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LETTER TO THE EDITOR

# Anti-tumor efficacy of *Calculus bovis*: Suppressing liver cancer by targeting tumor-associated macrophages

Ishita Kathuria, Bhupesh Singla

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## Abstract

Despite significant advances in our understanding of the molecular pathogenesis of liver cancer and the availability of novel pharmacotherapies, liver cancer remains the fourth leading cause of cancer-related mortality worldwide. Tumor relapse, resistance to current anti-cancer drugs, metastasis, and organ toxicity are the major challenges that prevent considerable improvements in patient survival and quality of life. *Calculus bovis* (CB), an ancient Chinese medicinal drug, has been used to treat various pathologies, including stroke, convulsion, epilepsy, pain, and cancer. In this editorial, we discuss the research findings recently published by Huang *et al* on the therapeutic effects of CB in inhibiting the development of liver cancer. Utilizing the comprehensive transcriptomic analyses, *in vitro* experiments, and *in vivo* studies, the authors demonstrated that CB treatment inhibits the tumor-promoting M2 phenotype of tumor-associated macrophages *via* downregulating Wnt pathway. While multiple studies have been performed to explore the molecular mechanisms regulated by CB, this study uniquely shows its role in modulating the M2 phenotype of macrophages present within the tumor microenvironment. This study opens new avenues of future investigations aimed at investigating this drug's efficacy in various mouse models including the effects of combination therapy, and against drug-resistant tumors.

**Key Words:** *Calculus bovis*; Liver cancer; M2-like tumor associated macrophages; Wnt/β-catenin pathway; Tumor environment

**Core Tip:** *Calculus bovis*, a traditional animal drug used in China, has been recognized for its therapeutic effects across various organ systems, including the central nervous, cardiovascular, respiratory, and digestive systems. Recent studies have also suggested its anti-tumor potential. While previous studies have explored the mechanisms of action of its active compounds, this study provides novel insights into its anti-tumor potential using a liver cancer xenograft model. M2 macrophages are associated with tumor progression because they promote tumor growth, angiogenesis, and metastasis while inhibiting effective anti-tumor immune responses. This study, for the first time, demonstrates that *Calculus bovis* modulates the tumor environment by governing M2-tumor-associated macrophages in a Wnt pathway-dependent manner, thereby suppressing tumor growth.

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## TO THE EDITOR

### *Liver cancer and treatment strategies*

Liver cancer is one of the most prevalent cancers worldwide and accounts for over 800000 deaths annually[1]. Treatment for liver cancer is tailored to individual needs, considering the tumor stage, the extent of the underlying disease, and the expected patient's response to available therapies[2]. For early-stage liver cancer, therapeutic interventions include surgical resection of tumor-bearing liver parts, transplantation with a healthy donor liver, ablation therapies to destroy tumors, and other modalities to kill cancer cells[3-5]. However, treatment options for intermediate- and advanced-stage cancer include transarterial embolization to block the blood supply to tumors, multiple kinase inhibitors such as sorafenib and lenvatinib, and immune checkpoint blockers like atezolizumab/bevacizumab[5-10]. These treatment strategies despite decreasing yearly mortality rate and improving patient survival, often possess significant adverse effects. Additionally, patients may experience tumor reoccurrence, metastasis, resistance to treatments, and liver toxicity[11-14]. These challenges indicate the limitations of current therapies and suggest the urgent need for more effective and safer therapeutic alternatives.

### *Role of tumor-associated macrophages and β-catenin pathway in liver cancer*

The heterogeneity of the tumor immune microenvironment (TME) significantly contributes to tumor metastasis, relapse, and drug resistance[15]. To develop effective treatment regimens and successfully treat primary liver cancer, it is crucial to understand the TME composition both at baseline and during treatment. The TME consists of various types of immune cells including T and B lymphocytes, regulatory T cells, macrophages, neutrophils, dendritic cells, natural killer cells, platelets, and mast cells, as well as non-immune components such as cancer-associated fibroblasts, adipocytes, endothelial cells, pericytes and lymphatic endothelial cells and the extracellular matrix[16]. Additionally, the liver cancer TME comprises hepatic stellate cells, myeloid-derived suppressor cells[17], and liver sinusoidal endothelial cells[18]. In order to support their growth, cancer cells induce a tumor-supportive environment by reprogramming non-cancerous cells, remodeling the extracellular matrix, and altering the vasculature. Tumor-associated macrophages (TAMs), the most abundant immune cell population within a tumorigenic liver, are key players in sustaining cancer cell growth and invasiveness, often correlating with poor prognosis[19]. TAMs exhibit a high level of plasticity, differentiating into either tumor-promoting (M2) or tumor-regressing (M1) phenotypes. Inflammatory stimuli, such as interferon-gamma or microbial products like lipopolysaccharide molecules induce a 'classical activated' or M1-like phenotype, characterized by increased antigen-presenting capability, high cytotoxic activity, expression of pro-inflammatory cytokines, and activation of T helper 1 immune response. Conversely, growth factors [interleukin (IL)-4, IL-13, IL-10] and T helper 2-related cytokines in the TME promote alternative activation of macrophages into an M2-like phenotype. These M2 macrophages are marked by high expression of cytokines such as IL-10, transforming growth factor-β (TGF-β), and CCL17 and have poor antigen-presenting ability. These anti-inflammatory M2-TAMs possess immunosuppressive properties and promote cancer cell growth and invasiveness, making them a viable therapeutic target[20].

The Wnt/β-catenin pathway plays a crucial role in adult tissue homeostasis and embryonic development. Dysregulated activation of this pathway is responsible for the development of multiple diseases, including cancer[21]. Modulated Wnt/β-catenin signaling is one of the main genetic alterations in the pathogenesis of liver cancer. Gain-of-function mutations in the *CTNNB1* gene encoding β-catenin and loss-of-function *AXIN1* mutation occur in a significant number of human liver cancer patients[22]. The Wnt/β-catenin pathway comprises four components: Extracellular (Wnt proteins: Wnt3a, Wnt1, and Wnt5a), membranous (Wnt receptors: Frizzled and lipoprotein receptor-related protein 5/6), cytoplasmic (β-catenin, AXIN1, casein kinase 1, *etc.*), and nuclear (β-catenin translocates to the nucleus and induces the transcription of downstream target genes)[23]. Activation of Wnt receptors by Wnt proteins stabilizes β-catenin, promoting its nuclear translocation and leading to transcription of downstream target genes. In the absence of Wnt signaling, β-catenin undergoes cytoplasmic degradation, thereby preventing this signaling cascade[24].

### *Major findings, future directions, and conclusions*

Huang *et al*[25] investigated the anti-tumor potential of *Calculus bovis* (CB), a well-known animal drug made from the dried gallstones of *Bos taurus domesticus* Gmelin cows[26]. Previous studies have shown that CB inhibits liver tumor growth by modulating the viability of primary liver cancer cells and inducing their apoptosis[27,28]. Further, a derivative of CB has been reported to reduce hepatic and gut injury in an estrogen-induced cholestasis rat model by regulating inflammation, oxidative stress, apoptosis, and bile acid profiles[29]. Huang *et al*[25] utilizing both *in vitro* studies and *in vivo* liver cancer xenograft mouse models, elucidated the mechanisms by which CB suppresses M2-TAM polarization and inhibits tumor growth, making this study highly informative. The authors identified lithocholic acid as a key pharmacological component in CB extract, and glycohyodeoxycholic acid in CB-enriched serum. Using bioinformatics and docking studies to determine underlying molecular mechanisms, they prioritized the Wnt pathway due to its important role in cell proliferation, apoptosis, invasion, and tissue homeostasis, all of which are linked to liver cancer progression and immune modulation[30-33]. The study demonstrated that CB inhibits the tumor-promoting M2 polarization of TAMs by suppressing Wnt/β-catenin signaling, thus shifting the TME towards regression. This effect is supported by the elevated expression of genes associated with M2-TAMs, including, CCL2, IL-10, TGF-β, and Arg-1. *In vitro* experiments further revealed reduced migratory and invasion capabilities of HepG2 cells when treated with CB serum (M2-TAM conditioned medium). The involvement of the Wnt/β-catenin signaling pathway was investigated using a Wnt agonist SKL2001, which reversed CB's effects on TAM polarization.

While the study provides strong evidence supporting CB's anti-tumor effects through M2-TAM polarization and Wnt pathway inhibition, further research is needed. It would be interesting to explore the involvement of other molecular signaling pathways identified in the transcriptomic sequencing analysis, such as Phosphoinositide 3-kinase-Akt, Ras-associated protein1, and Ras in liver cancer development and CB's potential effects on these pathways[34-36]. Besides, Wnt signaling involves nuclear translocation of the β-catenin for regulating the expression of target genes, and several Wnt proteins (nineteen) have been identified till date, the in-depth effects of CB on the levels of these Wnt proteins and β-catenin nuclear translocation would provide further insights[23]. Although Huang *et al*[25] substantiated their findings with complementary *in vitro* and *in vivo* experiments and transcriptomic data, some areas require future investigations. The most abundant active compound identified in the study, lithocholic acid (CB extract) has been demonstrated to have anti-cancer properties[37,38]. Similarly, glycohyodeoxycholic acid (CB-serum), a bile acid derivative, has inhibitory effects in the carcinogenesis of various organs[39]. These findings suggest that these active constituents of CB may be responsible for the inhibition of liver cancer in CB-treated animals. For future research, ursodeoxycholic acid, a secondary bile acid with established anti-tumor activities and already used in clinics for the treatment of gallstones, biliary cirrhosis, and hepatic dysfunction should be used as a control to compare CB's anti-tumor effects[40-43]. Moreover, determining the levels of M1-[Inducible nitric oxide synthase, cluster of differentiation (CD) 80, CD86, and human leukocyte antigen-DR)[44] and M2-(CD206, CD204, and CD163)[45] TAMs using multiple markers would be informative. Angiogenesis, the formation of new blood vessels, is crucial for cancer progression as it supplies nutrients, oxygen, and growth factors to the tumors[46]. Additionally, efferocytosis, the process by which macrophages clear apoptotic and cancer cells, promotes a shift to an M2-like phenotype. This shift can inhibit anti-tumor activity and support angiogenesis through vascular endothelial growth factor production[47,48]. Future studies are needed to understand the effects of CB on angiogenesis, comparing it to known angiogenesis inhibitors like Sorafenib, and on efferocytosis to gain deeper insights into the mechanisms. Additionally, safety studies assessing hematological, liver, and renal function are also important[49]. Besides, this study opens new avenues of research focusing on the effects of CB in combination with commercially available anti-tumor therapies, in other models of hepatocellular carcinoma (syngeneic orthotopic with/without underlying liver cirrhosis), on immune cells other than macrophages, and bioavailability and pharmacokinetics of CB.

In conclusion, Huang *et al*[25] effectively demonstrate that CB exerts its anti-tumor effects by inhibiting M2-TAM polarization, eventually reducing the migratory, invasion, and proliferative capacities of hepatocytes. Further, CB modulates the M2 phenotype by inhibiting Wnt pathway. However, future studies are warranted to better understand the mechanisms and its safety profile with longer-term therapy.

## FOOTNOTES

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