, and immune evasion mechanisms central to liver tumor progression (45). The following section explores each class of these phytochemicals in the context of HCC, integrating recent mechanistic insights and experimental validations.

Alkaloids

Alkaloids are nitrogen-rich plant metabolites known for their potent bioactivity, particularly in cancer therapeutics. In HCC, various alkaloids have demonstrated efficacy by initiating mitochondrial-mediated and receptor-mediated apoptotic pathways (46). In vitro studies have shown that berberine modulates the Bax/Bcl-2 ratio and activates caspase cascades, effectively limiting the viability of HCC cell lines. Moreover, berberine disrupts the PI3K/AKT/mTOR axis, a key survival pathway in HCC, thereby promoting apoptosis and autophagy (47).

Camptothecin, a quinolone alkaloid, inhibits DNA topoisomerase I, causing replication stress and apoptosis in hepatoma models. It also downregulates VEGF, impeding neovascularization, a critical feature of HCC progression (38). Vincristine, a vinca alkaloid, disrupts microtubule assembly, inducing mitotic arrest and inhibiting tumor growth, and has been repurposed in nanoformulations to enhance hepatic specificity with reduced systemic toxicity. Furthermore, recent research has highlighted the immunomodulatory effects of alkaloids in HCC (40). Some compounds inhibit nuclear factor kappa light chain enhancer of activated B (NF-κB) activation and reduce pro-inflammatory cytokines, which are implicated in HCC-associated chronic inflammation (42).

Flavonoids

Flavonoids have shown significant promise in liver cancer therapy due to their pleiotropic actions. Quercetin has shown apoptotic action in human hepatocellular carcinoma G2 (HepG2) cells by activating caspase-3/9 and generating intracellular reactive oxygen species (ROS), leading to mitochondrial dysfunction. In addition to apoptosis induction, quercetin downregulates cyclin D1 and cyclin-dependent kinase 4 (CDK4), arresting the cell cycle in the G1 phase (48).

Polyphenols such as epigallocatechin-3-gallate (EGCG), ellagic acid, and curcuminoids show significant promise against HCC. EGCG inhibits cell proliferation, angiogenesis, and invasion by downregulating MMP-2/9 and VEGF and enhancing Nrf2-mediated antioxidant response (46). Ellagic acid suppresses cell proliferation and migration via the PI3K/Akt pathway, while curcuminoids inhibit key pathways like NF-κB, STAT3, and Wnt/β-catenin. Luteolin inhibits STAT3 phosphorylation and suppresses EMT markers, thereby blocking metastasis. Apigenin acts as a chemosensitizer, enhancing sorafenib efficacy in resistant HCC cells by modulating MAPK and AMPK pathways (48). The novel paradigm of flavonoids' dual redox modulation, providing antioxidant protection in normal cells and prooxidant stress in cancerous cells, underpins their therapeutic selectivity (49).

Saponins

Saponins, particularly those derived from ginseng, soybeans, and quinoa, possess amphipathic structures that disrupt membrane integrity and enhance immune function. Ginsenoside Rg3, a triterpenoid saponin, has shown consistent anti-HCC activity by downregulating angiogenesis-related proteins and inhibiting hypoxia inducible factor-1α (HIF-1α) in both *in vitro* and *in vivo* models (50).

Rh2, another ginsenoside, promotes mitochondrial depolarization and activates the caspase-8/9 pathway in HepG2 cells. The ginsenoside Rh2 targets TGF-β/Smad signaling, an action that reverses hepatic fibrosis, a well-established precursor to HCC. In addition, saponins as a class demonstrate valuable immunomodulatory effects by promoting dendritic cell maturation and stimulating cytotoxic T cell activity (51). For instance, quillaja saponins

stimulate the production of tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ), thereby promoting an antitumor immune microenvironment. The ability of saponins to alter tumor immune evasion mechanisms is increasingly recognized as a valuable attribute in liver cancer immunotherapy (49).

Terpenoids

Terpenoids, a large class of natural compounds synthesized from isoprene units, have shown multifaceted anti-HCC actions. Derivatives of artemisinin, such as dihydroartemisinin, are being explored in combination with checkpoint inhibitors for their ability to trigger immunogenic cell death, while artemisinin itself promotes apoptosis through ROS elevation, confirmed by intracellular detection using the 2′,7′-dichlorofluorescin diacetate (DCFDA) assay (48).

Paclitaxel, originally derived from *Taxus brevifolia*, stabilizes microtubules and arrests the cell cycle in the G2/M phase. Nano encapsulation of paclitaxel has significantly improved its hepatic bioavailability and reduced off-target toxicity (52). Among newer discoveries, limonene, a monoterpene found in citrus peel, has been shown to inhibit hepatic tumor growth by targeting the PI3K/AKT/mTOR axis and reducing glutathione levels, sensitizing HCC cells to oxidative stress. Moreover, β-carotene, beyond its antioxidant action, exerts prooxidant effects in cancerous hepatocytes by disrupting mitochondrial electron transport, triggering apoptosis (53) (Table 1).

In vitro and *in vivo* investigations of herbs in liver cancer

In vitro studies and molecular mechanisms regulate the expression of non-coding RNAs such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), which are critical modulators of gene networks governing tumor growth, invasion, metastasis, and chemoresistance (54,55). By restoring balanced RNA-mediated regulation and inhibiting oncogenic signaling, these compounds induce cell cycle arrest at multiple checkpoints, thereby restricting HCC cell proliferation *in vitro*. Together, these findings underscore the synergistic modulation of signaling pathways and non-coding RNAs as a compelling mechanistic foundation for phytochemical-based HCC therapy and support further preclinical exploration (56).

In vivo evidence and immunomodulation

Preclinical investigations using ginsenoside Rg3 have also demonstrated quantifiable antimetastatic activity. Oral or intravenous dosing significantly reduced the number of pulmonary metastatic nodules in mice inoculated with B16-BL6 melanoma or colon 26-M3.1 carcinoma cells. Furthermore, carcinogen-induced HCC models and xenografts have shown measurable efficacy of phytochemicals (57). In the Yoshida AH-130 ascites hepatoma model, systemic administration of curcumin (20 μg/kg for six days) reduced tumor cell burden by approximately 31%. Similarly, in WAG/RijHsd rats with CC531 liver implants, daily treatment with curcumin (200

Table 1. Phytochemicals with key targets and cellular actions in hepatocellular carcinoma (HCC)

Phytochemical class	Representative compounds	Molecular targets and pathways	Cellular effects	Reference
Alkaloids	Berberine, camptothecin, and vincristine	Apoptosis: Caspase activation, Bax/Bcl-2 modulation. Cell cycle/Proliferation: DNA topoisomerase I, microtubule dynamics.	Induces apoptosis and autophagy, disrupts DNA replication, and arrests mitosis.	(38,40,42, 46,47)
Flavonoids	Quercetin, epigallocatechin gallate, ellagic acid, curcuminoids, luteolin, and apigenin	Apoptosis: Caspase-3/9. Cell cycle/Proliferation: Cyclin D1/CDK4, Wnt/β-catenin, STAT3, MAPK and PI3K/Akt. Angiogenesis/Metastasis: VEGF, MMP-2/9, NF-κB, and EMT. Oxidative stress/Defense: Nrf2, AMPK	Promotes mitochondrial apoptosis, induces cell cycle arrest, and inhibits proliferation.	(46,48,49)
Saponins	Ginsenoside Rg3, Rh2 and *Quillaja saponins*	Apoptosis: Caspase-8/9, mitochondrial disruption. Angiogenesis/Fibrosis: HIF-1α, TGF-β/Smad.	Triggers mitochondrial apoptosis and inhibits angiogenesis and fibrosis.	(49-51)
Terpenoids	Artemisinin, paclitaxel, limonene, and β-carotene	Apoptosis/DNA damage: Caspases, DNA interaction, microtubule disruption. Cell cycle/Proliferation: PI3K/AKT/mTOR pathway.	Induces apoptosis and DNA damage; enforces cell cycle arrest; triggers immunogenic cell death and sensitizes tumor cells to oxidative stress.	(52,53)

PI3K/AKT/mTOR: Phosphoinositide 3-kinase/protein kinase B/mechanistic target of rapamycin; VEGF: Vascular endothelial growth factor; CDK4: Cyclin-dependent kinase; STAT3: Signal transducer and activator of transcription 3, MAPK: Mitogen-activated protein kinase; MMP-2/9: Matrix metalloproteinase-2/9; EMT: Epithelial-mesenchymal transition, Nrf2: Nuclear factor erythroid 2-related factor.

mg/kg) slowed tumor progression by 5.6-fold compared to untreated controls (58). Beyond tumor growth and metastasis, curcumin has been shown to modulate TME, for instance, in HCC xenografts, it decreased myeloid-derived suppressor cell accumulation while suppressing TLR4/NF-κB activation and lowering circulating IL-6, IL-1β, GM-CSF, and G-CSF levels (54). These quantified reductions in tumor volume, metastatic spread, and immune suppressive signaling highlight the distinct pharmacological profiles of curcumin, ginsenoside Rg3, and silymarin, thereby supporting their translational relevance in HCC therapy (Table 2).

Clinical insights and translational challenges

Although clinical studies remain limited, the available data are encouraging. Silymarin, extracted from *Silybum marianum*, has demonstrated hepatoprotective and antioxidant effects in individuals with liver dysfunction, and preliminary evidence suggests its potential benefits in early-stage HCC (56). Similarly, curcumin has shown the capacity to improve symptoms and stabilize disease progression in pilot trials, despite bioavailability concerns that have prompted the development of enhanced formulations like nanoparticles and liposomal carriers (59). The ginsenoside Rg3 has exhibited efficacy in reducing chemotherapy-induced toxicity and improving treatment outcomes when used in combination with conventional therapies. Additionally, combining plant-derived compounds with immune checkpoint inhibitors, such as those targeting PD-1 and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), is emerging as a novel strategy to strengthen anti-tumor immune responses (60) (Table 3).

Synergistic integration with conventional therapies: Chemotherapy and immunotherapy

Integrating herbal compounds with conventional cancer treatments offers a promising strategy to enhance therapeutic efficacy and minimize adverse effects. Recent studies have demonstrated that compounds such as curcumin and EGCG can sensitize HCC cells to chemotherapeutic agents like sorafenib and doxorubicin (61). This sensitization occurs through modulation of drug efflux transporters, apoptosis regulators, and autophagy pathways. Furthermore, saponins and terpenoids have been shown to potentiate immune responses by activating NK cells, dendritic cells, and cytotoxic T lymphocytes (62). This activation amplifies the efficacy of immunotherapies, including immune checkpoint inhibitors, by overcoming tumor-induced immunosuppression within the hepatic TME.

Recent studies emphasize the role of herbal extracts in reversing tumor-induced immunosuppression within the hepatic TME, facilitating a more robust response to immune checkpoint blockade (63). Additionally, combination therapies utilizing herbal compounds and nanotechnology-based drug delivery systems are being explored to achieve targeted, controlled release and improved pharmacodynamics. These evolving strategies underscore the potential of phytochemicals as adjunctive agents in multimodal treatment protocols for HCC, aiming to optimize efficacy, reduce toxicity, and overcome therapeutic resistance (64) (Table 4).

Therapeutic promise of phytochemicals in the precision management of liver cancer.

Plant-based therapies rooted in traditional medicine

Table 2. Potency and dose profiles of phytochemicals in experimental models of hepatocellular carcinoma (HCC)

Compound	*In vitro* efficacy (IC_{50} / effective concentration)	*In vivo* dose	References
Curcumin	Reported IC_{50} values of 15–30 μM in HepG2 cell lines.	Demonstrated efficacy at 50–200 mg/kg orally in mouse models	(55)
Ginsenoside Rg3	IC_{50} values ranging from 287–462 μM in HCCLM3 cell lines	Shown to suppress tumor growth at 10–40 mg/kg/day in murine studies	(57)
Silymarin	Exhibited IC_{50} values of 58–75 μM in HepG2 and Hep3B cells under hypoxic conditions	Effective in rodents at 100–300 mg/kg, given orally or intraperitoneally	(54)

HCCLM3: Human hepatocellular carcinoma liver metastasis 3; HepG2: Human hepatocellular carcinoma cell line G2.

Table 3. Clinical evaluation of silymarin, curcumin, and ginsenoside Rg3 in hepatocellular carcinoma (HCC)

Compound	Study title	Study type	Sample size	Duration	Population	Reference
Silymarin	Silymarin treats patients with liver disorders caused by cancer therapy	Clinical trial	Not specified	Not specified	HCC patients with liver dysfunction	56
Curcumin	The potential immune-stimulating effect of curcumin, piperine, and taurine combination in HCC.	Phase II	26 patients	3 months	HCC patients	59
Ginsenoside Rg3	Ginsenoside Rg3 inhibits HCC.	*In vitro*/clinical pilot	Not specified	Not specified	HCC cell line (HepG2)	60

Table 4. Recent advances in synergistic effects of herbal phytochemicals with conventional therapies in Hepatocellular carcinoma (HCC)

Herbal/ Phytochemical extract	Conventional therapy	Synergistic effect	Mechanism /target	Recent findings	Reference
Curcumin	Chemotherapy (e.g., cisplatin)	Enhances apoptosis, reduces drug resistance	Inhibits PI3K/AKT signaling, modulates apoptosis regulators, and autophagy pathways.	Curcumin sensitizes cisplatin-resistant liver cancer cells.	(65)
EGCG	Chemotherapy (e.g., doxorubicin)	Increases drug uptake and inhibits cancer stem cells	Suppresses cancer stem-like cell markers and inhibits drug efflux transporters.	EGCG reverses doxorubicin resistance and targets liver cancer stem-like cells.	(66)
Ginsenoside Rg3	Chemotherapy (e.g., sorafenib)	Improves efficacy by reducing side effects	Modulates tumor angiogenesis, induces apoptosis, and enhances drug sensitivity.	Combination with sorafenib shows enhanced tumor suppression in HCC models.	(67)
Withaferin A	Immunotherapy (e.g., PD-1 inhibitors)	Enhances immune checkpoint blockade	Increases T-cell infiltration, modulates PD-L1 expression, and activates cytotoxic T lymphocytes.	Withaferin A increases T-cell infiltration and response to PD-1 therapy.	(67)
Quillaja saponins	Immunotherapy (e.g., cancer vaccines)	Act as adjuvants to boost the immune response	Activate dendritic cells, enhance antigen presentation, and stimulate NK cells.	Saponin-based adjuvants improve dendritic cell activation and vaccine efficacy.	(68)
Resveratrol	Chemotherapy + Immunotherapy	Reduces inflammation, enhances apoptosis, and immune activity	Modulates the TME, inhibits NF-κB, and promotes apoptosis.	Resveratrol modulates TME to improve combined therapy outcomes.	(69)

EGCG: Epigallocatechin gallate; TME: tumor microenvironment.

are increasingly recognized as promising alternatives to conventional liver cancer treatments, which often pose challenges such as systemic toxicity and drug resistance. These phytotherapeutic agents exhibit anti-cancer effects and may enhance treatment outcomes while minimizing side effects (70). Many herbal extracts and bioactive substances have demonstrated promise in the treatment of HCC by modifying important oncogenic pathways, controlling immunological responses, and halting tumor growth with comparatively minimal toxicity. This renewed interest in herbal therapy is a reflection of a larger trend towards integrative methods that offer new opportunities for safer and more efficient liver cancer treatments by fusing ancient knowledge with modern pharmacological findings (71).

Silybum marianum

Silymarin obtained from *S. marianum* is a well-known medicinal herb recognized for its therapeutic properties, particularly in the management of liver disorders, characterized by its distinctive purple flowers and white veined leaves; the plant has been utilized in traditional medicine for centuries (72). The pharmacologically active component extracted from the seeds is silymarin, a complex mixture of polyphenolic flavonolignans including silybin, silydianin, silychristin, and isosilybin (73).

Silymarin exhibits a wide range of biological effects, notably antioxidant, anti-inflammatory, immunomodulatory, hepatoprotective, anti-lipidemic, antidiabetic, and anticancer activities. Its strong antioxidant potential is largely attributed to its ability to scavenge ROS, stabilize cellular membranes, and regulate detoxifying enzymes (71). These mechanisms contribute significantly to its liver-protective role and its potential application in cancer prevention and therapy (74).

Despite its promising pharmacological effects, the oral bioavailability of silymarin is relatively low. This limitation is primarily due to its poor solubility in water and extensive first-pass metabolism in the liver. However, co-administration with dietary fats has been shown to enhance its absorption. Once absorbed, silymarin undergoes both phase I and phase II metabolism, with glucuronidation and sulfation playing major roles in its biotransformation and elimination through bile and urine (74). It binds to plasma proteins and is distributed to multiple organs, including the liver, lungs, kidneys, and prostate. Additionally, silymarin is capable of crossing the blood-brain barrier, expanding its therapeutic scope beyond hepatic applications (73).

From a mechanistic standpoint, silymarin activates the Nrf2 transcriptional pathway, a critical regulator of cellular antioxidant defense. Activation of this pathway leads to the increased expression of enzymes such as heme oxygenase-1 (HO-1) and NAD (P) quinone oxidoreductase 1 (NQO1), thereby enhancing the cellular capacity to neutralize oxidative damage (72). Simultaneously, it suppresses the NF-κB signaling pathway, a central mediator of inflammatory responses, resulting in reduced expression of pro-inflammatory cytokines and attenuation of liver fibrosis.

Curcuma longa

Curcuminoids are phenolic compounds primarily extracted from the roots of *Curcuma longa*, a perennial plant that belongs to the *Zingiberaceae* family. These compounds are responsible for turmeric's distinctive yellow to orange coloration. While native to India, turmeric is now widely cultivated in tropical Asian regions such as Indonesia and China, where warm and humid climates favor its growth (75). Traditionally valued both as a spice and natural pigment, turmeric has gained scientific recognition for its broad range of biological activities (76).

The curcuminoid fraction mainly comprises curcumin, desmethoxycurcumin, and bisdemethoxycurcumin. Additionally, turmeric contains essential oils, including turmerone, zingiberene, and elemene, as well as other phytochemicals such as saponins, tannins, sugars, resins, and proteins (77). Despite its therapeutic potential, curcumin faces challenges related to poor oral bioavailability, limited absorption, rapid metabolism, and quick elimination from the body. To address these issues, advanced delivery platforms such as liposomal carriers, nanoparticles, and phytosome formulations have been developed, which significantly enhance curcumin's stability and systemic availability (78).

HCC arises from uncontrolled hepatocyte proliferation and represents a serious health burden worldwide. Curcumin acts on hepatic cells through multiple mechanisms, including the regulation of oxidative stress, inflammation, apoptosis, and inhibition of tumor growth, making it a promising candidate for adjunct therapy in HCC management (79).

Withania somnifera

Ashwagandha, which belongs to the Solanaceae family, is widely cultivated across India, Nepal, China, and Yemen. This plant is well known for its adaptogenic and therapeutic potential due to its ayurvedic potential (80). In the context of hepatic malignancies, particularly HCC, *Withania somnifera* has garnered significant attention due to its multifaceted pharmacological activities, including anti-inflammatory, immunomodulatory, and anticancer effects. One of its key actions involves the normalization of elevated cortisol levels, which can indirectly modulate stress-induced tumor progression and inflammation in liver tissue (81). The plant is widely recognized for its medicinal potential, though adverse reactions such as gastrointestinal disturbances, drowsiness, hormonal effects, and occasional hepatotoxicity. However, experimental studies suggest its bioactive constituents possess anti-inflammatory and anticancer properties, indicating a possible supportive role in HCC management when used cautiously under medical supervision (81). The hepatoprotective and anticancer potential of this plant is primarily linked to a group of bioactive steroidal lactones called withanolides. Principal constituents such as withaferin A, withanolides A, B, C, and D, along with withanosides IV and withanone, demonstrated significant chemopreventive activity by inhibiting oxidative stress, inflammation, and oncogenic signaling pathways in hepatic cells (82) (Table 5). Meanwhile, withanolides have shown cytotoxic effects against liver cancer cell lines by modulating apoptotic and proliferative mechanisms. This dual therapeutic and chemopreventive role makes *W. somnifera* a promising candidate for integrative strategies targeting HCC (81).

Camellia sinensis

Green tea is recognized for its high content of polyphenolic compounds, particularly catechins, which are present in significantly greater concentrations than in black or

Table 5. Mechanistic insights into withaferin A in hepatocellular carcinoma (HCC)

Mechanism	Biological role in HCC	Key targets/ actions	References
Cysteine binding and protein modulation.	The α, β-unsaturated carbonyl group in withaferin A (WA) reacts with cysteine residues in target proteins, modifying their function.	Alters vimentin and β-tubulin, disrupts cytoskeletal structure and signaling pathways.	(82)
Autophagy regulation.	Promotes the degradation of damaged organelles, thereby maintaining cellular homeostasis and reducing the risk of malignant transformation.	Enhances autophagic flux to remove dysfunctional proteins and organelles in hepatic cells.	(83)
Proteasomal pathway interference.	Impairs the degradation of regulatory proteins, leading to tumor cell stress and apoptosis.	Inhibits proteasomal activity, increasing the accumulation of misfolded proteins.	(84)
Heatshock response activation.	Triggers cellular stress protection mechanisms, which may inhibit tumor progression.	Induces heat shock proteins (HSP70); maintains proteostasis and stress resilience.	(84)
Enhanced cytoprotection with low toxicity.	Structural modifications of WA improve the therapeutic index by lowering cytotoxicity.	Modified analogs exhibit reduced toxicity and improved safety for chemoprevention.	(85)
Nutraceutical and chemopreventive Potential	Acts through multiple pathways to prevent the initiation and progression of HCC.	Combines antioxidant, anti-inflammatory, and antiproliferative effects for preventive application.	(85)

oolong tea. The major catechins include epicatechin (EC), epigallocatechin (EGC), epicatechin-3-gallate (ECG), and EGCG, the latter being the most abundant and biologically potent. Among these, EGCG is widely studied for its chemopreventive potential against HCC due to its ability to regulate key oxidative and inflammatory processes (86).

Oxidative stress is a crucial factor in liver carcinogenesis, where an imbalance between ROS and antioxidant defenses leads to cellular damage, genetic mutations, and tumor development. EGCG helps mitigate this by neutralizing ROS and boosting the body's antioxidant defense system. It enhances the activity of detoxifying enzymes such as superoxide dismutase (SOD) and catalase, which reduce oxidative damage (87). EGCG contributes to DNA protection by preventing oxidative lesions, thereby lowering the risk of mutation and cancer initiation in hepatic cells (86).

Chronic inflammation, often linked to liver diseases like hepatitis, fibrosis, or cirrhosis, promotes a microenvironment conducive to tumor growth. EGCG exhibits strong anti-inflammatory activity by suppressing the release of key cytokines, including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) (87). It also inhibits the NF-κB signaling pathway, a central regulator of inflammatory gene expression involved in liver cancer progression. In addition, EGCG reduces the expression of inflammation-related enzymes such as cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), further limiting pro-tumorigenic signaling (88). The antioxidant and anti-inflammatory effects of EGCG may contribute to the prevention and management of HCC by regulating critical molecular pathways. However, high intake or concentrated extracts have been associated with hepatotoxicity, iron deficiency, cardiovascular complications, and renal strain, making careful monitoring essential in HCC patients with impaired liver function (89).

Scutellaria baicalensis

Scutellaria baicalensis, commonly known as Chinese skullcap, is a traditional medicinal herb belonging to the Lamiaceae family. It is widely cultivated across East Asia, including China, Korea, and regions of Russia. The plant derives its therapeutic potential from a broad spectrum of phytochemicals, particularly baicalin, baicalein, alkaloids, and terpenoids. Increasing research has highlighted its anticancer properties, with special emphasis on HCC, one of the leading causes of cancer-related deaths worldwide. Although adverse outcomes such as hepatotoxicity, herb drug interactions, pulmonary complications, and occasional acute hepatitis have been observed, its proven ability to suppress tumor growth, induce apoptosis, and regulate inflammatory signaling underscores its promise as a supportive approach in HCC (90,91).

Mechanistic studies indicate that baicalein exerts cytotoxic effects on HCC cells by inducing the generation of ROS, thereby initiating mitochondrial-mediated apoptosis (90). It also modulates signaling pathways critical to tumor progression, including the PI3K/Akt, MAPK, and NF-κB pathways. Baicalin, on the other hand, has been shown to suppress cancer cell migration and invasion by downregulating MMP-2 and MMP-9, thereby reversing the EMT phenotype (92).

Additionally, these flavonoids have been reported to enhance the therapeutic efficacy of standard chemotherapeutic agents. For instance, the coadministration of baicalein with sorafenib has been shown to potentiate antitumor effects and reduce resistance in HCC, primarily through the downregulation of survivin, an apoptosis-inhibiting protein. This combinatorial strategy has opened new avenues for integrative therapy in liver cancer management (93). To overcome the limitations associated with the poor bioavailability of these compounds, novel nanotechnology-based drug delivery systems have been developed (92). Nano formulations containing baicalein and baicalin have demonstrated improved pharmacokinetic properties, enhanced tumor-specific accumulation, and sustained antitumor activity in HCC models (Table 6). These advances support the potential integration of this plant and its bioactives into modern therapeutic regimens for liver cancer (91).

Artemisia annua

Artemisia annua, commonly known as sweet wormwood,

Table 6. Modulation of key molecular pathways in hepatocellular carcinoma (HCC) by *Scutellaria baicalensis*

Molecular target/pathway	Reported biological activity of *Scutellaria baicalensis*	Reference
Bax/Bcl-2 Ratio	Enhances apoptotic signaling by increasing the Bax/Bcl-2 ratio, favoring mitochondrial-mediated programmed cell death in HCC cells.	(92)
Connexins (Cx26, Cx43)	Suppresses metastatic potential by downregulating connexins, thereby impairing intercellular communication, which is critical to invasion and migration.	(93)
Endoplasmic reticulum (ER) stress marker	Triggers ER stress via ATF6 pathway activation, disrupting protein homeostasis and promoting cell death under oncogenic stress.	(94)
PI3K/Akt/mTOR signaling axis	Inhibits tumor proliferation and survival by downregulating PI3K/Akt/mTOR signaling, a pathway frequently upregulated in liver tumors.	(95)

Bax: Bcl-2-associated X protein (pro-apoptotic protein); Bcl-2: B-cell lymphoma 2 (anti-apoptotic protein); ATF6: Activating transcription factor 6.

is a traditional medicinal herb native to Asia and cultivated in various regions, including Vietnam, China, India, and Nigeria (96). While it is historically recognized for its potent antimalarial activity through the compound artemisinin, recent investigations have revealed its broader pharmacological potential, particularly in cancer therapeutics. It holds potential in HCC treatment, but its use can cause side effects. High or extended doses may result in liver toxicity, digestive disturbances, and increased oxidative stress. Additionally, it can affect cytochrome P450 enzymes, potentially altering the metabolism of anticancer medications and reducing their effectiveness, underscoring the need for careful dosing and thorough clinical assessment. The plant contains numerous bioactive constituents such as dihydroartemisinin, artesunate, flavonoids, polyphenols, phenolic acids and coumarins that contribute to its diverse biological effects (97).

In HCC, artemisinin derivatives exert their anticancer properties through multiple mechanisms. Dihydroartemisinin (DHA) induces apoptosis by promoting oxidative stress and mitochondrial dysfunction and disrupting cellular redox homeostasis. It modulates key oncogenic pathways, including the suppression of c-Myc expression and inhibition of Wnt/β-catenin signaling, thereby impairing tumor proliferation and invasiveness (98). Additionally, DHA has been shown to influence epigenetic regulators such as histone acetylation, leading to reprogramming of gene expression in liver cancer cells. Artesunate, another potent derivative, inhibits angiogenesis by downregulating hypoxia-inducible factors, while also inducing immunogenic cell death that enhances anti-tumor immune responses. It can trigger both apoptosis and ferroptosis, the latter being an iron-dependent cell death mechanism important in overcoming chemoresistance in HCC (99).

Combination therapy approaches have demonstrated that artemisinin derivatives sensitize HCC cells to chemotherapeutic agents like sorafenib, oxaliplatin and 5-fluorouracil by amplifying ER stress and blocking survival pathways such as PI3K/Akt/mTOR, which are critical for tumor cell viability. This synergistic action holds promise for enhancing therapeutic efficacy and overcoming drug resistance (95). Nanotechnology-based delivery systems have emerged as a solution to the poor bioavailability of artemisinin compounds (94). Encapsulation of DHA and artesunate into nanoparticles improves tumor-specific delivery, increases intracellular uptake, and reduces systemic toxicity in preclinical HCC models (100).

Limitations of the study

This review outlines the potential role of phytochemicals in HCC, yet some limitations must be acknowledged. Much of the available evidence is based on laboratory and animal experiments, which cannot fully capture the biological complexity of human tumors, and the number of clinical studies remains limited. Several promising compounds, including curcumin, silymarin, and withaferin A, face challenges such as poor solubility, rapid metabolism, and low systemic availability, which reduce their clinical applicability. Safety concerns also require closer attention, as certain herbal agents have been linked with hepatotoxicity, gastrointestinal discomfort, and possible interactions with conventional drugs, particularly in patients with compromised liver function. In addition, variability in plant material, cultivation practices, and extraction methods contributes to inconsistency in phytochemical content. Broader issues such as regulatory requirements, cost, and accessibility were not examined in detail but represent important barriers to clinical use. Addressing these gaps will require carefully designed clinical trials, novel delivery approaches to improve bioavailability, standardization of preparation methods, thorough safety assessment, and stronger collaboration among scientists, clinicians, and regulatory bodies to translate laboratory findings into safe and effective therapies for patients with HCC.

Conclusion

HCC arises from a complex interaction of environmental triggers, genetic mutations, and epigenetic changes. Chronic liver diseases such as viral hepatitis, alcohol related damage, and fatty liver conditions initiate ongoing cycles of inflammation and tissue repair, which lead to genetic instability and disruptions in key cellular functions. Mutations in crucial genes undermine the normal controls that regulate cell growth, allowing tumors to develop and progress. Additionally, changes in gene expression driven by epigenetic factors and the supportive TME further encourage cancer growth and help the tumor evade the immune system. Understanding these overlapping mechanisms is essential for developing effective prevention and treatment strategies. In recent years, herbal extracts have gained attention for their broad biological effects and relatively low toxicity. Natural compounds found in plants like milk thistle, turmeric, ashwagandha, and green tea offer antioxidant, anti-inflammatory, and anticancer activities by influencing critical molecular pathways such as NF-κB and PI3K/AKT, which play key roles in regulating inflammation, cell survival, and tumor progression. Improved formulation methods have enhanced the delivery and potency of these natural substances, supporting their integration with modern medical treatments. Combining traditional herbal wisdom with contemporary pharmacology presents a promising path toward more effective and safer options for managing liver cancer. Advancing HCC management requires rigorous evaluations, clinical trials, and regulatory clarity to integrate plant-derived agents into evidence-based therapy.

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Conflict of interests

The authors declare no conflict of interest.

Ethical considerations

This article is a review and does not involve human or animal samples. The manuscript complies with ethical publishing standards and is free from plagiarism, as verified by comprehensive checks. All information results from a fair synthesis of published literature, with strict adherence to academic integrity.

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