1.Comments:

1. **Several point mutations have been identified in human aquaporins (Hum. Mutat. 2008;29:1108–1117). Does expression of AQP3 and AQP9 protein in HCC associate with their gene mutation**?

I had read this review carefully, but so far there were no research reporting the expression of AQP3 and AQP9 in HCC associated with their gene mutation. Perhaps it still needs more explorations.

2. **Author mentioned that high AQP3 and low AQP9 expression predicts poor survival in HCC patients in separate analysis, what if the result if the analysis is combined for high AQP3 and low AQP9. Authors also mentioned that patients with high AQP3/low AQP9 expression showed increased metastasis formation (page 12). This statement should be corrected because authors did not perform metastasis/ migration assay. Otherwise, authors can also provide the migration data since AQPs are involved in the cell migration and proliferation.**

I have considered the result if the analysis is combined with high AQP3 and low AQP9 and I also had analyzed the data. However, I found no meaning by combining high AQP3 with low AQP9. Our study intended to evaluate the antioncogenic effects of Auphen and dbcAMP *in vivo* and investigate whether their underlying mechanism regulated AQP3 and AQP9 expression. And we found Auphen and dbcAMP could regulated the expression of AQP3 and AQP9. Due to the limited conditions, our cases are not large enough to gain the relationship between background (non-tumorous portion) AQP3/AQP9 expressions and the patients' prognoses. However, our study laid the foundation for the future large sample researches. We are committed to the future to collect more and more cases for further exploration.

Minor points:

a) **The immunohistochemistry protocol mentioned only for tumor tissues? Provide a clear method.**
   I had corrected it according to your comments.

b) **In Fig 1C, it is best to provide the IHC with a matched HCC and normal (adjacent) liver tissue and measure their protein expression level.**
   I had corrected it according to your comments.

c) **In all figures, for statistical results, it is best to mentioned the P value, odds ratio or the mean in the legend.**
   I had corrected it according to your comments.

d) **The legend of fig 3 and 4 is the other way around. It is a bit confusing by mentioning nude mouse survival. It is not appropriate to link the mouse survival and the treatment in this mouse model. It**

is better to remove / separate the mouse image in the figure, do not mix with the tumor mouse in one image/figure. The number of mice that authors use was not stated in the method. How did the authors measure the tumor inhibition rates?

I had corrected it according to your comments. The inhibition rates of tumors with the formula: inhibition rates (%) = (NS tumor weight (g)-medication tumor weight (g))/NS tumor weight (g) × 100%).

e) **The Tunnel assay for in vivo model was not clear in the method.**
I had corrected it according to your comments.

2. Regarding the clinical investigation, I would like to ask whether there was a relationship between background (non-tumorous portion) AQP3/AQP9 expressions and the patients' prognoses. Probably many readers are also interested in this point.
Our study intended to evaluate the antioncogenic effects of Auphen and dbcAMP *in vivo* and investigate whether their underlying mechanism regulated AQP3 and AQP9 expression. And we found Auphen and dbcAMP could regulated the expression of AQP3 and AQP9. Due to the limited conditions, our cases are not large enough to gain the relationship between background (non-tumorous portion) AQP3/AQP9 expressions and the patients' prognoses. However, our study laid the foundation for the future large sample researches. We are committed to the future to collect more and more cases for further exploration.

3. My specific queries and comments are below:
1. **Design: Page 10 line 214-220 - "Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) assay The tumor tissues were fixed with 10% formalin for 4 h and embedded in paraffin. The slices were deparaffinized in water and placed in 3% H2O2 for 10 min at room temperature. The TUNEL assay was carried out according to the manufacturer's instructions (KGI Biotechnology, Nanjing, China). A positive result was brown staining in the nucleus". Can the authors clarify this methodology in more details?**
I had corrected it according to your comments.

2. **Statistical analysis: Page 10 -11 - Were the data distributed normally? If not, then perhaps medians would be better than means. Can the authors clarify this point?**
The data were not distributed normally. I analyzed the data using SPSS to get the P value without using means ± SD.

3. Results: The results section and material and methods section are

conflated. Results should be reported in the results section and a description of the methodology should be presented in the material and methods section. The data were not deeply analysed.
I had corrected it according to your comments.

4. The legends of the figures should be reviewed. ?
I had corrected it according to your comments.