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LETTER TO THE EDITOR

Exploring a new chapter in traditional Chinese medicine: The potential of *Calculus bovis* in liver cancer treatment

Huang Du, Hong-Bin Chen, Yu Zhao

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Abstract

In the ongoing quest for new treatments in medicine, traditional Chinese medicine offers unique insights and potential. Recently, studies on the ability of *Calculus bovis* to inhibit M2-type tumour-associated macrophage polarisation by modulating the Wnt/β-catenin signalling pathway to suppress liver cancer have undoubtedly revealed new benefits and hope for this field of research. The purpose of this article is to comment on this study and explore its strengths and weaknesses, thereby providing ideas for the future treatment of liver cancer.

Key Words: *Calculus bovis*; M2 tumor-associated macrophage polarization; Liver cancer; Wnt/β-catenin pathway; The tumor microenvironment

Core Tip: *Calculus bovis* (*C. bovis*) has shown remarkable potential in liver cancer treatment research. It was found to modulate the Wnt/β-catenin signalling pathway and inhibit the polarisation of tumour-associated macrophages, thereby inhibiting liver cancer progression. These findings not only reveal the immunoregulatory mechanism of *C. bovis* but also provide a new strategy and theoretical basis for the treatment of liver cancer. However, since the specific anticancer components of *C. bovis* are not known, future studies should focus on the inhibition of the liver cancer pathway mediated by specific components of *C. bovis* to facilitate clinical advancements in liver cancer treatment.

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TO THE EDITOR

Epidemiological characteristics of liver cancer

The latest figures for 2020 indicate that liver cancer was the sixth most common cancer and the third leading cause of cancer deaths worldwide in 2020. There are approximately 906000 new cases per year, with an incidence rate of 9.5 per 100000, or 4.7 per cent, and 830000 deaths, with a mortality rate of 8.7 per 100000, or 8.3 per cent. Its incidence is growing globally, and it is estimated that by 2025, more than 1 million people will develop liver cancer each year. Hepatocellular carcinoma is the most common type of liver cancer, accounting for approximately 90 per cent of all cases[1]. Liver cancer is projected to become the third leading cause of malignancy-related deaths by 2030[2]. Hepatitis B virus (HBV) infection is the most important risk factor for the development of primary liver cancer, accounting for approximately 50 per cent of all cases. Although the risk of liver cancer due to hepatitis C virus (HCV) infection has been greatly reduced in patients with hepatitis C as a result of a sustained viral response with antiviral medications, patients with cirrhosis are considered to have an increased risk of developing primary liver cancer even after HCV clearance[3]. Alcohol consumption[4], aflatoxin exposure[5], and genetic predispositions[6] are also crucial contributors to liver cancer. Nonalcoholic steatohepatitis, which is linked to metabolic syndrome and diabetes mellitus, is emerging as the most rapidly increasing source of liver cancer in Western countries[7]. In addition, aristolochic acid and tobacco have also been reported as cocausal factors in liver cancer[8,9].

Treatment of liver cancer

The main treatments for primary liver cancer currently include surgery, radiotherapy, hepatic artery chemoembolisation (TACE), systemic therapy, and traditional Chinese medicine (TCM).

Surgical treatment, including hepatectomy and liver transplantation, has been the mainstay of primary liver cancer treatment and achieves the best results, with a 5-year survival rate of approximately 70-80 per cent[10,11]. The decision to resect or transplant must consider the patient's liver function, degree of portal hypertension, fitness status and tumour characteristics. The treatment of choice for liver cancer patients without cirrhosis is hepatectomy. However, the recurrence of liver cancer after hepatectomy remains an concerning issue[12]. Even in patients with a single tumour ≤ 2 cm, the recurrence rate is as high as 70% within 5 years. Liver transplantation is considered when the patient has concomitant cirrhosis and a limited tumour burden (Milan criteria: Single tumour ≤ 5 cm or 2-3 tumours ≤ 3 cm without concomitant vascular invasion)[13]. The prognosis for this treatment option is promising, with 5-year and 10-year survival rates of 70% and 50%, respectively, and a 5-year recurrence rate of only 10%-15%. Liver transplantation, which has a promising long-term survival prognosis, is considered superior to hepatic resection, which has a 10-year survival rate of 7%-15% and a recurrence rate of 70%[14].

Extracorporeal radiation therapy achieves a radiological response to different tumour sizes and stages of liver cancer and attenuates extrahepatic metastases[15]. A comprehensive analysis examined the prognosis of 102 patients with unresectable primary liver cancer and Child-Pugh A liver function who received more than 6 fractions of 24-54 Gy photonic stereotactic body radiotherapy, 54% of whom achieved objective remission with a median overall survival of 17 months[16].

TACE therapy has a positive impact on the survival of patients with intermediate-stage liver cancer and has been recognized as the standard of care for this patient population worldwide[17]. The American Association for the Study of Liver Diseases guidelines recommend TACE for the treatment of patients with intermediate-stage liver cancer, a decision supported by level 2 evidence[18].

The majority of liver cancer patients are diagnosed at an advanced stage, which often results in the loss of the opportunity for radical surgical treatment and leads to a poor clinical prognosis. It is estimated that approximately 50%-60% of patients with liver cancer will use systemic therapy during their lifetime[19], especially in the advanced stages of the disease, and the median survival time of symptomatic advanced liver cancer patients receiving systemic therapy is approximately 1.0-1.5 years[20]. Receptor tyrosine kinase inhibitors have been the first-line treatment of choice for patients with advanced liver cancer for nearly a decade or more[21,22]. At present, on the basis of positive phase III data, there are three regimens in the guidelines (regorafenib, ramucirumab, and cabozantinib) approved for second-line treatment of advanced liver cancer that has progressed after sorafenib treatment. The success of the phase III IMbrave150

trial in 2020 marked the beginning of a new era in the use of immune checkpoint inhibitors (ICIs) for liver cancer treatment. In liver cancer, ICIs have shown promising activity when paired with antiangiogenic agents and targeted therapeutics. During an Ib-phase study, an initial treatment of lenvatinib and pembrolizumab combination therapy was given to 100 individuals with inoperable liver cancer, and 46% of the patients experienced sustained, radiological responses according to mRECIST. The median PFS was 9.5 months, whereas the median overall survival was 22 months [23]. Several phase III trials are currently underway to explore combinations of TKIs (lenvatinib, cabozantinib, and apatinib) with ICIs as well as combinations of CTLA4 inhibitors (ipilimumab and tremelimumab) with other ICIs[24,25]. Currently, the focus of research in the treatment of liver cancer is on cutting-edge therapeutic technologies such as proteolysis-targeting chimaeras (PROTACs), antibody-coupled drugs (ADCs) and mRNA vaccines[26]. According to a previous report, almost 50% of patients with liver cancer harbour at least one oncogene mutation[27]. However, most mutated tumour proteins cannot be effectively targeted by conventional drugs. While some inhibitors have been developed to target TERT promoter mutation products and components of the WNT-β-catenin signalling pathway, satisfactory therapeutic outcomes have yet to be achieved[28].

PROTACs can induce the degradation of target proteins through the ubiquitin-proteasome system, offering a highly effective approach for eliminating proteins that were previously considered 'undruggable'[29]. Currently, most PROTACs used for the treatment of liver cancer, such as BETd-260 (targeting the BET protein)[30], ARV-771 (a BRD degrader)[31], JB170 (an Aurora A degrader)[32], CP-10 (targeting CDK4)[33], and BSJ-03-123 (targeting CDK6)[33], are still in the preclinical study stage, and their clinical efficacy still needs to be further verified. Recently, two PROTAC probes developed by Arvinas LLC, ARV-110 and ARV-471 (with undisclosed structures), have been in phase I clinical trials (NCT03888612 and NCT04072952 at clinicaltrials.gov) for prostate and breast cancer, respectively[34]. However, further clinical studies on liver cancer are still needed (Table 1).

ADCs represent a novel class of agents specifically designed to deliver potent cytotoxic substances directly into tumours with high specificity. They are composed of three main components: Monoclonal antibodies, linkers, and cytotoxic drugs[35,36]. Preclinical studies have demonstrated the therapeutic potential of ADCs in the treatment of liver cancer[37,38]. GPC3 is highly expressed in liver cancer and is considered a potential therapeutic target. Studies have shown that GPC3-specific ADCs exhibit potent tumour killing activity in GPC3-positive liver cancer cell lines (Hep3B and A431-GPC3 cells) and their xenograft models[38]. GPC3-targeted chimeric antigen receptor (CAR)-T-cell therapy has a high safety profile in patients with liver cancer. The combination of GPC3-CAR-T cells and sorafenib was shown to increase tumour cell apoptosis in mouse experiments, demonstrating the clinical potential of GPC3-targeted CAR-T-cell therapy for liver cancer[39]. Moreover, GPC3 is a potential diagnostic and therapeutic target for liver cancer. An *et al*[40] successfully developed sdAb-derived GPC3-targeted immuno-PET imaging strategies and demonstrated their excellent diagnostic accuracy in preclinical liver cancer models[40]. Furthermore, dysregulation of CLDN6 promotes the phenotypic transformation of liver cancer cells, which induces the development of sorafenib resistance. Clinical researchers have successfully conjugated the anti-CLDN6 monoclonal antibody with the cytotoxic drug DM1 (CLDN6-DM1) and verified the antitumour efficacy of this ADC both alone and in combination with sorafenib[37]. Currently, several ADCs are undergoing clinical evaluation to assess their safety and tolerability in the treatment of various advanced solid tumours, including liver cancer[41] (Table 1).

mRNA vaccines have emerged as a new trend in the treatment of liver cancer[42,43]. Typically, mRNA vaccines deliver engineered mRNAs into tumour cells, inducing the production of tumour-specific antigens or neoantigens. This process activates the immune system, enabling it to recognize and eliminate cancer cells that present these antigens, thereby enhancing the antitumour immune response. By expressing multiple neoantigens, mRNA-based cancer vaccines have the potential to address the high degree of heterogeneity among tumour cells[42]. In 2017, a study reported the first clinical use of an mRNA neoantigen vaccine that demonstrated a significant reduction in the risk of metastasis and prolonged progression-free survival (PFS) in patients with melanoma[44]. Subsequent studies have further demonstrated the therapeutic value of mRNA vaccines in many types of cancer, including lung, colorectal and pancreatic cancers[45-47]. mRNA-based cancer vaccines have therapeutic potential for treating malignant tumours, including those in liver cancer. Deng *et al*[48] optimized and synthesized stable mRNA encoding the costimulator Oxford 40 ligand (OX40L). *In vivo* studies in mice revealed that LNPs with OX40L mRNA significantly reduced the rate of tumour growth and increased the survival rate of H22 tumour-bearing mice[48]. A phase I trial (NCT05738447) conducted in 2023 aimed to apply mRNA immunotherapy technology in patients with HBV-related refractory liver cancer. Another ongoing trial is a phase I trial (NCT05738447) that aims to apply mRNA immunotherapy technology in patients with HBV-related refractory liver cancer[49] (Table 1).

Tradition meets modernity: The anti-cancer potential of Calculus bovis

Calculus bovis (*C. bovis*), a valuable herb used in TCM, has long been recognized in folklore for its unique therapeutic effects. However, with advancements in modern science and technology-particularly the rapid progress in molecular biology and bioinformatics-we are now able to analyse the scientific mechanisms underlying its effects more deeply. This study reveals the immunomodulatory effects of *C. bovis* in the treatment of liver cancer, particularly its impact on immune cells within the tumour microenvironment. Through detailed compositional analyses and network pharmacological predictions, this research represents a significant breakthrough in the modernization of TCM.

Regulation of the immune microenvironment: Polarisation and reversal of M2-type tumour-associated macrophages

The tumour microenvironment is a critical site for tumorigenesis, progression, and metastasis, where tumour-associated macrophages (TAMs), a key population of immune cells, directly influence tumour progression through their polarisation status. M2-type TAMs have emerged as significant targets for tumour therapy because of their roles in promoting tumour growth, angiogenesis, and immunosuppression. In this study, through advanced techniques such as transcriptome

Table 1 Novel therapeutic techniques in liver cancer applications

Name	Target	Stage	Potential pros	Potential cons
PROTACs				
JB170	AURKA	Preclinical	Versatile drug design potential; high target specificity; reduced risk of drug resistance	Higher complexity in design and development cost off-target effects; limited clinical data available
BETd-260	BET	Preclinical		
ARV-771	BRD2/3/4	Preclinical		
CP-10	CDK6	Preclinical		
BSJ-03-123	CDK6	Preclinical		
ADCs				
MGC018	CD276	Preclinical	High target specificity; reduced systemic toxicity	Limited scope of targetable antigens off-target effects; challenges in stability and drug release
ABBV-400	MET	Preclinical		
hYP7-DC	GPC3	Preclinical		
CLDN6-DM1	CLDN6	Preclinical		
mRNA vaccines				
PGV002	Neoantigen	Phase I	Personalized treatment; potential; potential for broader; immune response; lower drug toxic	Potential for immune-related; side effects; Limited clinical data in; cancer treatment
PCV	Neoantigen	Phase I		
ABOR2014	Neoantigen	Phase I		

PROTACs: Proteolysis-targeting chimaeras; ADCs: Antibody-coupled drugs.

sequencing, we demonstrated that *C. bovis* inhibits the progression of liver cancer by regulating the polarization of M2-type TAMs. This finding not only enhances our understanding of the mechanisms underlying tumour-immune microenvironment regulation but also provides an important theoretical foundation for the development of novel anticancer drugs.

The role of the Wnt/β-catenin signalling pathway: From mechanisms to applications

More strikingly, this study revealed the crucial role of the Wnt/β-catenin signalling pathway in the regulation of M2-type TAM polarisation by *C. bovis*. As a signalling pathway that plays a vital role in cell proliferation, differentiation, and migration, the aberrant activation of Wnt/β-catenin signalling is closely associated with the development of various tumours. By inhibiting the activation of this pathway, *C. bovis* effectively blocks the polarization process of M2-type TAMs, opening new avenues for the treatment of liver cancer. The elucidation of this mechanism not only provides a scientific explanation for the anticancer effects of *C. bovis* but also offers guidance for future drug development targeting this pathway (Figure 1)[50].

Limitations of the study

This study provides new vigour and hope for the study of primary liver cancer; however, this study did not fully consider the complex components of *C. bovis*. This study was conducted by examining an extract consisting of 22 compounds, but it was not able to accurately determine the effect of a particular ingredient on the Wnt/β-catenin pathway. Zhang *et al*[51] identified 11 components of *C. bovis* with anti-primary liver cancer effects *via* oral bioavailability (OB) and drug-likeness (DL) screening and suggested that *C. bovis* plays a key role in the treatment of liver cancer, mainly through apoptosis-related pathways (apoptosis of SMMC-7721) and immune-related pathways[51]. Luo *et al*[52] reported that *C. bovis*-based Pientzehuang inhibited the migration, invasion and epithelial-mesenchymal transition of HCC cells through the inhibition of the PDGFRB/YAP/CCN2 axis[52]. The three studies on *C. bovis* were conducted in different ways, yielding different active ingredients and possible signalling pathways, which inevitably raises questions for both the future development of new drugs and for readers about the mechanism of *C. bovis* in treating liver cancer. The field of liver cancer treatment includes extensive research involving Chinese medicine, as evidenced by numerous studies[53,54]. In the systematic evaluation of the studies on Astragalus and its active ingredients in the treatment of liver cancer, it was noted that among the 50 journal articles published on Astragalus in this decade, only 8 were included in the SCI index, and a number of studies have shown that Astragalus and its active ingredients do not significantly affect the growth of liver cancer cells in *in vitro* cellular experiments, which makes the treatment of the complex TCM contingent more difficult. Currently, we should focus on the antitumour mechanism and clinical research of the specific components of TCM to ensure the reproducibility and reliability of TCM treatment in the treatment of liver cancer.

Second, this study proposes that *C. bovis* inhibits the growth of liver cancer through the Wnt/β-catenin pathway, but further experimental validation is needed to assess its future clinical translational potential. In addition to its complex compositional factors, Wnt/β-catenin signalling pathway immunotherapy-related drugs are currently used for targeted

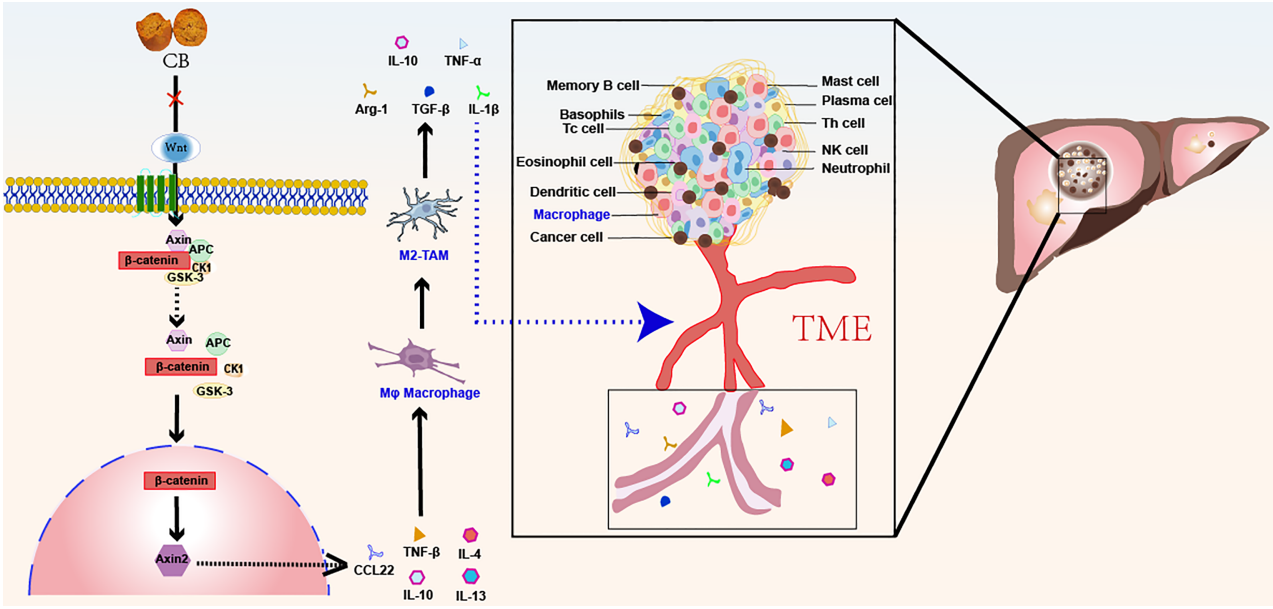

Figure 1 Schematic diagram of anti-liver cancer mechanism of *Calculus bovis*. *Calculus bovis* exerts its anti-liver cancer effect by inhibiting the Wnt/β-catenin pathway and suppressing the polarization of M2 tumor-associated macrophage. Citation: Huang Z, Meng FY, Lu LZ, Guo QQ, Lv CJ, Tan NH, Deng Z, Chen JY, Zhang ZS, Zou B, Long HP, Zhou Q, Tian S, Mei S, Tian XF. Calculus bovis inhibits M2 tumor-associated macrophage polarization *via* Wnt/β-catenin pathway modulation to suppress liver cancer. *World J Gastroenterol* 2024; 30: 3511-3533. Copyright© The Authors 2024. Published by Baishideng Publishing Group Inc. The authors have obtained the permission for figure using from the Baishideng Publishing Group.

inhibition of liver cancer, and the process of clinical treatment has achieved positive therapeutic effects[55]. Therefore, future research should focus on the inhibition of liver cancer pathways mediated by specific components to promote the development of clinical treatments for liver cancer, and future studies should focus on the structure-function relationships between bile acids and bilirubin in *C. bovis* and elucidate the differences in their pharmacological effects through pharmacokinetic studies. Currently, C. bovis is derived from four main sources: Natural *C. bovis* (NCB), *C. bovis* sativus (CBS), cultured *C. bovis* (CCB) and *C. bovis* artefactus (CBA)[56]. The chemical compositions of CB from various sources differ[57,58]. The efficacies of NCB and CBA vary considerably, and CBA should not be used as a substitute for NCB[59]. However, whether these compositional differences affect treatment remains to be investigated.

Looking to the future: The road to modernisation for TCM

The findings concerning the use of *C. bovis* in the treatment of liver cancer represent a microcosm of the modernisation of TCM. TCM contains a wealth of bioactive components and unique pharmacological mechanisms. As long as we use modern scientific and technological methods for in-depth exploration and elucidation, we can discover more drugs or drug-like compounds with potential clinical application value. In the future, with the continuous expansion of research and advancements in technology, we believe that TCM will play an increasingly important role in the treatment of cancer and the entire field of medicine.

Future research on liver cancer should consider the following: (1) The combination of an ICI with a TKI or VEGF inhibitor almost doubles the response rate and survival benefit for tumours compared with a single agent[23]. It is unknown whether combination regimens with other drugs are equally effective; (2) While therapeutic approaches related to vaccines have not yet led to notable clinical outcomes, there is an increasing focus on cell-based strategies such as CAR T-cell therapy, which is now being studied in early-stage liver cancer[60]; and (3) Researchers are using naked antibodies and antibody-drug couplings to find novel antibody targets against epitopes unique to liver cancer[61].

CONCLUSION

The treatment of liver cancer remains a global challenge, with its incidence continuously increasing worldwide. The need for neoadjuvant and adjuvant therapies for liver cancer has not yet been met. Exploring the pathogenesis of liver cancer and discovering new biomarkers will aid in the development of emerging combination therapies. TCM, an established medical system, has been recognized by the World Health Organization. To date, increasing evidence has confirmed that Chinese herbs such as Pien Tze Huang, Bupleurum, Astragalus, and Poria have anti-liver cancer effects[62]. Therefore, advancements in the understanding of the mechanisms involved in TCM and liver cancer are expected to lead to the development of new therapeutic drugs. However, most current research has focused on the effects of complex TCM components on liver cancer signalling pathways, and it is still unclear which compounds play a role in regulating these pathways, thus further clarification from future studies is necessary. Research on *C. bovis* in the treatment of liver cancer not only reveals its unique anticancer mechanisms but also provides valuable experience and insights for the modern-

isation of TCM. Future clinical or animal studies should be dedicated to investigating the specific components that regulate liver cancer signalling pathways to facilitate the development of new drugs and provide more effective treatments for clinical use.

FOOTNOTES

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