CHAPTER 32

Potential of Herbal Therapeutics for Treatment of Patients with Hepatocellular Carcinoma

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SUMMARY

The advent of targeted molecular therapies has transformed hepatocellular carcinoma (HCC) treatment by providing more personalized and effective options. Breakthroughs in genomic and proteomic profiling have led to the development of key drugs such as sorafenib, Lenvatinib, and immune checkpoint inhibitors like nivolumab, which harness the body's immune system to combat cancer. Despite these advances, challenges like drug resistance and tumor heterogeneity remain. Continued research and innovation in the field of medicinal plants are crucial to overcoming these obstacles, improving patient outcomes, and offering new hope for extended survival.

INTRODUCTION

Liver cancer, especially hepatocellular carcinoma (HCC), is a leading cause of cancer deaths worldwide. Most liver cancers are HCC, which often develops from chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, alcohol-related liver disease, and nonalcoholic fatty liver disease. The risk of HCC increases with age and is higher in men compared to women. HCC is a significant health concern, being one of the top causes of cancer-related deaths globally. Each year, it leads to around 840,000 new cases and over 780,000 deaths. Its prevalence differs around the world, with most cases found in less developed areas (Bray et al., 2018).

The development of HCC involves various risk factors, with HBV infection and exposure to Aflatoxin B1 being particularly common in these regions (Schweitzer et al., 2015). HCC is the most common type of liver cancer, responsible for the majority of cases and deaths. Currently, HBV and HCV are the main risk factors. However, their impact is expected to decline due to newborn HBV vaccinations and effective treatments for chronic HBV and HCV infections. Despite this, liver cancer prevalence is expected to keep rising in the coming years. HCC arises from various risk factors, including chronic viral hepatitis, chronic alcohol consumption, diabetes, obesity, and exposure to food toxins. The spread of these risk factors varies by geographical location and host-specific determinants.

DIAGNOSIS AND STAGING

Liver cancer treatment has come a long way, with over 10 different staging systems developed to help predict outcomes and choose the best treatment options The Barcelona Clinic Liver Cancer (BCLC) staging system is the most well-known and widely used (Liu et al., 2016). It classifies HCC into five stages: 0, A, B, C, and D. This system is especially helpful for identifying patients in the early stages, who are the best candidates for potentially life-saving treatments like liver transplantation. Despite these advances, survival rates for patients overall still leave much to be desired, highlighting the ongoing need for more effective therapies (Llovet et al., 1999).

High-risk individuals can often be diagnosed with HCC using just imaging techniques. The American College of Radiology has developed the Liver Imaging Reporting and Data System to help radiologists interpret and report findings from multiphase CT scans and MRIs (Elsayes et al., 2019). Lesions identified through this system are categorized into five groups, ranging from definitely benign to definitely cancerous. The sensitivity of these categories varies, with rates of 38, 74 and 94%, meaning that the accuracy improves as the categories become more definitive (van der Pol et al., 2019). Serum tumor markers, like AFP, aren't always reliable for diagnosing HCC since they can be elevated in other gastrointestinal cancers as well. Biopsies are typically only performed for patients who have unusual imaging results When it comes to classifying and grading (Elsayes et al., 2019). In HCC, doctors rely on specific histopathologic criteria. In some cases, certain stains like

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glypican-3, glutamine synthetase, and heat shock protein 70 can be helpful in making a diagnosis (Schlageter *et al.*, 2014).

MECHANISM OF HEPATOCELLULAR CARCINOMA PROGRESSION

HCC predominantly results from chronic hepatitis B virus infection in Asia and from non-alcoholic steatohepatitis, alcoholic cirrhosis, and chronic HCV infection in the Western world (Medavaram & Zhang, 2018). Additional risk factors include aflatoxin exposure, obesity, type 2 diabetes, heavy alcohol consumption, nonalcoholic fatty liver disease, and use of tobacco (Dimitroulis et al., 2017; Siegel et al., 2018). Effective therapy and early diagnosis of HCC remain challenging, as many patients are asymptomatic until advanced stages. Symptoms, when present, can include right upper abdominal pain, anorexia, weight loss, jaundice, fever, diarrhea, fatigue, and bone pain from metastasis. Early detection significantly improves prognosis, allowing for treatments such as surgical resection or liver transplantation. However, many patients are diagnosed too late for surgery, making chemotherapy the primary treatment option. Sorafenib, a multi-tyrosine kinase inhibitor, is commonly used but only modestly extends survival by 7 to 10 months (Keating, 2017; Personeni et al., 2018).

TREATMENT

Several factors influence the treatment options for HCC, including the disease stage, liver condition, physical health, financial status, and the quality of medical facilities. Patients with a single, small liver lesion and no cirrhosis may undergo curative resection. Radiofrequency ablation (RFA) or liver transplantation might be considered for multiple lesions, even with cirrhosis. Palliative care options like transarterial chemoembolization (TACE) or sorafenib are available for those with larger tumors, portal vein invasion, metastasis, or poor health. The BCLC staging system guides treatment decisions globally, including in Thailand, where TACE is commonly used due to its accessibility. Liver transplantation and hepatic resection are important therapies, especially for those who meet specific criteria. RFA is also used for that ineligible for surgery, with good response rates and low complications. Combination therapies, like TACE plus surgical resection, show better outcomes than single treatments. RFA combined with TACE is another effective option for larger tumors. Sorafenib is recommended for advanced HCC if locoregional therapy isn't feasible, showing improved survival rates in studies. For patients in the terminal stage, best supportive care is crucial, focusing on managing symptoms and providing psychological support. Understanding treatment goals and addressing end-of-life care are essential aspects of care for these patients.

PRESENT DAY INNOVATIVE MEDICINES

Surgery, particularly liver transplantation (LT) and liver resection, is crucial in treating HCC. However, guidelines vary in their criteria for selecting patients for these procedures, posing challenges in decision-making. Some patients with well-preserved liver function may still face hurdles for resection due to factors like portal vein hypertension. The Milan criteria, used for LT selection, have limitations that exclude some patients. Alternative criteria proposed by the University of California in San Francisco show promise but need further validation. Developing a universally accepted classification system for assessing liver status in HCC patients remains essential for optimizing treatment decisions.

Currently, sorafenib is the only FDA-approved systemic medication for HCC treatment. However, several new drugs are under clinical trials with varying outcomes. The BCLC clinical algorithm is widely used for staging HCC, considering factors like liver function, bilirubin levels, portal hypertension, and performance status. Other staging systems, like the Japanese Integrated Scoring system (JIS) and the Cancer of the Liver Italian Program (CLIP), are also used in different regions. With all these available treatment options and advancements, medicinal plants are gaining popularity as potential candidates for curing the cancer.

PLANT-BASED THERAPEUTIC APPROACHES

Because of their capacity to regulate oxidative stress, inflammation, and epigenetic changes—all of which are crucial in the pathophysiology of HCC—phytochemicals have shown great promise as adjuncts in the treatment of liver cancer (Table 1). By focusing on molecular pathways linked to cell division, death, and metastasis, a number of chemicals extracted from medicinal plants have shown anticancer efficacy (Daher et al., 2018). For example, it has been observed that flavonoids, polyphenols, and alkaloids from Curcuma longa, Camellia sinensis, and Silybum marianum cytotoxically affect HCC cells via altering pathways such PI3K/Akt, TGF-β signalling, and NF-κB (Singh et al., 2018). Plant-based treatments, which are triggered by viral infections or aflatoxin exposure, provide an extra line of defence by means of antioxidant and immunomodulatory mechanisms. The development of HCC is aided by chronic hepatitis B and C infections, which increase oxidative damage and the release of inflammatory cytokines (TNF-α, IL-6) (Tarocchi et al., 2014). Immunomodulatory phytochemicals, such those from Phyllanthus niruri and Andrographis paniculata, have shown promise in lowering viral loads and boosting immunological responses, which may slow the course of disease.

Moreover, the development of HCC is significantly influenced by epigenetic dysregulation, which includes DNA methylation and histone modification (Hardy & Mann, 2016). These epigenetic markers can be altered by substances like resveratrol and epigallocatechin gallate (EGCG), which prevents cancer and restores normal cellular activities. These results highlight how crucial it is to incorporate plant-derived treatments into precision medicine plans for the treatment of HCC.

Curcuma Longa (Turmeric)

Curcumin, a polyphenolic molecule with strong anti-inflammatory and antioxidant effects, is abundant in curcuma longa, commonly referred to as turmeric. Curcumin has been shown to suppress the growth of cancer cells and trigger apoptosis in HCC via altering several signaling pathways, such

Table 1. Important plants having potential for treating patients with hepatocellular carcinoma

Plant Name	Active Compound(s)	Mechanisms of Action	Relevance to HCC	Reference
Curcuma longa	Curcumin	Inhibits NF-κB, PI3K/Akt, and STAT3 pathways; induces apoptosis via Bax/Bcl-2 modulation	Reduces tumor growth and inflammation	Abdel-Moneim *et al*., 2016
Camellia sinensis	EGCG (catechin)	Inhibits DNA methyltransferase, suppresses VEGF; antioxidant activity	Epigenetic reactivation of tumor suppressor genes; anti-angiogenic	Shimizu *et al*., 2005
Silybum marianum	Silymarin	Enhances glutathione; inhibits TGF-β and EGFR; reduces lipid peroxidation	Protects against fibrosis and aflatoxin-induced genotoxicity	Polyak *et al*., 2010
Phyllanthus niruri	Lignans, flavonoids	Anti-HBV activity; inhibits viral polymerase; antioxidant effects	Prevents HBV-related progression to cirrhosis and HCC	Venkateswaran *et al*., 1987

as PI3K/Akt, STAT3, and NF-κB. Furthermore, it alters the expression of proteins that promote and inhibit apoptosis, including Bax and Bcl-2, making HCC cells more susceptible to programmed cell death. These actions aid in preventing tumor growth and spread, especially in liver malignancies caused by inflammation (Abdel-Moneim et al., 2016).

Camellia sinensis (Green Tea)

Green tea is made from *Camellia sinensis* leaves, which are rich in catechins, particularly epigallocatechin-3-gallate (EGCG), which has been shown to have anticarcinogenic properties. By blocking DNA methyltransferases, EGCG disrupts carcinogenesis and reverses the epigenetic silencing of tumour suppressor genes. Additionally, it has a hepatoprotective effect by improving the detoxification of reactive oxygen species and suppressing tumour angiogenesis by blocking VEGF expression. Because of this, green tea may be useful in controlling chronic liver inflammation linked to the advancement of HCC and preventing the early stages of hepatic carcinogenesis (Shimizu et al., 2005)

Silybum marianum (Milk Thistle)

Silymarin, a flavonolignan complex found in milk thistle, has anticancer and hepatoprotective properties. Silymarin reduces oxidative damage to hepatocytes in HCC via modulating cell cycle arrest, increasing glutathione levels, and lowering lipid peroxidation. Additionally, it suppresses the EGFR and TGF-β pathways, which are linked to the development of tumours and liver fibrosis. Crucially, silymarin shields liver cells against the genotoxicity caused by aflatoxin B1, a recognized carcinogen that is common in developing nations like Pakistan (Polyak et al., 2010)

Phyllanthus niruri

Phyllanthus niruri, also known as "Bhumi amla," has long been used to treat liver conditions, particularly viral hepatitis. Viral replication suppression and host immune response regulation are the mechanisms by which it exerts its hepatoprotective effect. By inhibiting HBV DNA polymerase, the plant demonstrates anti-HBV action, lowering the viral load and inflammatory response of the liver. This process is essential for stopping cirrhosis brought on by HBV and its development to HCC. Furthermore, its antioxidant components enhance liver integrity by lowering hepatic oxidative stress (Venkateswaran et al., 1987).

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