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PEER-REVIEW REPORT

Name of journal: *World Journal of Clinical Oncology*

Manuscript NO: 94009

Title: Preparation of kakkatin derivatives and their anti-tumor activity

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 03308606
Position: Peer Reviewer
Academic degree: MD, PhD

Professional title: Associate Professor, Staff Physician

Reviewer's Country/Territory: Israel

Author's Country/Territory: China

Manuscript submission date: 2024-03-21

Reviewer chosen by: AI Editor

Reviewer accepted review: 2024-06-29 09:53

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Review time: 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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

SPECIFIC COMMENTS TO AUTHORS

Hepatocellular carcinoma (HCC) is the common malignancy with a high mortality rate and an increasing incidence all over the world. In addition to the surgical treatment, the multi-kinase inhibitor sorafenib has been suggested for the treatment. However, sorafenib has only limited effects in HCC patients, and drug resistance occurs within six months. In addition, it has many side effects. All that require to develop new therapeutic approaches for patients with HCC. In this MS, authors tried to use plant-derived compounds from Puerariae flos that has been used for thousands of years to strengthen the immune response. Modern pharmacological studies have also confirmed that it has significant biological activities against liver damage, tumors and inflammation. Kakkatin is an isoflavone polyphenolic compound isolated from Puerariae flos flower. In that MS, new kakkatin derivative (6-(hept-6-yn-1-yloxy)-3-(4-hydroxyphenyl)-7-methoxy-4H-chromen-4-one, HK) was synthetized, and its anti-tumor activity on HCC and gastric cancer were assessed in vitro. Major remarks: The anti-tumor activities of kakkatin and kakkatin derivate against HK against HCC SMMC-7721 cells and gastric cancer MGC803 cells were evaluated and

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compared to the effects of cisplatin. It is not clear, why it was not compared with the effect of sorafenib that is known to be a main treatment approaches for HCC. It was also important to combination effect of derivate with sorafenib and cisplatin. The results are presented in the table, but it is not indicated the number of samples. In the cloning assay, it was not indicated how was made quantification of the assay, please add. In the Fig.4, it is also not indicated the number of evaluated samples, and it is no statistic. The results of GO analysis suggested that derivate mainly regulated metal ion binding, calcium ion transport, cellular response to hydrogen peroxide and positive regulation of MAP kinase activity. The results of KEGG pathway enrichment analysis showed that the effect of HK on HCC SMMC-7721 cells mainly involved the cAMP signaling pathway and the formation of neutrophil extracellular traps. By RT-qPCR validation in Figure 7, it was found upregulation of PDE3B (cuproptosis-related gene, can reduce cancer invasion and migration) and NFκB1 The role of NFKB1 in liver cancer is controversial. Thus, it was important to assess also the effects of the derivate on the pro- or anti-inflammatory properties of HCC cells. The attitude cells in vitro and in vivo can be rather different. Thus, it is important to assess the effects of kakkatin derivate in in vivo experiments. Minor remarks Many technical mistakes, please check the MS carefully