

PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Cases*

Manuscript NO: 78360

Title: Screening of traditional Chinese medicine monomers as ribonucleotide reductase M2 inhibitors for tumor treatment

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05776245

Position: Peer Reviewer

Academic degree: BSc, MSc

Professional title: Academic Research, Research Scientist, Senior Scientist, Teaching Assistant

Reviewer's Country/Territory: Poland

Author's Country/Territory: China

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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 Grade E: Do not publish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 checked="" 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

Dear Authors, great work regarding RRM2 research through the prism of TCM monomers usage. I appreciate the attention to detail when preparing initial manuscript version - it was pleasant to read. Some aspects obviously required further polishing, that is why I recommend minor revisions. Please answer or consider the following: (1) Consider changing "inhibitor" to "inhibitors" in the title. I think it is more suitable to write "components as RRM2 inhibitors" than in singular form. (2) Try to limit the usage of "and" in sentences. Example is "The expression level of RRM2 gene in normal tissues and cancer tissues and the effect of RRM2 on the overall survival rate of cancer patients were analyzed by GEPIA database". Change the last "and" to "as well as". (3) In Abstract, "autodock" should be "AutoDock". (4) More major point - why did you use only overall survival and not disease-free survival data? The events caused by disease recurrence occur earlier than death from the disease and moreover DFS also include tumors that do not necessarily lead to death, which is not included in the OS. (5) In sentence "Literature mining showed that berberine, ursolic acid, gambogic acid, cinobufotalin, quercetin, daphnetin and osalmide could can act on RRM2 targets", leave "could" or "can", not both. (6) Correct obvious typos like "occured", "Key words", "caner" (should be "cancer", there are at least few such examples), "can not". (7) I miss citations at the beginning of Introduction, maybe add a few more? (8) In sentence "Human ribonucleotide reductase is composed of two large subunit M1 and two small subunit M2", I think "subunit" should be "subunits"? (9) In part "which is considered to be the target of cancer therapy", should the "considerated" be "considered"? (10) I did not like the beginning of

methodology, section 2.1 to be precise. At first, the title is very similar to first section of Results and is unfamiliar to methodology. The title for section 2.1 could be e.g. "Tumor patients' data acquisition", while the way you write sentence should be like "GEPIA was employed to analyze [...] as well as to evaluate its effect [...]". Please double-check the entire paper in search for sentences having improper tense. The first sentence of section 2.3 is an example of such sentence. (11) The part "Search and download articles related to TCM monomers acting on cancer RRM2 targets via [...]" I would change to "Searching and downloading articles related to TCM monomers that act on cancer RRM2 targets was performed with the use of [...]". (12) "the relevant parameters of RRM2 protein were set to" <- this part starts the sentence so the first letter should be uppercased. (13) In the case of Figure 1, I am unsure whether putting cohorts' abbreviations below bar plot as a part of graph, is a proper way. I think it can be put in figure description or alternatively, you can create a table in methodology (potentially for section 2.1) and explain all abbreviations in this location. This is optional but I think the paper would benefit from it. Moreover, please delete "Note" below the figure, and just change in the title "The RRM2 gene expression" to "The median RRM2 gene expression". (14) Figure 2 is illegible. Could you please upload full size image of high quality in the next round of revisions? Alternatively, I suggest to leave only statistically significant results and discard the rest. So the main figure would be smaller, while the rest could be in supplementary materials. In terms of title, please write "Effect of various RRM2 gene expression on [...]". (15) The sentence "Through literature search on Pubmed and CNKI, we found seven TCM monomers that can be used as RRM2 inhibitors, as follows (Table 1)" could be "Through literature search on Pubmed and CNKI, we found seven TCM monomers that can be used as RRM2 inhibitors (Table 1). They are described in subsequent sections.". Notice the change at the end of quotation. (16) For sentences like "The main mechanism is that berberine promotes cell cycle arrest and death of cancer cell lines by binding to P53,

NF- κ B, MMP, Bcl-2, ER and other receptors", it might be required to provide explanations of abbreviations, but please follow the journal guidelines to be sure. Moreover, from the current sentence it can be assumed that all mentioned proteins are receptors. Please change it e.g. to "binding to P53, NF- κ B, MMP, Bcl-2 or receptors e.g. ER". (17) "Anti apoptotic" or "anti allergic" should have hyphen, similar to "anti-cancer". Please double-check the entire paper. (18) Delete "and so on" in "Its major targets include NF- κ B, Bcl-2, CyclinD1, MMP-9, VEGF, EGFR, P53, mTOR, MMP-2 and so on". (19) In section 3.2.3, is "garcinic acid" a synonym to "Gambogic acid"? (20) In sentence "After cinobufagin treatment, the expression of RRM2 in endometrial carcinoma (Ishikawa cell line) decreased significantly at gene and protein levels, so as to inhibit cell proliferation and reduce invasiveness", change "so as to inhibit [...] and reduce [...]" to "inhibiting [...] and reducing [...]". (21) *In vivo* or *in vitro* should be italicized. Please double-check the entire paper. (22) In part "Meanwhile, It also has the characteristics of anti-malaria and antipyretic", the "It" must be lowercased. (23) For Table 1, do you think that inclusion of additional columns will be of use for readers? In my opinion, addition of whether the inhibitor is predicted or curated will be important, same in terms of what kind of studies confirmed it (*in vitro*, *in vivo*). (24) Section 3.3, change the title of it to "Selected monomers were found to bind RRM2", and in the text change "showed the interaction the above selected TCM monomers" to "showed the interaction between the aforementioned TCM monomers". (25) The part "exhibiting a good binding effect" (or similar) in each subsection of section 3.3 is unnecessary, because at the beginning there is mention that "they all had strong binding ability". Moreover, you can try to combine this subsection into one table, making the columns like binding energy, the type of bond (with Angstroms if applicable), implicated residues and some other if needed. The current figures could be put into supplementary materials as a single but large figure. However, I leave this suggestion optional. (26) "Cancer is a large group of disease that

seriously threatens human health and life [...]", should "threats" be "threaten"? (27) In part "It is known that some clinical anticancer chemotherapy are extracted from", should "chemotherapy" be "chemotherapeutics"? (28) In sentence "TCM monomer as a compound of TCM, its function still needs to be further explored and studied", I would change "[...] TCM, its function still needs to be [...]" to "[...] TCM, including its function, still needs to be [...]". (29) In sentence "Therefore, RRM2 can be used as a target of cancer therapy, inhibition or down-regulation of RRM2 expression may improve the prognosis of cancer patients", change second coma to semicolon. (30) What is "surmounte acquired tamoxifen resistance"? (31) In Discussion, change "most of RRM2 inhibitors developed act on" to "most of developed RRM2 inhibitors act on". (32) First letter of "conclusion" should be uppercased. (33) In "Authors' contributions" section after main text, most likely it will be required to provide more details. I suggest CRediT taxonomy, while equal contribution could be marked as # or * symbol at the beginning of paper, close to affiliation data.

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Peer-review model: Single blind

Reviewer's code: 06118161

Position: Editorial Board

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Professional title: Professor

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Author's Country/Territory: China

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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 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



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**Peer-reviewer
statements**

Peer-Review: [☒] Anonymous [☐] Onymous

Conflicts-of-Interest: [☐] Yes [☒] No

SPECIFIC COMMENTS TO AUTHORS

none

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Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

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Peer-reviewer statements	Peer-Review: [<input type="checkbox"/>] Anonymous [<input checked="" type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Very interesting article Figure number 2 needs to be replaced, the actual image is impossible to see