

## **Reviewer 1**

The structure of manuscript is in keeping with the common required criteria. The topic of the work is very actual, because cholangiocarcinoma cancer is a very aggressive malignancy with a poor prognosis. Authors investigate the effects of Raddeanin A treatment on bile duct cancer. Authors' results suggested that Raddeanin A treatment caused increased apoptosis and impaired cell functions in cholangiocarcinoma cell lines via wee1-dependent mechanism and that Raddeanin A is an enhancer of 5-Fu in bile duct cancer through activating a group of the cell cycle and apoptosis pathways, such as cox-2, Bax, bcl-2, and cyclin E/D1. These findings together indicated that Raddeanin A is a potential novel therapeutic treatment for bile duct cancer. Work is clearly legible, brings summarizes new knowledge. The citations are actual and their format respect usual standards. The conclusion reflects the author's results and these can be accepted. I recommend the manuscript to be published. Kosice, 18. April 2019 MUDr. Jana Katuchova, PhD. Professor of Department of Surgery University Hospital Košice Slovakia

Appreciate reviewer's comments and the time spending in this manuscript.

## **Reviewer 2**

This study demonstrates that raddeanin A induced apoptosis and the potential association with Wee1. In Figures, the labels with a, b, c, d etc. in bar graphs are not explained in Figure legend. The manuscript would be more readable if the labels are explained more in detail. Please re-check the X-axis of Figure 1A so that the unit would be precise. For descriptions of protein expression in Figure 6, the concentration of 5-FU may be added in the text in Line 178-185.

Appreciate reviewer's comments and the time spending in this manuscript.

Response 1: To be clearer, the descriptions of letter labeling have been revised in the figure legends.

Response 2: X-axis of Figure 1A has been reedited.

Response 3: The concentration of 5-FU has been added in the manuscript.