



PEER-REVIEW REPORT

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Title: Synergistic combination of curcumin targeting anti-liver cancer with total ginsenosides

Reviewer's code: 03569706

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Romania

Author's Country/Territory: China

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Reviewer chosen by: Jie Wang

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Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
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 type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input 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



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SPECIFIC COMMENTS TO AUTHORS

Avoid abbreviations in the title of the manuscript. Abstract: - provide the values for incidence, mortality, and recurrence rates for liver cancer. - define HepG2 and DDP abbreviations. - Numbers and results of comparisons must be provided in the Results section. Introduction: - "Liver cancer has high morbidity and recurrence rates" please provide the numbers supported by references. - I would not say that Cur is a cytotoxic drug. - This section must clearly present state of the art. Please briefly introduce the main results reporting curcumin and/or on liver cancer. Materials and Methods: - Is there any reason to use only male mice? Please provide an explanation in your manuscript. - Use the symbol instead of \times (1×10^7) - Provide the references for the used doses of Cur and TG. - How was the distilled water administrated? - The rationale of using different methods of administration for the drugs between groups must be explained. The trauma associated with intraperitoneal administration is higher than that of the oral dose. - Briefly present in the manuscript how the mice were euthanized. - Only the volume was tested? - Use the symbol instead of \times in "1 \times TBST" - The significance level needs to be adjusted according to the number of groups (which is 7). Results: - Move the following sentences to the methods section "During the experiment, the tumor volume of mice was measured every 7 days to evaluate their growth. After 21 days of treatment, the mice were sacrificed, and the tumor volume was measured." Briefly describe how the measurements were done. - The following section belongs to Discussion "The data indicated that Cur combined with TG inhibited tumor growth in mice with liver cancer, which had synergistic strengthening effects, and TG showed dose dependence." - References are not allowed in this section. - The following information belongs to state of the art "Recent studies have shown that cancer cells are sometimes able to evade the host immune system in the tumor microenvironment. One of the most



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critical checkpoint pathways in this system is tumor-induced immune suppression (immune checkpoint) mediated by the PD-1 and its ligand, PD-L1. Inhibiting the expression of PD-1 and PD-L1 can effectively inhibit the anti-tumor immunity of cancer cells (10-12)." - Provide P-values with four decimals and use the threshold of significance after adjustment to the number of compared groups. - The following information belongs to Discussion section "This indicates that the synergistic effects of Cur and TG mainly focus on the PD-L1 signaling pathways, and the combination of the two drugs may further inhibit the binding of PD-1 and PD-L1 to act on the immune system by inhibiting the expression of PD-L1." - The following information belongs to state of the art "The synergistic effects of Cur and TG mainly focus on PD-L1. Studies have shown that the expression level of PD-L1 on T lymphocytes is closely associated with Tregs (13,14), and that PD-L1 regulates and induced the development, maintenance and function of Tregs (15). CD4+CD25+Foxp3+ Tregs is a group of immunoregulatory cells with an inhibitory effect; tumor cells can recruit Tregs to inhibit anti-tumor immunity and promote tumorigenesis (16)." - The following information belongs to the Methods section: "To further investigate the mechanism of the interaction of Cur combined with TG through the PD-L1 signaling pathway, CD4+CD25+Foxp3+ Tregs were evaluated by flow cytometry to detect the expression in tumor tissues." - The following information belongs to the Discussion section "Therefore, it was speculated that the combination of Cur and TG could further inhibit the expression of CD25+Foxp3+ by inhibiting the expression of PD-L1." - The following information belongs to state of the art: "Cur had no effect when used alone, but Cur and TG in combination had synergistic effects on PD-L1. Cur has been proven to have powerful anti-inflammatory properties (17-19). Cur mediated the suppression of NF- κ B, NF- κ B is the master switch in the inflammatory cascade, is an extremely critical mechanism of its widespread therapeutic profile (20). The development of liver cancer is not only regulated by the immune system, but also



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closely associated with inflammation. A previous study proposed the theory of “hepatic inflammation-fibrosis-liver cancer axis” (IFC axis) (21). The formation of liver cancer at the end of the IFC axis is associated with NF- κ B signal transduction factors downstream of the pathway (22,23), while TLR4 can induce the activation of NF- κ B downstream of the pathway to produce inflammatory factors (24,25), activate the IFC axis and promote the development of liver cancer. Furthermore, NF- κ B-mediated cascades also act on the PD-L1 signaling pathway (26)." - The following information belongs to the Methods section "In order to determine whether Cur and TG prevent liver cancer by inhibiting inflammatory mechanisms or by suppressing inflammation-driven immunosuppression, the protein expression of TLR4 and NF- κ B were further investigated in tumor tissues." - The following information belongs to the Discussion section "Therefore, we speculated that the combination of Cur and TG might play an anti-liver cancer role and downregulate PD-L1 through TLR4 and NF- κ B mediated inflammatory signalling pathway." - The following information belongs to the Introduction section "Tumor angiogenesis is an important condition for tumor growth and metastasis (27). Meanwhile, this process is also regulated by the NF- κ B signaling pathway, which can modulate the iNOS or MMP9 expression to produce inflammatory cascades and promote tumor vascular development (28)." - The following information belongs to the Methods section "In order to determine whether Cur and TG inhibit tumor angiogenesis, the protein expression of iNOS and MMP9 was evaluated by western blot analysis." - The sentence starting to "It was identified that TG and chemotherapy could downregulate iNOS, but had no synergistic effects with Cur." are discussions not results. - The following sentence belongs to the Discussion section "In conclusion, these data indicated that Cur combined with TG plays an important role in anti-liver cancer vascular development by inhibiting the NF- κ B and MMP9 signaling pathway." - Fig 1B. I think that it is correct "Tumor volume" instead of "Tumor size". - Fig. 2A, 3A. It is not



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clear which groups were statistically significant different (*, **). Which is the significance of "#"? - Presents the results of statistical analysis using the statistic of the test and associated significance. - The use of column graph is misleading because you want to demonstrate the differences between means and a mean is a point value not a continuous one. Discussion: - Do not summarize your study in this section or state of the art (first paragraph). - Start this section with the main result. - Discuss your findings with references to your Tables and Figures, in the light of the scientific literature. - Avoid expression "recent". - Discuss the limits of your study. Did you consider of using liposomal curcumin (https://www.dovepress.com/articles.php?article_id=49861; https://www.dovepress.com/articles.php?article_id=49861; http://www.revistafarmacia.ro/201905/2019-05-art-23-Bulboaca_Bolboaca_Dogaru_905-911.pdf, <https://www.mdpi.com/1420-3049/24/5/846>) or nano-particles (<https://www.hindawi.com/journals/omcl/2019/7847142/>, <https://www.mdpi.com/1420-3049/24/15/2802>, <https://www.mdpi.com/2076-3921/8/10/504>) of curcumin to increase de disponibility? - Discuss the practical implication of your results.