



PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 99750

Title: Reevaluating Calculus bovis: Modulating the liver cancer immune microenvironment via the Wnt/ β -catenin pathway

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 08293294

Position: Peer Reviewer

Academic degree: PhD, Postdoctoral Fellow

Professional title: N/A

Reviewer's Country/Territory: China

Author's Country/Territory: China

Manuscript submission date: 2024-07-29

Reviewer chosen by: Shang Wu

Reviewer accepted review: 2024-10-10 00:56

Reviewer performed review: 2024-10-10 02:39

Review time: 1 Hour

Scientific quality	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



Scientific significance of the conclusion in this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This Editorial manuscript discusses in detail the role of Calculus Bovis and the wnt/ β -catenin pathway in the immune regulation of liver cancer. With the work published in World Journal of Gastroenterology, Calculus Bovis Modulates Liver Cancer Microenvironment via Wnt/ β -Catenin, as the core and entry point, the authors first review the dilemmas of liver cancer treatment, the early research progress of Calculus Bovis, and the role of Wnt/ β -catenin signaling pathway in tumor regulation. The authors then discuss in detail the article by Huang et al. published in the World Journal of Gastroenterology and objectively evaluate the findings and implications of their original study. What's more, the authors discuss it in greater depth. They reviewed the study of Wnt/ β -Catenin and M2 macrophages in liver cancer and its significance, and also discussed in detail the research progress of the anti-anti-cancer mechanism of Calculus Bovis, and made a discussion of the problems that still existed in the study of Calculus Bovis with a unique point of view. Overall, this editorial manuscript is fluent in language, scientifically and rigorously discussed, has its own insights, and is recommended for acceptance and publication. Small issues: 1. Abbreviations in articles



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should be scrutinized. For example, PLC appears without its full name, and the abbreviation "PLC" is not given for "Primary liver cancer" in the "INTRODUCTION" section. There were many other similar problems with abbreviations, including IL6, VEGFA, etc. There are also recurring abbreviations, such as TME, where the full name and abbreviation are given more than once. In addition, terms that appear only once do not need to be abbreviated, such as TNBC. 2. Paragraph "This editorial's study not only highlights new perspectives on CB's traditionalespecially in This editorial's study not only highlights new perspectives on CB's traditional especially in synergy with modern immunotherapy and chemotherapy." is suggested to be rewritten, the current description is too wordy. Other similar issues in the text are also suggested to be examined, especially the "CLINICAL SIGNIFICANCE AND APPLICATION PROSPECTS" and "CONCLUSION" sections. 3. In the picture in Figure 1, the capitalization of words needs to be harmonized, including "trace elements", "antopxidation", "anti-inflammatory", "cytostasis", etc. 4. The authors discussed the potential of combining CB and immune checkpoint inhibitors in the manuscript; are there any preclinical studies or clinical trials of combining CB and immune checkpoint inhibitors? If not, the progress of studies on the Wnt/ β -Catenin signaling pathway and M2 macrophages as targets for combination with immune checkpoint inhibitors is suggested to be added to the discussion.



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Peer-review model: Single blind

Reviewer's code: 08115782

Position: Peer Reviewer

Academic degree: Assistant Professor, PhD

Professional title: N/A

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input checked="" type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Scientific significance of the conclusion in this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

The manuscript makes a significant contribution to the field of liver cancer research by addressing a critical gap in the literature regarding the role of Calculus Bovis (CB) in liver cancer treatment, with a particular focus on its impact on tumor-associated macrophages (TAMs) and the Wnt/ β -catenin pathway. The study is well-organized, presenting a clear hypothesis that is methodically tested, with results and discussion sections that logically build upon each other. The experimental design is particularly robust, utilizing both in vitro and in vivo models to validate the findings, thereby strengthening the conclusions drawn. The authors are commended for their effort in discussing the potential clinical implications of their findings, which highlight CB's significance as a therapeutic agent in liver cancer treatment. However, the manuscript could be further enhanced by a more detailed analysis of the individual components of CB and their specific contributions to the observed effects, including any synergistic effects among the components. A more detailed comparison of CB's action with existing treatments would also be beneficial, placing the findings within the context of current therapeutic strategies and highlighting the potential advantages of CB. The study



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demonstrates CB's inhibitory effects on M2-TAM polarization, but the underlying mechanisms are not fully elucidated, suggesting a need for further exploration into the molecular interactions to provide deeper insights into CB's mode of action. Additionally, while the discussion on the potential for combination therapy with modern immunotherapies is promising, it lacks specific details; including preliminary data or a rationale for specific combination strategies could strengthen this section. I recommend that the authors expand the discussion on the specificity of CB's action compared to existing treatments, particularly in the context of liver cancer, and provide additional data on the long-term effects of CB treatment, including potential side effects or resistance development, to fully assess its therapeutic potential. With these revisions, the manuscript will not only provide novel insights into the potential of traditional Chinese medicine in modulating the tumor immune microenvironment but also become a significant asset to the scientific community.



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Reviewer's code: 08200937

Position: Peer Reviewer

Academic degree: Associate Professor, MD, PhD

Professional title: N/A

Reviewer's Country/Territory: China

Author's Country/Territory: China

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Review time: 3 Days and 21 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
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Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

In this editorial, authors comment on the work by Huang et al. published in the World Journal of Gastroenterology, which highlights the potential therapeutic value of CB in modern liver cancer treatment and suggests further investigation into its specific mechanisms and clinical applications to provide more effective and safer treatment options for liver cancer patients. And this editorial summarizes the innovative research findings on CB's regulation of the liver cancer immune microenvironment via the Wnt/ β -catenin signaling pathway, establishing the relationship between CB and tumor immune, and further emphasizes the tumor immune microenvironment and liver cancer progression mechanisms which provides a scientific basis for developing new liver cancer treatment strategies based on traditional Chinese medicine. Meanwhile, this editorial highlights the anti-liver cancer mechanism of CB. CB, a precious traditional Chinese medicinal material, exhibits various biological activities. Its main components include bilirubin, bile acids, amino acids, sterols, and other trace elements, with the composition varying among different sources of CB, such as natural Calculus Bovis (NCB), artificial Calculus Bovis (CBA), fed Calculus Bovis (CBS), and cultured Calculus



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Bovis (CCB). The combined effects of these components confer CB its extensive pharmacological effects and significant anti-tumor activity[10]. Among the primary active ingredients of CB, More important, this editorial suggests some future research directions include: exploring the specific mechanisms of CB in different liver cancer subtypes, evaluating its effects in combination with modern therapies such as immune checkpoint inhibitors, targeted therapies, and traditional chemotherapy, and utilizing genomics and proteomics technologies to identify the key active components and targets of CB, aiming to achieve personalized treatment and improve treatment safety and efficacy. limitations of the editorial: 1. the authors implied that the components of CB include bilirubin, bile acids, amino acids, sterols, and other trace elements, but they didn't explain whether there is a key component execute anti-tumor or immune regulation functions. 2. the authors mentioned the different sources of CB, such as natural Calculus Bovis (NCB), artificial Calculus Bovis (CBA), fed Calculus Bovis (CBS), are there any difference among different sources of CB?, do they performed the same functions?



RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 99750

Title: Reevaluating Calculus bovis: Modulating the liver cancer immune microenvironment via the Wnt/ β -catenin pathway

Provenance and peer review: Invited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 08115782

Position: Peer Reviewer

Academic degree: Assistant Professor, PhD

Professional title: N/A

Reviewer's Country/Territory: China

Author's Country/Territory: China

Manuscript submission date: 2024-07-29

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2024-11-06 01:39

Reviewer performed review: 2024-11-06 01:44

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation



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Scientific significance of the conclusion in this manuscript	<input checked="" type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input checked="" type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

This manuscript has been improved after peer review, and now I think it is ready to be accepted.