LETTER TO THE EDITOR

Promise and challenges of traditional Chinese medicine, specifically *Calculus bovis*, in liver cancer treatment

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Abstract

Liver cancer, one of the most common malignancies worldwide, ranks sixth in incidence and third in mortality. Liver cancer treatment options are diverse, including surgical resection, liver transplantation, percutaneous ablation, transarterial chemoembolization, radiotherapy, chemotherapy, targeted therapy, immunotherapy, and traditional Chinese medicine (TCM). A multidisciplinary team (MDT) is essential to customize treatment plans based on tumor staging, liver function, and performance status (PS), ensuring individualized patient care. Treatment decisions require a MDT to tailor strategies based on tumor staging, liver function, and PS, ensuring personalized care. The approval of new first-line and second-line drugs and the establishment of standard treatments based on immune checkpoint inhibitors have significantly expanded treatment options for advanced liver cancer, improving overall prognosis. However, many patients do not respond effectively to these treatments and ultimately succumb to the disease. Modern oncology treatments, while extending patient survival, often come with severe side effects, resistance, and damage to the body, negatively impacting

quality of life. Huang *et al*'s study published at *World Journal of Gastroenterology* rigorously validates the anticancer properties of *Calculus bovis*, enhancing our understanding of TCM and contributing to new liver cancer treatment strategies. For over 5000 years, TCM has been used in East Asian countries like China to treat various diseases, including liver conditions. Analysis of real-world clinical data suggests that for patients with advanced-stage tumors lacking effective treatments, integrated TCM therapies could provide significant breakthroughs.

Key Words: Traditional Chinese medicine; Liver cancer; *Calculus bovis*; Treatment; Promise; Challenges

Core Tip: Huang *et al* discovered that *Calculus bovis* (CB) inhibits liver cancer growth by mediating the suppression of M2-TAM polarization through the Wnt/β-catenin pathway. This article highlights the current research, potential, and challenges of using traditional Chinese medicine, exemplified by CB, in liver cancer treatment, and points to future research directions.

TO THE EDITOR

Liver cancer ranks among the most common tumors worldwide and is a major cause of cancer-related deaths. According to the latest Global Cancer Statistics report published in 2024, nearly 20 million new cancer cases and approximately 9.7 million cancer deaths were reported globally in 2022[1]. Additionally, the American Cancer Society forecasts that the United States will see 2001140 new cancer cases and 611720 cancer deaths in 2024. Between 2015 and 2019, the incidence of liver cancer in United States women rose by 2% to 3% annually[2]. Almost half (49.2%) of these newly diagnosed cancer cases and more than half (56.1%) of cancer-related deaths took place in Asia[3]. According to the latest report, China leads the world in cancer mortality rates, with lung, liver, and stomach cancers being the primary causes of cancer deaths. Primary liver cancer ranks as the fourth most common cancer and the second leading cause of cancer deaths in China, posing a serious threat to public health[4].

Statistics from the National Cancer Center of China show that in 2020, there were 410000 new liver cancer cases and 390000 deaths attributed to liver cancer in China. This made it the second leading cause of cancer deaths in men and the fifth in women[4]. Liver cancer includes both primary and metastatic types. Primary liver cancer (PLC) includes three pathological forms: Hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and hepatic sarcoma. Surgical resection, liver transplantation, chemotherapy, and ablation are common treatments for PLC. Metastatic liver cancer typically requires systemic chemotherapy or local ablation based on the pathology of the primary tumor. For advanced liver cancer, chemotherapy is the preferred treatment, with transarterial chemoembolization (TACE) being the clinical standard[5-12]. However, challenges such as recurrence, donor liver shortages, resistance, long-term toxicity of chemotherapy drugs, and poor overall recovery after surgery persist after surgery continue to exist.

There is an urgent need to develop safe and effective treatments. Numerous clinical studies have reported that traditional Chinese medicine (TCM) effectively improves symptoms associated with advanced PLC, reduces tumor recurrence, and controls disease progression. Additionally, TCM as an adjuvant therapy may extend survival time and improve the overall survival rate of HCC patients. Combining TCM formulations with TACE can lower alpha-fetoprotein levels and reduce the incidence of TACE-related adverse reactions. TCM can also enhance postoperative cellular immune function and natural killer cell levels in liver cancer patients[13]. Further research into the efficacy and safety of integrating TCM with Western medicine for the prevention and treatment of PLC will deepen our understanding and potentially improve patient outcomes.

CURRENT STATUS of USING *CALCULUS BOVIS* in LIVER CANCER TREATMENT

Liver cancer remains one of the most lethal malignancies globally, with limited effective treatment options. Huang *et al* [14] have adopted an innovative approach that combines TCM with modern biomedical techniques, showcasing the potential of *Calculus bovis* (CB) in inhibiting liver tumor growth[14]. Their comprehensive study employs various validation methods, including network pharmacology, transcriptomics, and molecular docking, providing a detailed understanding of CB's impact on the tumor microenvironment (TME).

The study identifies 22 active components in CB, with 11 detectable in the blood. These components work synergistically to inhibit liver tumor growth by targeting the Wnt/β-catenin pathway. The research reveals that CB suppresses the polarization of M2-TAMs, which promote tumor growth and metastasis. By modulating this pathway, CB effectively

reduces the proliferation and invasion capabilities of liver cancer cells.

This study has broader implications for integrating TCM with modern oncology. It not only provides scientific evidence for the traditional use of CB in liver cancer treatment but also opens new avenues for developing CB-derived therapeutic strategies. The research highlights the potential of TCM as a complementary approach to existing cancer treatments, offering a multi-target mechanism that reflects the complexity of tumor biology.

However, while promising, this study has several limitations that need to be addressed in future research

Component-specific effects: Although the study identifies 22 active components in CB, it remains unclear which specific compounds are most effective in regulating macrophage polarization. Further research is needed to isolate and evaluate the individual and synergistic effects of these components.

Clinical validation: The current study primarily involves preclinical models. Clinical trials are necessary to validate the efficacy and safety of CB in human patients, ensuring that the observed anticancer effects translate into clinical outcomes.

Mechanistic depth: While the study emphasizes the Wnt/β-catenin pathway as a key mechanism, other potential pathways and molecular targets affected by CB remain unexplored. Comprehensive mechanistic studies are required to fully understand the breadth of its anticancer activity.

Broader immunological impact: The study focuses on CB's impact on M2-TAMs but does not explore its effects on other immune cells within the TME, such as T cells and natural killer cells. Understanding CB's broader immunomodulatory effects could provide a more complete picture of its therapeutic potential.

Long-term effects and toxicity: Long-term studies are needed to assess the chronic effects and potential toxicity of CB. This is crucial for evaluating its safety and ensuring its suitability for long-term therapeutic use.

This research underscores the importance of further investigation into the integration of TCM with modern cancer therapies, paving the way for innovative treatment strategies that could improve patient outcomes.

NEW INSIGHTS AND FUTURE DIRECTIONS

Exploring combination therapies

Future research should investigate the potential synergistic effects of combining CB with existing liver cancer treatments, such as immune checkpoint inhibitors or targeted therapies. These combination treatments may enhance the efficacy of CB, offering more comprehensive therapeutic strategies and improving patient survival rates and quality of life.

Identification of novel biomarkers

A deeper understanding of CB's molecular mechanisms could lead to the discovery of new biomarkers. These biomarkers would not only help in evaluating treatment efficacy but also aid in early diagnosis and prognosis. Key molecules in the Wnt/β-catenin pathway regulated by CB could serve as potential biomarkers for liver cancer treatment.

Personalized medicine approaches

Given CB's multi-component, multi-target nature, further research is needed to explore its application in personalized medicine. Genomic and proteomic analyses of patients could identify those who would benefit most from CB treatment, allowing for customized therapies tailored to individual patient profiles and optimizing treatment outcomes.

Interdisciplinary research

This study highlights the potential of integrating TCM with modern biomedical sciences. Future research should promote interdisciplinary collaboration, combining bioinformatics, systems biology, and chemical analysis to fully elucidate CB's mechanisms of action. This comprehensive approach could reveal more therapeutic targets and advance the modernization of TCM.

Socioeconomic and environmental factors

As a traditional herbal medicine, CB is relatively inexpensive and abundant. Assessing its economic feasibility and accessibility could provide a viable treatment option for regions with limited medical resources. Additionally, sustainable use of herbal resources must be ensured. Research should focus on improving extraction and utilization efficiency while conserving natural resources, promoting the long-term sustainability of TCM practices.

CB plays a significant role in compound formulations with anticancer properties. Previous studies have shown that Xihuang capsules, which contain CB, can reverse chemotherapy resistance, reduce chemotherapy-induced leukopenia and other side effects, improve patient vitality, inhibit pro-inflammatory cytokines such as IL-17 and IL-6, and ameliorate hypercoagulable states in patients with advanced tumors. When combined with radiotherapy, targeted therapy, and interventional treatments, Xihuang capsules enhance efficacy, reduce toxicity, boost immunity, improve clinical symptoms, enhance quality of life, and extend survival time[11,15]. Thus, integrating CB with modern medical treatments holds significant potential for cancer therapy research and applications.

However, current studies involve small sample sizes and lack evidence-based research support. The mechanisms underlying its synergistic effects and therapeutic efficacy require further exploration. Additionally, previous research on

Pien Tze Huang has demonstrated its anti-inflammatory, antioxidant, anti-apoptotic, and lipid and alcohol metabolism-promoting properties. Pien Tze Huang has been widely used in treating chronic inflammation, alcoholic liver disease, chemical liver injury, and liver cancer[16-23]. Research has also shown that replacing natural CB with synthetic CB in Ke Huang capsules enhances their inhibitory effect on Huh7 Liver cancer cells. Despite these promising findings, most studies are published in Chinese journals, with fewer than 60 articles, indicating a vast potential for further research in this field.

TCM has persisted for thousands of years, demonstrating its rationale and efficacy in treating complex diseases. The success of artemisinin in treating malaria, which earned a Nobel Prize, illustrates that unveiling the mysteries of TCM could be key to solving cancer challenges. The global scientific community should recognize the importance of TCM research, with scientists from various countries collaborating to study TCM mechanisms, purification, and clinical applications.

Western countries, having earlier embraced modern science, emphasize rigorous, logical, and profound scientific inquiry. In contrast, TCM reflects the inclusive, experiential, and naturalistic thinking inherent in traditional Chinese philosophy. Chinese scientists should strengthen collaborations with Western researchers, using modern scientific methods to bridge the gap with traditional medicine.

Furthermore, previous studies indicate that HCC is a common consequence of alcohol-related liver disease, with varying incidence rates among heavy drinkers. A genome-wide association study identified WNT3A-WNT9A as susceptibility loci for alcohol-related HCC, implicating the Wnt/β-catenin pathway in the early development of alcohol-related HCC. In Huang *et al*'s study, a subcutaneous tumor model was used to simulate liver cancer, which may not accurately represent human visceral tumors[14]. Future research should consider different pathological types, alcohol-related liver disease, and other risk factors to refine and specify CB's anticancer effects.

POTENTIAL of TCM in TREATING LIVER CANCER

Previous studies have shown that combining TCM with Western medicine for treating PLC is more effective than solely using Western medicine (65.11% *vs* 44.31%, $P < 0.05$). These TCM treatments include commercially available Chinese medicine preparations, formulas, and individual herbs. Commonly used single herbs include Poria, Astragalus, Atractylodes, Bupleurum, and Licorice[24,25]. Nonetheless, unresolved issues persist regarding the specific active substances and doses, side effects, and interactions with Western drugs. More rigorous research is required on the chemical composition, formulation, dosing, toxicology, and ethics of TCM.

Cancer progression involves multiple complex stages, including initiation, promotion, and progression, relying on inflammatory responses, angiogenesis, and reduced host immunity. Most cancer patients exhibit decreased immunity in the middle to late stages of cancer. Inflammation aids cancer progression at all stages, while angiogenesis exacerbates cancer cell proliferation and metastasis. Clinically, a common method to prevent angiogenesis is to eliminate existing tumor blood vessels and prevent new ones from forming, thus restricting tumor cell nutrition. Studies have reported that TCM mechanisms for treating liver cancer include inducing apoptosis and autophagy, promoting cell cycle arrest, inhibiting normal cell autophagy, altering the TME, inhibiting angiogenesis and metastasis, and providing anti-inflammatory, antioxidant, and immunosuppressive effects. TCM has anti-inflammatory, immunomodulatory, and anti-angiogenic properties, supporting its use throughout PLC development stages. Additionally, TCM may have low toxicity, strong specificity, and high efficacy, warranting further real-world studies, large-sample randomized controlled trials, and observational studies led and organized by TCM experts and major hospitals to collect and analyze data.

CHALLENGES of TCM in TREATING LIVER CANCER

TCM can alleviate liver cancer symptoms, reduce side effects, prolong survival, and enhance quality of life. However, TCM encounters skepticism due to its complexity, holistic concepts, and symptom-focused research. Many doctors trained in modern oncology do not fully trust TCM's efficacy, partly because exclusive TCM use has sometimes delayed treatment. However, these extreme cases might be attributed to the high malignancy and rapid progression of certain pathologies or resistance to TCM. Such severe cases are rare, and even modern targeted therapies can encounter broad-range resistance initially. Additionally, communication among doctors within the same medical institution can influence patients' adoption of TCM treatments. Younger doctors, influenced by their seniors, might not advocate for TCM, and the dominant theories of experienced doctors can shape the perspectives of many generations. This dilemma stems from the high degree of specialization in modern medicine, where specialists often lack a thorough understanding of TCM principles and seldom interact with patients who use TCM, resulting in a lack of firsthand experience but still holding a significant sway over patient decisions. Therefore, enhancing collaboration between TCM and Western medicine, organizing mutual lectures, or having Western doctors train in TCM departments could modernize TCM research. Moreover, TCM, much like a cocktail, involves complex interactions among its components, which can be either synergistic or antagonistic, making it challenging to isolate and purify individual components for basic research related to liver cancer. The tradition of family inheritance and secrecy in TCM hampers its progress and development. Many TCM experts have extensive clinical experience and possess secret formulas that greatly enhance patient survival and quality of life, but they are unable to disclose crucial parameter information due to intellectual property concerns. Unlike Western medicine with standardized guidelines, TCM relies on personal experience, leading to varying levels of consistency. Formulas such as Pien Tze Huang are kept confidential, which obstructs the comprehension of their synergistic effects,

material basis, dosage ratios, pharmacological actions, and clinical effects. Traditional TCM practitioners often lack modern statistical knowledge, making it difficult to design large-scale clinical studies or fundamental experiments to explore mechanisms. We did not find relatively standard clinical trials and experimental data *in vivo* and *in vitro* for the treatment of liver cancer by CB after an extensive literature search. This will also become a key area for future research and development. The lack of clinical trials is likely because most liver cancer patients seek treatment from experienced and reputable senior TCM practitioners, who usually provide personalized treatment based on experience and are not accustomed to conducting standardized prospective or retrospective clinical trial designs. They focus more on empirical treatment rather than rigorous statistics and calculations. Collaboration between professional clinical trial administrators and TCM experts will help advance clinical trials in the future. The government should fund the protection of TCM experts' intellectual property while ensuring these effective secret formulas are made public so that more scientists can efficiently investigate their mechanisms. Furthermore, to standardize the diagnosis and treatment of PLC in TCM, a standardized plan should be developed based on systematic literature reviews and the inheritance of expert experiences.

CONCLUSION

Huang *et al*'s research meticulously demonstrated CB's anti-cancer properties, deepening our understanding of TCM and aiding in developing new liver cancer therapies[14]. While TCM shows considerable research and application potential for liver cancer treatment, delivering real benefits to patients globally necessitates the joint efforts of scientists, government bodies, and traditional TCM practitioners.

FOOTNOTES

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