**Point to point responses**

Reviewer A

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| No. | Issues | Responses |
| 1. | The manuscript is well written in the introduction but poorly describing the methods, results, and discussion. The authors used WiDr cells as a colon cancer model. However, in this cell line, the p53 is mutated, so the authors need to give further explanation the reasons why did they use WiDr cells to observe p53 expression and also give sufficient references related to this problem | Thank you for this pointing out. We already added in line 317-318. |
| 2. | Comment on Abstract: The authors need to give more detailed results and conclusions  . | Thank you for pointing this out. We already revised in line 29-35. |
| 3. | Comment on Materials and Methods: a. When describing Materials, give information of the company that produces the materials for example the antibody, MTT reagent, apoptosis kit staining reagent, cisplatin, quercetin standard.  b. Give information of the company that made the equipment for example the plate reader, flow cytometry, microscope.  c. When describing the method of the experiment please describe it until the data analysis. Separated the statistical analysis in a subsection. Give reference when applying an equation and special analysis data, for example, the combination index. | a-b Thank youi for pointing this out. We already added in line 109. 112, 120, 128-129, 131, and 142-143  c. Thank you for pointing this out. We already revised in line 148-149, 196, 203, 217-218, and 229-231 |
| 4. | 4. Comment on Results and Discussion: a. The authors should discuss the problem correlated with cisplatin as chemotherapy in colon cancer b. Please describe the results in a more well-organized paragraph. Describe the data and the interpretation sequentially. | a. Thank you for pointing this out. We already added in line 298-308.  b. Thank you for pointing this out. We already revised in line 329-338, 351-354, and 363-370 |
| 5. | 5. Comment on Figures: a. Some cells figure is too dark b. How many experiment replications were performed? Please give SD bar in the graph. c. The authors should give a scale bar of the measurement of the cell. The graph is not clear, hard to read. Please show the flow cytometry graph. Note: I gave my detailed comments in the manuscript file | 1. Thank you for your suggestion. We already revised our figures in line 444, 448, 452-460. 2. Thank you for pointing this out. We already added in line 614-618. 3. Thank you for your suggestion. We already revised 613, 615, 616, and 618. |
| 6. | 6. Comment on Tables: Give the reference of Table 1 | Thank you for pointing this out. We already added in line 657. |

Reviewer A, No.5

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| No. | Issues | Responses |
| 1. | Please check for writing the Latin word throughout the manuscript | Thank you for pointing this out. We already checked and revised in line 1, 10, 14, 39 |
| 2. | Please state the IC50 value | Thank you for pointing this out. We already added in line 23-24. |
| 3. | Give the CI value | Thank you for pointing this out. We already added in line 25. |
| 4. | Mention the proteins | Thank you for pointing this out. We already added in line 28-29. |
| 5. | Please clarify this sentence | Thank you for pointing this out. We already added in line 29-30. |
| 6. | Colon cancer is often associated with *p53* mutation, leading to the loss activity of p53 (cell cycle check point control, apoptosis) --> please mention about this | Thank you for pointing this out. We already added in line 76-80. |
| 7. | WiDr cells is a colon cancer cell line with *p53-mutant*, so the apoptosis induction should activate *p53* independent pathway. Please give reason why did the authors want to observe p53 expression level in a p53 mutant cell line? | Thank you for pointing this out. We already added in line 317-318. |
| 8. | When describing Materials, give information of the company that produce the materials for example the antibody, MTT reagent, apoptosis kit staining reagent, cisplatin, quercetin standard.  Give information of the company that made the equipment for example the plate reader, flowcytometry, microscope | Thank you for pointing this out. We alreade added in line 109, 111, 116, 122-125, 127, 138-139. |
| 9. | When describing method of experiment please describe it until the data analysis. Separated the statistical analysis in a subsection.  Give reference when applying an equation and special analysis data, for example the combination index | Thank you for pointing this out. We already revised in line 229-231.  Thank you for pointing this out. We already added in line 148, 196, 203, 217-218, 222-223 |
| 10. | Please clarify how did the authors get the fresh parijoto fruit? The source of the sample | Thank you for pointing this out. We already added in line 109. |
| 11. | Please give reference of this method | Thank you for pointing this out. We already added in line 111. |
| 12. | Clarify was the cisplatin was given or purchase and the company which produce it | Thank you for pointing this out. We already added in line 117 |
| 13. | What is the abbreviation stands for?  DMSO | Thank you for this pointing out. We already revised in line 120. |
| 14. | Clarify the laboratory | Thank you for this pointing out. We already revised in line 115-117. |
| 15. | Clarify the antibiotic used in the experiment | Thank you for this pointing out. We already revised in line 128. |
| 16. | Clarify the incubation condition | Thank you for this pointing out. We already revised in line 137. |
| 17. | Please give the reference here | Thank you for this pointing out. We already revised in line 148-149. |
| 18. | Point 2.6 and 2.7 is the same | Thank you for pointing this out. We already removed point 2.7. |
| 19. | Put all the analysis in after describing the method not as a separated sub section like this | Thank you for pointing this out. We already revised in line 197, 204, 212, 216, and 224. |
| 20. | Results and Discussion  The authors should discuss the problem correlated with cisplatin as chemotherapy in colon cancer  Please describe the results in a more well-organized paragraph. Describe the data and the interpretation sequentially. | Thank you for pointing this out. We already revised in line 299-310. |
| 21. | No description of the combination data and the cytotoxicity toward normal cells (Vero cells) in the results section | Thank you for pointing this out. We already added in line 326-330. |
| 22. | Give the unit, µg/mL? | Thank you for pointing this out. We already revised in line 240. |
| 23. | It should be in the method section | Thank you for pointing this out. We already removed in line 279-280. |
| 24. | Please clarify this sentence. Please describe the data in a more details | Thank you for pointing this out. We already revised in line 246-247. |
| 25. | Please describe it in a more details. For example, why did the authors choose Bcl2, p53, and caspase 9. How was the expression level of each protein based on the data of the experiment? | Thank you for pointing this out. We already revised in line 252-254. |
| 26. | Please describe it in a more details. For example, how much was the quantity of quercetin in the PME? | Thank you for pointing this out. We already revised in line 258-259. |
| 27. | How much was the IC50 of PME in Vero cells? | Thank you for pointing this out. We already revised in line 273. |
| 28. | Give the reference | Thank you for pointing this out. We already revised in line 290. |
| 29. | What was the unit of cisplatin concentration? In methods section the authors describe it in µg/mL | Thank you for pointing this out. We used µg/mL for the unit of cisplatin. |
| 30. | Please clarify this sentence | Thank you for pointing this out. We already added in line 285-290. |
| 31. | Please clarify whether this data also based on the experiment using WiDr cells? The mechanism of action also depends on the cell line molecular characteristic. As I mention before, in WiDr cell the p53 is in a mutant state. | Thank you for pointing this out. We already added in line 317-318. |
| 32. | PME contains not only quercetin. Please give information whether quercetin is the major constituents of PME? When describing the mechanism of actions it would be better if the authors also describe other possible mechanism from other bioactive components in PME. | Thank you for pointing this out. We already revised in line 357-359. |
| 33. | Nurulita’s study used *Gynura procumbens* ethyl acetate fraction, not quercetin. | Thank you for pointing this out. We already revised in line 380. |
| 34. | Please describe the conclusion in the abstract. | Thank you for pointing this out. We already added in line 33-35. |
| 35. | Increase …compared to? | Thank you for pointing this out. We already added in line 387. |

Reviewer B

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| No. | Issues | Responses |
| 1. | General comment: a. Some confusing results were occurred b. Author need to obey the journal guideline | Thank you. We have revised it. |
| 2. | Comment on Abstract: a. Author need to rearrange sentences (lines 21-23) b. Author need to use consistent phrase especially for method | 1. Thank you for pointing this out. We already revised in line 21-22. 2. Thank you for pointing this out. We already revised in line 110, 111, 133, 191. |
| 3. | Comment on Introduction: a. Author need to use reference style of the journal b. Some references in the body did not mentioned in the reference list | 1. Thank you. We have revised it. 2. Thank you for pointing this out. We already added in line 570-574. |
| 4. | Comment on Materials and Methods: a. subheading 2.7 and subheading 2.6 are similar. b. Author need to use consistent phrase especially for method (total flavonoid or quercetin level) b. Author need to rearrange some equation because some words are wrongly placed | 1. Thank you for this pointing out. We already remove it. 2. Thank you for this pointing out. We used both of them. We evaluated total flavonoid and quercetin level. 3. Thank you for pointing out. We already revised in line 148-150 |
| 5. | Comment on Results and Discussion: a. Author need to rearrange sentences b. Every figures or tables in the Results need to be explained c. Is Author sure about the result in table 2? In table 2, Author wrote that IC50 of PME on WiDr cells (198.6 ug/ml) was higher than Vero normal cells (52.58 ug/ml). It means that cytotoxicity of PME on Vero normal cells was stronger than on WiDr cancer cells. If the values in table 2 were wrong, it should be corrected (lines 272-274, table 2) d. Concentrations did not match with table 3 (lines 277-278) e. Author need to use references to explain the results (lines 285-289) | 1. Thank you. We have revised it. 2. Thank you for pointing this out. We already added in line 281-290, 320-322. 3. Thank you for pinting this out. We already revised in line 281-286. 4. Thank you for pinting this out. We already revised in line 294. 5. Thank you for pinting this out. We already revised in line 295-290. |
| 6. | Comment on References: Author need to use the journal reference style | Thank you. We have revised it |
| 7. | Comment on Figures: a. Figure 3 did not mentioned in the result. b. The information in figure 4 was not clear enough. Author need to change the graphic presentation. Simple clustered graphic can be used. or stacked graphic can be used for 100% cells count in 1 sample. c. Author need to use scale for cells figure. Figure 5-7 (A-D) seem not in the same scale. d. Some figures did not mention correct samples name (figures 5-7) | 1. Thank you for pointing this out. We already added in line 320-322. 2. Thank you for pointing this out. We already revised in line 608. 3. Thank you for pointing this out. We used different magnification. We already added noted in our figure in line 645-647, 654-657, 664-667. 4. Thank you for pointing this out. We already added our figure noted in line 649-651, 658-661, 668-671 |
| 8. | Comment on Tables: Table 2 did not match with results explanation. Reviewer suggest typo data or wrong calculation of SI in the manuscript. Author need to correct it. | Thank you for this pointing out. We already revised in line 281-290. |