Dear Editor and Reviewers:

First of all, I'm very grateful to you for giving me an opportunity to revise my manuscript. I appreciate you very much for your positive and constructive comments and suggestions on my manuscript entitled " Screening of TCM monomers as RRM2 inhibitors for tumor treatment via literature mining and molecular docking technology" (ID: 78360).

I have studied the reviewers' comments carefully and tried my best to revise my manuscript according to the comments. The following are the responses and revisions I have made in response to the reviewers' questions and suggestions on an item-by-item basis. Thanks again for the hard work of the editor and reviewer.

Response to the comments to Reviewer #1:

Comment: Figure number 2 needs to be replaced. The actual image is impossible to see.

Response: I would like to thank you again for reviewing my manuscript and giving me valuable comments and suggestions. Figure 2 has been replaced by two clear figures in the revised manuscript, Figure 2 and Figure 3.

Response to the comments to Reviewer #3:

First of all, I apologize for so many places in my paper that need to be modified. Secondly, I would like to thank the reviewer again for reviewing my manuscript in detail and giving me valuable comments and suggestions, which will make my paper a qualitative improvement. At present, I have revised the manuscript for all the issues raised. Since there are really too many items that need to be modified, I will directly answer your questions one by one.

Comment No 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.

Response: The "inhibitor" in the title has been changed to "inhibitors".

Comment No 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".

Response: The usage of "and" in the revised manuscript has been reduced or replaced with other synonyms as suggested by the reviewer.

Comment No 3: In Abstract, "autodock" should be "AutoDock".

Response: The "autodock" in the Abstract has been modified to "AutoDock".

Comment No 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.

Response: Indeed, this is the limitation of our paper. In the GEPIA database, we only found data on the correlation between RRM2 and the overall survival rate of cancer patients, and no data on the impact of RRM2 on the disease-free survival rate of patients.

Comment No 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.

Response: Thank you for your reminding, the "can" in this sentence has been deleted.

Comment No 6: Correct obvious typos like "occured", "Key words", "caner" (should be "cancer", there are at least few such examples), "can not".

Response: All typos in the text have been corrected.

Comment No 7: I miss citations at the beginning of Introduction, maybe add a few more?

Response: At the beginning of the introduction, the corresponding citation has been added, which is the World Cancer Report: Cancer Research for Cancer Prevention from the World Health Organization.

Comment No 8: In sentence "Human ribonucleotide reductase is composed of two large subunit M1 and two small subunit M2", I think "subunit" should be "subunits"?

Response: The "subunit" in the Abstract has been modified to "subunits".

Comment No 9: In part "which is considered to be the target of cancer therapy", should the "considered" be "considered"?

Response: This typo has been corrected.

Comment No 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.

Response: The title of Section 2.1 has been revised as required by the reviewer. All the improper tense has been corrected throughout the entire paper.

Comment No 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 [...]".

Response: This sentence has been revised according to the requirements of the reviewer.

Comment No 12: The relevant parameters of RRM2 protein were set to" <- this part starts the sentence so the first letter should be uppercased.

Response: The first letter of this sentence has been uppercased.

Comment No 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".

Response: Regarding the tumor abbreviations in Figures 1 to 3, a table has been created in the method to describe them in the revised version (Table 1). The "The RRM2 gene expression" in the title has been revised to "The median RRM2 gene expression".

Comment No 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 [...]".

Response: Figure 2 has been replaced by two clear figures, figure 2 and figure 3. Their title also has been modified as required.

Comment No 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.

Response: 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)" has been revised to "Through literature search on Pubmed and CNKI, we found seven TCM monomers that can be used as RRM2 inhibitors (Table 1).

Comment No 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-κB, 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-κB, MMP, Bcl-2 or receptors e.g. ER".

Response: Following the magazine guide, we have explained some abbreviations, for example: matrix metalloproteinase (MMP). In addition, the sentence has been revised as suggested.

Comment No 17: "Anti apoptotic" or "anti allergic" should have hyphen, similar to "anti-cancer". Please double-check the entire paper.

Response: Similar errors in the full text have been corrected.

Comment No 18: Delete "and so on" in "Its major targets include NF-κB, Bcl-2, CyclinD1, MMP-9, VEGF, EGFR, P53, mTOR, MMP-2 and so on".

Response: The "and so on" in this sentence has been deleted.

Comment No 19: In section 3.2.3, is "garcinic acid" a synonym to "Gambogic acid"?

Response: This is a spelling error. The " garcinic acid " has been corrected to "gambogic acid".

Comment No 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 [...]".

Response: The sentence has been revised as required.

Comment No 21: In vivo or in vitro should be italicized. Please double-check the entire paper.

Response: The "in vivo" and "in vitro" in the whole paper have been italicized.

Comment No 22: In part "Meanwhile, It also has the characteristics of anti-malaria and antipyretic", the "It" must be lowercased.

Response: The sentence has been revised.

Comment No 23: For Table 1, do you think that inclusion of additional columns with 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).

Response: Thanks for the valuable suggestion. The previous Table 1 has been deleted, and Table 2 related to TCM inhibitors that have been predicted or confirmed to inhibit RRM2 in tumors has been added, which lists the confirmed studies in which tumor studies have been confirmed (in vitro, in vivo, or bioinformatics analysis).

Comment No 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".

Response: The Title and sentences have been modified as requested by reviewers.

Comment No 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 Angstrems 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.

Response: We have deleted the "exhibiting a good binding effect" (or similar) in each subsection of section 3.3, it is really better to write this way. In addition, we have also sorted some contents in this section into Table 3 in the revised version.

Comment No 26: "Cancer is a large group of disease that seriously threats human health and life [...]", should "threats" be "threaten"?

Response: The "Threats" in this sentence has been corrected to "Threaten".

Comment No 27: In part "It is known that some clinical anticancer chemotherapy are extracted from", should "chemotherapy" be "chemotherapeutics"?

Response: We have revised this sentence.

Comment No 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 [...]".

Response: We have revised this sentence according to the suggestions of the reviewer.

Comment No 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.

Response: This sentence has been adjusted.

Comment No 30: What is "surmounte acquired tamoxifen resistance"?

Response: The "surmounte acquired tamoxifen resistance" has been revised to "improving acquired tamoxifen resistance".

Comment No 31: In Discussion, change "most of RRM2 inhibitors developed act on" to "most of developed RRM2 inhibitors act on".

Response: This sentence has been revised as suggested by the reviewer.

Comment No 32: First letter of "conclusion" should be uppercased.

Response: The first letter of "conclusion" has been uppercased.

Comment No 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.

Response: The author's contribution has been supplemented as required.

Best wishes,

Yours sincerely,

Yaya Qin