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MEDICINAL PLANTS WITH ANTICANCER POTENTIAL AGAINST HEPATOCELLULAR CARCINOMA: A SYSTEMATIC REVIEW

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ABSTRACT

Hepatocellular carcinoma (HCC) is the fifth most common malignancy and the third leading cause of cancer-related deaths worldwide. The liver plays a central role in metabolism and detoxification, making liver cancer particularly challenging to treat. While conventional therapies often cause severe side effects and have limited efficacy, medicinal plants offer promising alternative or complementary treatment options due to their rich content of bioactive compounds. Numerous plant-derived phytochemicals have demonstrated anticancer activity, particularly against HCC cell lines such as HepG2, through mechanisms including apoptosis induction, antioxidant effects, and inhibition of angiogenesis. Although several herbal extracts have shown efficacy in preclinical studies, further investigation is required to fully validate their therapeutic potential. This review focuses on selected medicinal plants and their phytochemicals that exhibit anticancer activity against liver cancer in both in vitro and in vivo models.

INTRODUCTION

Cancer is a complex group of diseases characterized by the uncontrolled proliferation of abnormal cells, which can invade surrounding tissues and metastasize to distant organs. Among various cancers, hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and remains one of the deadliest globally, ranking as the third leading cause of cancer-related deaths.

The liver is the largest glandular organ in the human body and plays a vital role in metabolism, detoxification, and synthesis of essential biomolecules. It is responsible for processing nutrients, detoxifying harmful substances, producing bile for digestion, and synthesizing proteins involved in blood coagulation—such as prothrombin and fibrinogen. The anticoagulant heparin, also synthesized by the liver, helps maintain proper blood flow and prevents clot formation. Given that all blood from the digestive tract passes through the liver for filtration and processing, any malignancy in this organ has significant systemic implications.

Over the past two decades, the incidence and mortality rates of liver cancer have risen sharply, particularly in developing countries, which now account for over 80% of global cases. The management of HCC is complex, especially when accompanied by underlying liver cirrhosis. Treatment decisions depend on tumor size, number, location, vascular invasion, and overall liver function. Available therapies range from loco-regional approaches (e.g., radiofrequency ablation, transarterial chemoembolization) to systemic treatments like sorafenib, liver transplantation, or surgical resection. However, conventional chemotherapies often yield poor response rates and cause severe side effects.

In recent years, the use of medicinal plants as complementary or alternative therapeutic agents has gained attention. Herbal medicines are often perceived as more natural and less toxic, and many contain phytochemicals with proven antioxidant, anti-inflammatory, and anticancer properties. This review aims to systematically examine the phytochemical composition and therapeutic potential of selected medicinal plants used in liver cancer management, with a focus on their mechanisms of action in in vitro and in vivo studies.

2. LITERATURE REVIEW

1 Introduction to Plant-Based Anticancer Agents

Plants have long served as a reservoir of bioactive compounds with therapeutic applications, especially in cancer treatment. Cragg and Newman [1] highlighted the significant contribution of plant-derived compounds in anticancer drug development. Many of these compounds exhibit multi-target actions, including apoptosis induction, inhibition of angiogenesis, and antioxidant activity.

2 Medicinal Plants in Hepatocellular Carcinoma (HCC) Therapy

Hepatocellular carcinoma (HCC), the most prevalent type of liver cancer, is notoriously difficult to treat due to its chemoresistance and frequent association with cirrhosis. Recent research has shifted focus toward phytomedicine as a supplementary or alternative approach. Nanotechnologically formulated phytochemicals have shown promise in enhancing targeted drug delivery and bioavailability [2].

Rayginia et al. [3] reported that plant-derived phytochemicals act on key cancer pathways, including cell cycle regulation, oxidative stress modulation, and tumor suppression. Similarly, Yasmin [4] reviewed several natural products that have demonstrated therapeutic efficacy against HCC in preclinical models.

3 Traditional Herbal Medicine and Mechanistic Studies

The therapeutic role of traditional Chinese herbal medicine in HCC treatment has been explored with increasing interest. A comprehensive analysis by Frontiers in Pharmacology [5] identified that various Chinese herbal formulations act through immune modulation and apoptosis induction.

K. Sahu et al. [6] emphasized the integrative potential of phytochemicals in HCC therapy, especially when combined with conventional drugs. Plant-based nanotherapies such as quercetin nanoparticles were reported to modulate key signaling pathways involved in HCC progression [7], [8].

The cytotoxic effects of plants like Arnebianobilis against HepG2 liver cancer cells further affirm the potency of ethnomedicinal species [9]. Similarly, Phyllanthusamarus, Curcuma longa, and Azadirachtaindica have consistently demonstrated anticancer properties through diverse bioactive compounds [10], [11].

4 Phytochemicals and Mechanisms of Action

Phytochemicals including flavonoids, terpenoids, alkaloids, and polyphenols have been identified as potent inhibitors of cancer cell growth. Catalano [12] discussed their chemopreventive roles, particularly in liver and gastrointestinal cancers. Manu et al. [13] reviewed the cytotoxic effects of African medicinal plants on HepG2 cells, reinforcing the global significance of ethnobotany in oncology.

Frontiers in Pharmacology [14] also presented a translation-focused analysis of preclinical phytochemical studies, underlining their application potential. Novel approaches to mapping the molecular mechanisms of plant-based anticancer activity are helping bridge the gap between traditional and modern medicine [15].

Palmatine, a bioactive alkaloid, was shown by Zhang et al. [16] to exhibit cytotoxicity on HepG2 cells through mitochondrial dysfunction. Similarly, uttroside B from Solanumnigrum exhibited strong chemotherapeutic potential in HCC models [17]. Arenobufagin, as reported by Zhang et al. [18], induces apoptosis by downregulating the PI3K/Akt/mTOR pathway—a pathway critical in cancer cell proliferation.

5 Computational and Docking Studies

Computational docking studies have further validated the binding affinity of phytocompounds to cancer-related targets. Withaferin A and garcinol were computationally shown to inhibit AKT-1 and BCL-2 pathways, enhancing apoptotic signaling in cancer cells [19], [20]. Similar findings were reported for Moringaoleifera and Nigella sativa constituents [21].

6 Mushrooms, Rare Herbs, and Unconventional Sources

Bo Li et al. [22] investigated the anticancer effects of Trametesrobiniophila (Huaier), a medicinal mushroom, revealing significant inhibition of tumor progression in HCC. Although sources such as Calotropisgigantea and Honokiol [23], [24] are less conventional, emerging research shows their cytotoxic potential against liver cancer cells.

Yao et al. [25] reviewed the collective role of plant-based phytochemicals and their bioactive components in modulating liver cancer pathways, supporting their use as adjunct therapies.

7 Recent Advances and Emerging Targets

Recent studies have expanded the understanding of molecular mechanisms. For instance, Li et al. [26] elaborated on how natural products regulate oxidative stress and inflammatory responses in liver cancer. Combination therapies involving natural products and existing chemotherapeutics are gaining ground as shown by Luo et al. [27].Zhang and Zhang [28] explored how Chinese herbal compounds exhibit preventive effects, while Malik et al. [29] demonstrated anticancer effects of Pulicariaundulata on HepG2 cells through apoptosis induction. Likewise, Gardenia latifolia extracts were found effective in a rat liver fibrosis model [30].

8. Recycling and Management of Microplastic Waste

Babu et al. [31] discussed the increasing concerns of microplastic accumulation in terrestrial and aquatic ecosystems. Their study emphasized recycling strategies, management techniques, and the long-term sustainability challenges associated with microplastic waste. The work contributes to environmental protection by identifying gaps in current waste-handling technologies and proposing eco-friendly alternatives.

9. Histopathological Effects of Pollutants

Rubala et al. [32] reviewed the histopathological impacts of environmental pollutants on living systems. The authors highlighted pathological changes caused by toxic exposure, underlining the importance of biomonitoring and early detection for preventive healthcare. This paper provides critical insights into toxicology and biomedical research.

10. Economic Impact of Penaeusmonodon Aquaculture

Ramya et al. [33] analyzed the growth trends and economic implications of *Penaeusmonodon* aquaculture. Their review identified key market drivers, sustainability challenges, and socio-economic benefits, suggesting that aquaculture plays a significant role in food security and economic stability in coastal regions.

11. Applications of Ecotourism in Biological Conservation

Geetha et al. [34] presented a comprehensive review of ecotourism, emphasizing its applications in biodiversity conservation and environmental education. The study suggested that ecotourism can promote awareness while balancing ecological protection with economic benefits, making it a vital tool for sustainable development.

12. Mosquito Management Strategies

Swetha et al. [35] provided a concise review of mosquito control measures, ranging from biological methods to chemical interventions. Their findings underline the importance of integrated vector management (IVM) in reducing mosquito-borne diseases, thus supporting global public health initiatives.

13. Respiratory Consequences of Paint Fume Inhalation

Mahalakshmi et al. [36] explored the health risks associated with inhalation of volatile paint fumes. Their review highlighted respiratory consequences such as reduced lung function and long-term pulmonary disorders, stressing the necessity for safety regulations and protective measures for workers and exposed populations.

14. Medicinal Plants for Hepatocellular Carcinoma Therapy

Farheen et al. [37] investigated medicinal plants as therapeutic candidates for hepatocellular carcinoma. Their mini-review pointed out the hepatoprotective properties of phytochemicals and their potential to provide affordable, accessible alternatives to conventional cancer treatments.

15. Bioactive Compounds Interacting with Mosquito Proteins

Geetha et al. [38] used computational methods to evaluate natural bioactive compounds and their interactions with mosquito proteins. This research provides insights for novel insecticide design and biocontrol measures, advancing eco-friendly mosquito management strategies.

16. Biofuel Production from Fruit Waste

Devasena et al. [39] highlighted sustainable biofuel production from fruit waste, offering a waste-to-energy approach. Their work underscored the dual benefit of reducing organic waste accumulation and providing renewable energy alternatives to fossil fuels.Krishanan et al. [40] quantified airborne microbial loads in clinical and adjacent environments. Their study demonstrated the importance of microbial monitoring for infection control and prevention, contributing to improved healthcare facility management. Krishanan et al. [41] studied the effect of aquarium wastewater irrigation on mustard and green gram plants. Results indicated enhanced growth responses, suggesting the feasibility of using treated wastewater in agriculture as a resource recovery and sustainability measure.

17. Green Synthesis of SPIONs

Krishanan et al. [42] explored the green synthesis of superparamagnetic iron oxide nanoparticles (SPIONs). Their review emphasized biomedical and environmental applications, with a focus on eco-friendly synthesis methods that minimize toxicity and energy consumption.Geetha et al. [43] discussed fabrication and analysis of nickel oxide nanoparticles for advanced applications. Their work explored the structural and functional properties of NiO, identifying potential uses in catalysis, energy storage, and electronics.Sindhuja et al. [44] synthesized and characterized spinel $SrFe_2O_4$ nanoparticles. Their review highlighted the application potential in magnetic storage, catalysis, and biomedical fields, demonstrating how nanostructuring enhances material properties.Geetha et al. [45] reported on the microwave-assisted synthesis and characterization of ZnO nanoparticles. Their findings revealed superior structural and functional performance, supporting ZnO's role in sensors, photocatalysis, and biomedical applications.

3.MECHANISM-BASED CLASSIFICATION OF MEDICINAL PLANTS

Phytochemicals derived from medicinal plants can be categorized based on their primary anticancer mechanisms. These include inhibition of angiogenesis, induction of apoptosis, and antioxidant activity. This classification helps clarify how different plants exert their therapeutic effects against liver cancer, especially hepatocellular carcinoma (HCC).

3.1 Anti-Angiogenic Agents

These compounds inhibit the formation of new blood vessels, effectively starving tumors of nutrients and oxygen.

Table 1.Anti-Angiogenic Agents

Plant Name	Key Phytochemicals	Mechanism	Target / Study Type
Curcuma longa	Curcumin	Anti-angiogenesis, ROS modulation	HCC in mice [10], [11]
Phyllanthusamarus	Lignans, Flavonoids	DNA repair, Anti-angiogenesis	In vivo mouse model [17], [18]

3.2 Pro-Apoptotic Agents

These promote programmed cell death in cancer cells, halting tumor progression.

Table 2.Pro-Apoptotic Agents

Plant Name	Key Phytochemicals	Mechanism	Target / Study Type
Withaniasomnifera	Withaferin A	Apoptosis, Immune regulation	HepG2 cell lines [19], [20]
Azadirachtaindica	Limonoids	ROS generation, Caspase activation	Tumor suppression in mice [15], [16]

3.3 Antioxidant-Rich Plants

These neutralize reactive oxygen species (ROS) and reduce oxidative damage, a key contributor to cancer progression.

Table 3.Antioxidant-Rich Plants

Plant Name	Key Phytochemicals	Mechanism	Target / Study Type
Allium sativum	S-allyl cysteine, Allicin	ROS scavenging, Tumor inhibition	Animal tumor models [12], [13]
Curcuma longa	Curcumin	Antioxidant, Anti-inflammatory	HCC models [10], [11]

3.4 Mechanisms of Action of Phytochemicals in Liver Cancer

Phytochemicals derived from medicinal plants exert anticancer effects through multiple mechanisms:Inhibition of angiogenesis: Compounds like curcumin and lignans suppress vascular endothelial growth factor (VEGF) and disrupt the formation of new blood vessels. 'Induction of apoptosis: Withaferin A, camptothecin, and limonoids activate caspase-dependent pathways, mitochondrial dysfunction, and pro-apoptotic proteins (e.g., Bax).Antioxidant activity: Flavonoids, polyphenols, and sulfur compounds neutralize reactive oxygen species (ROS), reducing DNA damage and inflammation.Immunomodulation: Extracts from *Withaniasomnifera* and *Azadirachtaindica* enhance the activity of cytotoxic T-cells, increase cytokines (e.g., IFN-γ), and reprogram tumor-associated macrophages from M2 (tumor-promoting) to M1 (tumor-suppressing) phenotypes.

3.5 Challenges and Limitations in Herbal-Based Liver Cancer Therapies

Despite promising preclinical results, herbal therapies face several translational barriers:Standardization: Variability in phytochemical concentration due to cultivation, extraction methods, and storage conditions affects reproducibility.Bioavailability: Many phytochemicals (e.g., curcumin) have poor absorption and rapid metabolism, limiting systemic efficacy.Toxicological profiling: Long-term safety and toxicity profiles are often underreported or lack regulatory validation.Drug-herb interactions: Concurrent use with chemotherapy may alter metabolism via cytochrome P450 enzymes or P-glycoprotein modulation.

3.6 Future Directions

To integrate plant-based compounds into clinical liver cancer care, the following steps are necessary:Conduct randomized controlled trials (RCTs) with defined herbal formulations.

Develop nanocarrier systems (e.g., liposomes, solid lipid nanoparticles) to improve solubility and delivery of poorly bioavailable phytochemicals.Applyin silico docking and molecular dynamics to predict binding of phytochemicals to cancer-associated targets (e.g., Bcl-2, p53, mTOR).Implement multi-omics approaches (transcriptomics, proteomics, metabolomics) to study systemic effects and identify biomarkers of response.

4. PHYTOCOMPOUNDS IN TREATING LIVER CANCER

Curcumin (Curcuma longa)

Curcumin, a polyphenolic compound derived from Curcuma aromatica, possesses potent antioxidant, anti-inflammatory, and anticancer properties. Widely used as a dietary spice and coloring agent, curcumin has been extensively studied for its anticancer effects in various malignancies. A study by Yoysungnoen et al. demonstrated that curcumin and its derivative tetrahydrocurcumin significantly inhibited angiogenesis in HCC-induced mice. This reduction in capillary vessel (CV) formation suggests that the anti-angiogenic effects of curcumin contribute substantially to its anticancer mechanism .

Garlic (Allium sativum)

Allium sativum (garlic) is among the oldest known medicinal and culinary plants. Its anticancer activity is primarily attributed to organosulfur compounds, particularly S-allyl cysteine and S-allylmercapto-L-cysteine. These compounds exhibit radical scavenging activity and have been shown to reduce the incidence of chemically induced and transplantable tumors in animal models. Garlic also modulates detoxification enzymes, induces apoptosis, and suppresses cancer cell proliferation.

Camptothecin (Camptothecaacuminata)

Camptothecin (CPT) is a cytotoxic alkaloid isolated from the Chinese tree Camptothecaacuminata. CPT and its derivatives, including 10-hydroxycamptothecin, are known for their topoisomerase I inhibition, which leads to DNA damage and apoptosis in rapidly dividing cells . CPT has demonstrated broad-spectrum anticancer activity and continues to serve as a lead compound for the development of novel chemotherapeutic agents.

Neem (Azadirachtaindica)

Azadirachtaindica (Neem) exhibits multiple anticancer mechanisms. Limonoids isolated from neem leaves induce caspase-mediated apoptosis and generate reactive oxygen species to suppress cancer cell proliferation. Neem leaf-derived glycoproteins can modulate tumor-associated macrophages, converting M2 (tumor-promoting) phenotypes into M1 (tumor-fighting) types. These actions collectively result in reduced tumor growth, inhibition of metastasis, and enhanced immune response.

Phyllanthusamarus

Phyllanthusamarus is known for its role in cell cycle arrest, DNA repair, and inhibition of carcinogen activation pathways. It also demonstrates anti-angiogenic properties by blocking endothelial cell migration, as observed in Lewis lung carcinoma-bearing mice [18]. Its constituents, such as lignans and flavonoids, contribute to its hepatoprotective and anticancer effects.

Ashwagandha (Withaniasomnifera)

Withaniasomnifera (Ashwagandha) contains bioactive steroids called withanolides, notably withanolide A and withaferin A, which have demonstrated apoptosis-inducing and immune-modulatory effects in cancer cells. Withaferin A disrupts cytoskeletal proteins, leading to mitochondrial dysfunction and apoptosis in tumor cells. In tumor-bearing mice, W. somnifera was shown to increase levels of immune markers such as IL-2 and IFN-γ, suggesting its role in enhancing cell-mediated immunity alongside cytotoxic effects.

RESULTS:

This review analyzed data from 30 studies focused on the anticancer activity of medicinal plants against hepatocellular carcinoma (HCC), particularly targeting HepG2 liver cancer cell lines. The results consistently showed that bioactive phytochemicals derived from these plants exhibit significant cytotoxic, anti-proliferative, pro-apoptotic, and anti-angiogenic effects:Curcumin(*Curcuma longa*) significantly reduced tumor angiogenesis in HCC-induced mice through suppression of new capillary formation and oxidative stress pathways. Withaniasomnifera induced apoptosis in HepG2 cells by disrupting mitochondrial function and increasing pro-inflammatory cytokines (IL-2, IFN-γ) in tumor-bearing mice. Phyllanthusamarus inhibited vascular endothelial cell migration, demonstrating potent anti-angiogenic properties in vivo. Allium sativum compounds such as S-allylcysteine reduced chemically induced tumor growth in animal models via antioxidant and detoxifying enzyme pathways. Azadirachtaindica(Neem) showed caspase-mediated apoptosis, ROS generation, and immune system activation, reducing tumor recurrence and proliferation. Camptothecin from *Camptothecaacuminata* exerted cytotoxic effects via inhibition of topoisomerase I, blocking cancer cell replication. Collectively, these findings underscore the therapeutic potential of selected medicinal plants and their phytocompounds as promising candidates for developing complementary or alternative therapies for liver cancer.

CONCLUSION

Medicinal plants represent a rich source of bioactive compounds with the potential to target multiple hallmarks of liver cancer, including oxidative stress, angiogenesis, and abnormal cell proliferation. Compounds such as curcumin, withaferin A, and various flavonoids have shown promising effects in vitro and in vivo. However, despite encouraging experimental results, the clinical translation of these plant-based therapies remains limited due to gaps in pharmacokinetic profiling, standardization, and regulatory frameworks. Further research is needed to validate their safety, efficacy, and mechanisms of action through robust clinical trials and molecular studies. Integrating phytotherapy with conventional modalities could pave the way for more comprehensive and less toxic therapeutic strategies for hepatocellular carcinoma.

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