IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
**Review Article**
July 2024 Vol.:30, Issue:7


# Hepatocellular Carcinoma: Summary and Recommendations

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

**Abdul Muqhtadeer[1*], Ishu[2], Aashutosh Sinwal[2], Nisha[2], Priyanshi Jain[2], Vaibhav Sinwal[2]**

*[1]Malla Reddy College Of Pharmacy, Maisammaguda, Hyderabad, Telangana, India- 500100*

*[2]School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan, India,302017*

**Submitted:** 20 June 2024
**Accepted:** 27 June 2024
**Published:** 30 July 2024


ijppr.humanjournals.com

**Keywords:** Liver Cancer, Hepatocellular carcinomas, Surveillance Epidemiology End Results, Hepatitis D virus, Radiofrequency ablation, Nonalcoholic steatohepatitis

**ABSTRACT**

The condition known as primary liver cancer occurs when cancerous cells start to grow in the liver's tissues. Primary liver cancer is not the same as cancer which starts in another place of the body and travels to the liver. Among the biggest organs in the body is the liver. Important risk factors for the development of HCC include liver cirrhosis, infection with hepatitis B and C viruses, heavy alcohol intake, aflatoxin B1 ingestion, and nonalcoholic steatohepatitis (NASH). Worldwide, hepatocellular carcinoma ranks second in cancer-related fatalities and ranks fifth in cancer incidence. Hepatocellular carcinoma is most commonly caused by long-term infections with hepatitis B and C viruses. Chronic liver disease is a prerequisite for more than 90% of hepatocellular carcinoma cases. Most strongly associated with HCC is cirrhosis of any cause. 60% of HCC cases in Asia and Africa are caused by HBV infection, while 20% of cases in the West are caused by the same virus. Alcoholic liver disease, cirrhosis, and HCC are all outcomes of chronic heavy alcohol consumption. Many gene correlations with hepatocellular carcinoma have been reported in gene sequencing studies, however, the majority of the genetic processes that initiate hepatocellular carcinoma are still unknown. Surgical resection, adjuvant treatment following surgical resection, and liver transplantation are the three primary types of surgery performed on patients with HCC. Among the many tyrosine kinases involved in cellular angiogenesis, proliferation, differentiation, and survival are Raf-1 and others; sorafenib is a multi-kinase inhibitor that inhibits their activity. For patients with advanced HCC, modestly preserved liver functions, and who are not candidates for liver transplantation or surgical resection, it is the first medicine authorized for systemic treatment, and it serves as the front-line therapy.

## INTRODUCTION

For both primary and secondary liver cancers, hepatocellular carcinoma accounts for three-quarters of all occurrences in the US. In line with the regional etiology of chronic liver disease or cirrhosis, the trend for both estimated new cases and incidences of mortality is growing. More than eighty percent of all liver cancers are hepatocellular carcinomas (HCCs), which originate in hepatocytes. Compared to North America and Europe, where the average age from diagnosis is 63–65 years, the prevalence of HCC is greater in China between the ages of 55 and 59. Southeast Asia, East Africa, and East Asia overall have higher rates of HCC. Globally, around 745,000 people lost their lives to liver cancer in 2012, according to the most recent estimates from GLOBOCAN. Consequently, HCC is ranked as the second most common cancer killer by the World Health Organisation (WHO). The development of HCC is caused by a complex interplay between genetic and environmental variables. Important risk factors for the development of HCC include liver cirrhosis, infection with hepatitis B and C viruses, heavy alcohol intake, aflatoxin B1 ingestion, and nonalcoholic steatohepatitis (NASH). [1,2]

Patients diagnosed with HCC have a different prognosis based on the cancer stage when they are diagnosed. A five-year survival rate is achievable with early diagnosis and adequate therapy, but it is likely to take a few months in the later stage. When caught early, treatment options are more limited and effective; nevertheless, a bad prognosis is anticipated after the disease has progressed and conventional chemotherapy has failed to provide sufficient results. Patients' chances of survival improve when curative therapies such as liver transplantation, local ablation, or surgical resection are administered at an early stage of HCC. As a result, improving the quality of life and increasing survival rates for HCC patients requires early identification and sufficient therapy. [3] Sorafenib has been found to improve survival rates in patients with advanced stage C liver cancer, whether or not their tumor has invaded blood vessels and their liver function is retained, according to the Barcelona Clinic Liver Cancer (BCLC) classification. As a biomarker in the diagnosis of HCC by serum, alpha-fetoprotein (AFP) has been utilized. Unfortunately, AFP's lack of specificity and sensitivity makes it an inaccurate measure. Since this is the case, we require a biomarker with superior diagnostic accuracy and dependability. Many tumor biomarkers in HCC have been recently found, including microRNAs, Glypican-3 (GPC3), Golgi 73 protein (GP73), and others. In addition to shedding light on the next steps in molecular medicine's application to

cancer, current genetic research can aid in HCC diagnosis, prognosis, and therapy. This review focuses on the most up-to-date information available on hepatocellular carcinoma, including its etiology, therapies, biomarkers, clinical features, and outcomes. [4]

## EPIDEMIOLOGY

Worldwide, hepatocellular carcinoma ranks second in cancer-related fatalities and ranks fifth in cancer incidence. Hepatocellular carcinoma is most commonly caused by long-term infections with hepatitis B and C viruses. The incidence rate in the United States grew by 3.1% every year, according to the Surveillance, Epidemiology, and End Results (SEER) Database. Incidence rates for men are 11.5 per 100,000, whereas women only have 3.9. Additionally, there has been a 2.8% rise for males and a 3.4% increase for females in the yearly mortality rates of hepatocellular carcinoma. In the elderly, hepatocellular carcinoma often manifests following a protracted course of chronic liver illness. The exposure risk factor determines the regional and racial/ethnic differences of hepatocellular carcinoma. [5] Although HBV is more common globally, 30% of U.S. infections are due to HCV. Liver cancer death rates are five times higher among Americans born between 1945 and 1965 due to the fivefold rise in the frequency of HCV. With 841,080 new cases in 2018, liver cancer ranks sixth among all cancers. It is also the fourth biggest cause of cancer-related deaths globally. Although hepatocellular carcinoma (HCC) is on the rise in certain regions of the United States and Europe, it is more common and deadly in East Asia and Africa. HCC has been the top cause of cancer-related deaths in the US since the early 2000s, according to Surveillance Epidemiology End Results (SEER). If current trends continue, it is anticipated to become the third greatest cause of cancer-related deaths by 2030. [6]

## RISK FACTOR AND CAUSES

Chronic liver disease is a prerequisite for more than 90% of hepatocellular carcinoma cases. Most strongly associated with HCC is cirrhosis of any cause. The yearly incidence of HCC ranges between 1-6%, making it the top cause of mortality among cirrhotic patients. Hepatocellular carcinoma (HCC) can develop in people who drink alcohol regularly, have diabetes or obesity, and are infected with hepatitis B or C virus. Other, less common causes of HCC include hemochromatosis, α1-antitrypsin deficiency, and cirrhosis from primary biliary cholangitis. Cirrhosis patients with hemochromatosis have an increased risk of

hepatocellular carcinoma (HCC), with as many as 45 percent of these patients having HCC at some point in their lives. [7]

**Hepatitis B virus infection**

60% of HCC cases in Asia and Africa are caused by HBV infection, while 20% of cases in the West are caused by the same virus. Hepatitis B virus (HBV) is a DNA virus that can integrate into host genomes, causing insertional mutagenesis and ultimately activating oncogenes. Although cirrhosis is present in the majority of patients with HBV-induced HCC, HBV raises the risk of HCC regardless of cirrhosis. Due to the high rate of endemic HBV infection in East Asia, there is a need for monitoring programs since the risk of HCC surpasses the cost-effectiveness thresholds in males aged 40 and in women aged 50. Exposure to aflatoxin B1, which increases the risk of HCC in a synergistic fashion with HBV, is likely to blame for the high prevalence of HCC among African patients in their early 30s and 40s. Although many jurisdictions in Asia have not yet instituted universal immunization programs, there have been areas where HBV vaccination programs have reduced the prevalence of HCC. [8,9]

**Hepatitis C virus infection**

Patients with HCC in the US, EU, and Japan most commonly have a chronic HCV infection as an underlying liver condition. Cirrhosis and chronic liver injury with bridging fibrosis are the main risk factors for hepatocellular carcinoma (HCC) due to HCV, an RNA virus that does not integrate into the host genome. This is in contrast to HBV. A growing number of patients with HCV infection have been effectively treated to attain an SVR with the use of direct-acting antiviral (DAA) medication, which has reduced the risk of HCC by 50-80%. Still, many patients have not been tested for HCV and do not know they have it; this is especially true among racial and ethnic minorities as well as those living in economically disadvantaged areas. Furthermore, it is important to closely monitor individuals with HCV-induced cirrhosis since their risk of developing HCC (>2% per year) persists even after SVR. [10]

**Hepatitis D virus infection**

The RNA virus known as hepatitis D virus (HDV) can only replicate and infect when certain surface antigens are present. Liver fibrosis and cirrhosis are more common in individuals

with HDV than in those with HBV alone; this is because HDV affects an estimated 20–40 million people worldwide. In a similar vein, other cohort studies have shown that compared to HBV infection alone, HBV co-infection with HDV increases the risk of HCC. Acute HDV infection (RR 6.1, 95% CI 2.8-11.7) and chronic HDV infection (RR 3.9, 95% CI 1.6-7.2) were associated with a much greater risk of HCC than HBV infection alone, according to one of the biggest studies conducted to date. [11]

**Alcohol**

Alcoholic liver disease, cirrhosis, and HCC are all outcomes of chronic heavy alcohol consumption. A growing number of people are suffering from cirrhosis as a result of non-alcoholic steatohepatitis (NASH). Depending on the location, alcohol-related cirrhosis accounts for around 15-30% of hepatocellular carcinoma (HCC) cases and has an annual incidence that ranges from 1% in population-based studies to 2-3% in tertiary care referral centers. Multiple studies have shown that HBV carriers who drink alcohol have a higher risk of HCC than those who do not drink alcohol, suggesting that chronic alcohol consumption may raise the risk of HCC from a variety of causes. Even though alcohol intake is associated with several pathophysiological processes in cirrhosis, especially nonalcoholic steatohepatitis (NASH), there is evidence that individuals experience alcohol-specific pro-tumorigenic pathways. [12,13]

**NASH**

In individuals with diabetes mellitus or obesity, non-alcoholic steatohepatitis (NASH) is a common aetiological risk for cirrhosis. NASH is the first stage in the development of hepatocellular carcinoma (HCC). Because obesity is on the rise, nonalcoholic steatohepatitis (NASH) is now the leading cause of cirrhosis worldwide. There has been a dramatic rise in the proportion of HCC cases in the West attributable to NASH since 2010, and it now accounts for 15-20% of cases. In addition, because metabolic syndrome and NASH often coexist in individuals with other liver illnesses, the population-attributable proportion of both conditions is likely to be greater than 20%. [14] The yearly incidence of HCC is less in NASH-related cirrhosis (1-2%) than in viral-mediated cirrhosis (3-5%), but it is still >1.1 per 100 person-years, suggesting that monitoring is worthwhile and should be done routinely. Recent research has shown that monitoring programs that just focus on individuals with cirrhosis are ineffective since 25-30% of NASH-associated HCC occurrences occur in people

without cirrhosis. Nevertheless, a cohort analysis conducted by the National Veterans Affairs health system deemed monitoring unnecessary because the yearly incidence of HCC in patients with non-cirrhotic NASH is less than the cost-effectiveness threshold. [15]

**Age, sex, and other factors**

In individuals with cirrhosis in particular, HCC has been linked to several sociodemographic factors. The strongest age-specific incidence has been seen in those over the age of 70, indicating that aging is a significant risk factor. In addition, sex hormone variations and a concentration of risk factors in males may explain why HCC is more common in men than in women (male-to-female ratio of 2-3:1). Hispanics, along with other racial or ethnic minorities, have a greater prevalence of HCC than white people, according to studies. The high occurrence of single-nucleotide variations in PNPLA3, which are related to NASH-associated HCC, may be one explanation for this disparity in incidence. Epidemiological studies have also shown that smoking increases the risk of HCC. Aside from research demonstrating that coffee and aspirin can prevent HCC, the exact impact of food in reducing this risk is unknown. [16]

**PATHOPHYSIOLOGY**

Many gene correlations with hepatocellular carcinoma have been reported in gene sequencing studies, however, the majority of the genetic processes that initiate hepatocellular carcinoma are still unknown. One possible driver of carcinogenesis in liver cancer is genomic instability, which can manifest as chromosomal or single nucleotide polymorphism. One of the main causes of hepatocellular carcinoma is the involvement of certain signaling pathways with recurrently somatically altered genes. These genes include the TERT promoter, TP53, CTNNB1, ARID1A, and FGF. Because hepatocellular cancer is so genetically diverse, no clear driver or focused treatment has surfaced. Ki-67 protein expression and TP53 gene mutation are conventional prognostic indicators of hepatocellular carcinoma. These markers have been shown to correspond with a poor prognosis time and time again. [17]

When dealing with younger patients, the most critical pathologic concern is differentiating the fibrolamellar variety from tumor encapsulation. Compared to classical hepatocellular cancer, which typically presents in the elderly with chronic illness and fewer than 25% resectable instances, these lesions have a higher likelihood of being resectable, are less

commonly associated with viral infections or cirrhosis, go hand in hand with normal AFP levels, and have a generally better prognosis. [18]

**Current therapies and their limitations**

Cell cycle, apoptosis, and signal pathway modifications are at the heart of several HCC treatment modalities. What follows is an explanation of the many ways the therapies are categorized. [19]

**Pharmacological therapy**

Among the many tyrosine kinases involved in cellular angiogenesis, proliferation, differentiation, and survival are Raf-1 and others; sorafenib is a multi-kinase inhibitor that inhibits their activity. For patients with advanced HCC, modestly preserved liver functions, and who are not candidates for liver transplantation or surgical resection, it is the first medicine authorized for systemic treatment, and it serves as the front-line therapy. Based on the findings, sorafenib response is mostly associated with improving survival rate in advanced HCC patients by correcting abnormal glycosylation in the erythroblastosis 26-1 (Ets-1) protein in HCC cells. Sorafenib resistance develops rapidly in many people. [20] For patients with HCC who have not responded to surgery and who have developed a resistance to sorafenib, Lenvatinib is an effective medication that can boost their survival rate by prescribing responses to lymphangiogenesis and angiogenesis. Another second-line oral medication produced by Bayer, Regorafenib, was authorized for unresectable HCC in June 2017 by the FDA. As a human anti-VEGFR-2 monoclonal antibody, ramucirumab blocks the binding of VEGFR ligands. Drug resistance is a constant concern for many medications, and side effects including hypertension, diarrhea, and decreased appetite are caused by treatments like sorafenib and lenvatinib. [21]

**Surgery**

Surgical resection, adjuvant treatment following surgical resection, and liver transplantation are the three primary types of surgery performed on patients with HCC. For individuals who were able to keep their liver function intact, the therapy for HCC is surgical resection. Less blood loss during surgery, shorter recovery time, and shorter hospital stays are all benefits of laparoscopic liver resection. Patients with early HCC (5 cm) with optimally maintained liver function can have a 5-year survival rate of 40-70% after surgical excision. Problems with

recurrence after surgical resection can be addressed with salvage liver transplantation, radiofrequency ablation, or a second hepatectomy. [22] Adjuvant treatment, administered after surgical resection, kills any cancer cells that remain and prevents the liver from developing cancer again. Interferons, intra-arterial and systemic chemotherapy, acyclic retinoid, sorafenib, adoptive immunotherapy, and intra-arterial radiolabeled lip iodol are all parts of these treatments. Patients with moderate to severe cirrhosis or early-stage HCC are best treated with a liver transplant, which also lowers the risk of postoperative liver failure. Although the 10-year survival rate after a liver transplant is higher than that after liver resection, the procedure is not without its hazards, such as the donor liver being rejected by the body and the high cost of short-term death. [23]

**Loco-regional therapy**

Cryotherapy, ethanol injection, and radiofrequency ablation are all forms of loco-regional ablative treatment. If a patient with HCC cannot undergo surgery, this medication will serve as a bridge to a liver transplant or a relaxing procedure to increase the likelihood that the patient will survive the disease-free period. For early-stage HCC patients, ablative treatment with percutaneous ethanol injection (PEI) is the gold standard; however, radiofrequency ablation (RFA), which uses coagulative necrosis to thermally destroy HCC cells, is considerably superior. In addition, as compared to liver resection, RFA significantly lowers the risk of morbidity in individuals with minor HCC. [15]

**Cytotoxic chemotherapy**

Patients with underlying liver conditions other than cirrhosis are more likely to respond to chemotherapy. Advanced HCC patients cannot be regularly treated with chemotherapy because HCC is a tumor type that is resistant to chemotherapy. Patients who already have liver problems cannot withstand systemic chemotherapy. Several chemotherapeutic treatments are available; for example, in patients with advanced HCC, a 75 mg/m2 dosage of single-agent doxorubicin produces an objective response rate of 20% or lower. Systemic chemotherapy, unlike gemcitabine- and doxorubicin-based chemotherapy, has a low response rate and considerable toxicity when applied to HCC, and it does not improve the survival rate much. [21,24]

**Natural compounds**

Fruits, vegetables, and spices include a variety of natural chemicals that can inhibit cancer-causing pathways and activate cancer-prevention systems. These chemicals support systems that fight inflammation, free radicals, tumors, and cell proliferation. Certain chemicals kill cancer cells but have no impact on healthy cells. [19] To increase plasma concentrations, chemotherapy medications may one day be used in conjunction with natural compounds like piperine, which block enzymes involved in drug metabolism. Curcumin, oleocanthal, allium extracts, and Cnidium officinale Makino are among the other natural substances that are utilized to slow the advancement of HCC. Natural chemicals have the potential to enhance the efficacy of existing pharmacological therapies while minimizing harm to the host. For example, polysaccharides derived from Tricholoma matsutake and Lentinus edodes enhance 5-fluorouracil's inhibitory activity on H22 cells from HCC patients. [17]

**Oncolytic virus therapy**

A novel method of combating cancer, oncolytic viral treatment entails the production of oncolytic viruses in cancer-causing tissues to destroy tumor cells. Antitumor, tumor-selective, and multi-mechanistic, these medicines work by using transgene-encoded proteins to target cancer cells directly as well as through a pleiotropic cytotoxic immune effector action. [20] Various kinds of viruses, including adenovirus, parvovirus, herpes, simplex virus, reovirus, and paramyxovirus, are utilized in this process. To enhance their medicinal properties, several of these viruses have been genetically modified. By generating tumor cell lysates, oncolytic viruses can identify newly released tumor antigens and induce immunogenic tumor cell death while simultaneously regulating cellular tumor-resistance pathways. Adenoviral E1A promoter was substituted with the tumor-specific telomerase reverse transcriptase (hTERT) promoter, allowing oncolytic viruses like telomerase-specific replication, telomelysin (OBP-301), and competent oncolytic adenovirus to efficiently replicate in telomerase-positive tumour cells in HCC. [21,23]

**Immunotherapy**

Immunotherapy strategies for HCC aim to activate and stimulate the body's existing tumor-specific immune response to target tumor cells. Treatment for metastatic melanoma patients under this protocol involves the use of antibodies that block immune-checkpoint mechanisms, such as anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4). [24] Activated T and B cells

control peripheral immunological tolerance through the co-inhibitory receptor programmed death 1 (PD-1). A crucial immunological barrier and immune suppressive mechanism is the interaction between PD-1 and its ligands, such as programmed death ligand 1 (PD-L1) (B7-H1) and PD-L2 (B7-DC). Recognising tumor-associated antigens (TAAs) by cytotoxic T lymphocytes (CTLs) is another immunotherapy that can enhance host immunity. Several squamous cell malignant antigens are present in HCC tumors, including TAA, cyclophilin B, AFP, hTERT, GPC3, and MAGE-A. Because sorafenib blocks immunosuppression, it is possible to use it in conjunction with other immunotherapy drugs. [25]

**Nanotechnology**

To improve retention, permeability, and pharmacokinetics, nanotechnology is a new tool that changes the paradigm of conventional combination treatment approaches. To maximize the drug's effects, the nanoparticles strategy combines many medicines into a single therapy program. For example, when used in conjunction, nanoparticles enhance the outcomes by adding another chemical to the process, which is particularly useful when dealing with chemo-sensitized cancer cells that develop drug resistance. There was less cytotoxicity than free doxorubicin and doxorubicin-nanoparticles after 48 hours of doxorubicin administration with lipid nanoparticles as chemo-sensitizers released into HepG2 cells, suggesting the possibility of synergy. When it comes to liver tumors caused by diethylnitrosamine, the combination of doxorubicin and curcumin, as opposed to free doxorubicin and curcumin, inhibits tumor growth synergistically. [26]

**CONCLUSION**

Primary liver cancer, specifically hepatocellular carcinoma (HCC), is a serious condition primarily caused by factors such as liver cirrhosis, hepatitis B and C infections, heavy alcohol consumption, and genetic predispositions. Surgical resection, adjuvant treatments, liver transplantation, and the use of multi-kinase inhibitors like sorafenib are common approaches in managing advanced HCC cases. Pharmacological therapies like sorafenib, lenvatinib, and regorafenib are effective in treating advanced HCC, while surgical resection and liver transplantation are crucial for maintaining liver function. Loco-regional therapies such as radiofrequency ablation are beneficial for early-stage HCC patients, and natural compounds like curcumin and oncolytic virus therapy show promise in enhancing existing treatments.

Immunotherapy and nanotechnology offer innovative approaches to improving treatment outcomes for HCC patients.

## REFERENCES


1. Arias-Flórez, J. S., Martínez-Delgado, A. M., Alarcón-Tarazona, M. L., Insuasty-Enriquez, J. S., & Díaz-Martínez, L. A. (2018). Conventional serum tumor markers in liver cancer. Rev Med Chil, 146(12), 1422–1428.
2. Sayiner, M., Golabi, P., & Younossi, Z. M. (2019). Disease burden of hepatocellular carcinoma: A global perspective. Digestive Diseases and Sciences, 64(4), 910–917.
3. Puustinen, L., Barner-Rasmussen, N., Pukkala, E., & Färkkilä, M. (2019b). Incidence, prevalence, and causes of death of patients with autoimmune hepatitis: A nationwide register-based cohort study in Finland. Digestive and Liver Disease: Official Journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver, 51(9), 1294–1299.
4. Colombo, M., & Lleo, A. (2018). Refining surgical therapy of liver cancer in cirrhosis: etiology makes the difference. Translational Gastroenterology and Hepatology, 3, 104–104.
5. Petrick, J. L., & McGlynn, K. A. (2019). The changing epidemiology of primary liver cancer. Current Epidemiology Reports, 6(2), 104–111.
6. Gogna, S., & Goyal, P. (2018). Recent strategies and paradigm shift in management of hepatic metastasis from colorectal cancer. Indian Journal of Surgical Oncology, 9(4), 456–460.
7. Labadie, K. P., Schaub, S. K., Khorsand, D., Johnson, G., Apisarnthanarax, S., & Park, J. O. (2019). Multidisciplinary approach for multifocal, bilobar hepatocellular carcinoma: A case report and literature review. World Journal of Hepatology, 11(1), 119–126.
8. Zhang, Y.-L., Ding, C., & Sun, L. (2019). High expression B3GAT3 is related with poor prognosis of liver cancer. Open Medicine (Warsaw, Poland), 14(1), 251–258.
9. Zucman-Rossi, J., Villanueva, A., Nault, J.-C., & Llovet, J. M. (2015). Genetic landscape and biomarkers of hepatocellular carcinoma. Gastroenterology, 149(5), 1226-1239.e4.
10. Yang, J. D., & Roberts, L. R. (2010). Hepatocellular carcinoma:A global view. Nat Rev Gastroenterol Hepatol, 7, 448–458.
11. Rahimi, R. S., & Trotter, J. F. (2015). Liver transplantation for hepatocellular carcinoma:outcomes and treatment options for recurrence. Ann Gastroenterol, 28, 323–330.
12. Breu, R. M., Ferreira, C. S., & Nasser, P. D. (2013). Hepatocellular Carcinoma:The final moments of life. J Cancer Ther, 4, 377–383.
13. Tunissiolli, N. M., Castanhole-Nunes, M. M. U., Biselli-Chicote, P. M., Pavarino, É. C., da Silva, R. F., da Silva, R. de C. M. A., & Goloni-Bertollo, E. M. (2017). Hepatocellular carcinoma: A comprehensive review of biomarkers, clinical aspects, and therapy. Asian Pacific Journal of Cancer Prevention: APJCP, 18(4), 863–872.
14. Anwar, S. L., & Lehmann, U. (2015). MicroRNAs:Emerging novel clinical biomarkers for hepatocellular carcinomas. J Clin Med, 4, 1631–1650.
15. Dargel, C., Bassani-Sternberg, M., Hasreiter, J., Zani, F., Bockmann, J.-H., Thiele, F., Bohne, F., Wisskirchen, K., Wilde, S., Sprinzl, M. F., Schendel, D. J., Krackhardt, A. M., Uckert, W., Wohlleber, D., Schiemann, M., Stemmer, K., Heikenwälder, M., Busch, D. H., Richter, G., … Protzer, U. (2015). T cells engineered to express a T-cell receptor specific for glypican-3 to recognize and kill hepatoma cells in vitro and in mice. Gastroenterology, 149(4), 1042–1052.
16. Haruyama, Y., Yorita, K., Yamaguchi, T., Kitajima, S., Amano, J., Ohtomo, T., Ohno, A., Kondo, K., & Kataoka, H. (2015). High preoperative levels of serum glypican-3 containing N-terminal subunit are associated with poor prognosis in patients with hepatocellular carcinoma after partial hepatectomy: High preoperative levels of serum glypican-3. International Journal of Cancer. Journal International Du Cancer, 137(7), 1643–1651.
17. Mittal, S., & El-Serag, H. B. (2013). Epidemiology of hepatocellular carcinoma:consider the population. J Clin Gastroenterol, 47, 2–6.

18. Groopman, J. D., Smith, J. W., Rivera-Andrade, A., Alvarez, C. S., Kroker-Lobos, M. F., & Egner, P. A. (2021). Aflatoxin and the aetiology of liver cancer and its implications for Guatemala. World Mycotoxin Journal, 14(3), 305–317.
19. Russell, S. J., Bell, J. C., Engeland, C. E., & McFadden, G. (2022). Advances in oncolytic virotherapy. Communications Medicine, 2(1), 33.
20. Jindal, A., Thadi, A., & Shailubhai, K. (2019). Hepatocellular carcinoma: Etiology and current and future drugs. Journal of Clinical and Experimental Hepatology, 9(2), 221–232.
21. Milosevic, I., Vujovic, A., Barac, A., Djelic, M., Korac, M., Radovanovic Spurnic, A., Gmizic, I., Stevanovic, O., Djordjevic, V., Lekic, N., Russo, E., & Amedei, A. (2019). Gut-liver axis, gut Microbiota, and its modulation in the management of liver diseases: A review of the literature. International Journal of Molecular Sciences, 20(2), 395.
22. Shen, F., Zheng, R.-D., Sun, X.-Q., Ding, W.-J., Wang, X.-Y., & Fan, J.-G. (2017). Gut microbiota dysbiosis in patients with non-alcoholic fatty liver disease. Hepatobiliary & Pancreatic Diseases International: HBPD INT, 16(4), 375–381.
23. Lanaya, H., Natarajan, A., Komposch, K., Li, L., Amberg, N., Chen, L., Wculek, S. K., Hammer, M., Zenz, R., Peck-Radosavljevic, M., Sieghart, W., Trauner, M., Wang, H., & Sibilia, M. (2014). EGFR has a tumour-promoting role in liver macrophages during hepatocellular carcinoma formation. Nature Cell Biology, 16(10), 972–977.
24. Svinka, J., Mikulits, W., & Eferl, R. (2014). STAT3 in hepatocellular carcinoma: new perspectives. Hepatic Oncology, 1(1), 107–120.
25. Dong, Y., & Wang, A. (2014). Aberrant DNA methylation in hepatocellular carcinoma tumor suppression (Review). Oncology Letters, 8(3), 963–968.
26. Guo, L., & Teng, L. (2015). YAP/TAZ for cancer therapy: opportunities and challenges (review). International Journal of Oncology, 46(4), 1444–1452.