Comments to the Authors,

In present study, Gu and colleagues reported that three miRNAs clusters (miR-99a/125b, miR-17/92 and miR-106b/25) were significantly associated with Berberine (a prestigious Chinese traditional medicine) mediated multiple myeloma therapy process. The discovery is quite interesting and would be a model to connect herbal medicine, epigenetics and disease mechanism. However, several small problems should be considered in the present manuscript.

**Major Compulsory Revisions,**

1, Only two human multiple myeloma cell were collected and applied in current study. Why RPMI-8266 and U266 were selected? Why not other MM cell lines? How to evaluate the relationship and phenomenon could be repeated in other cell lines? When we found miR-106b/25 were over-expressed in 8266 and U266 and then onco-MiR were defined. What should we do if we found miR-106b/25 were low expressed in some other MM cell lines? The sample size and the materials were too limited to get solid conclusion. Please make the study design more solid, especially considering the cancer were highly heterogeneous among different cells and different patients.

**Minor Essential Revisions,**

1, In Figure 1, expression level of miRNAs in different groups should be compared with its own internal control, rather than CD138+ cells. In addition, only miRNA-106 and miRNA-25 were detected in the Figure 1, why miR-93 was not detected? What’s the correlation between the expression of miR-106 and miR-25 in current study? The expression level of these miRs should be shown as boxplot with explicit outliner. Finally, why there is no error bar for CD138+ group?

2, In Figure 2, the author provided the P-value of the association between miRs with some disease, however, not only P-value, but the effect size was also very important to evaluate the association between miR with disease. This information should be provided. Also, I really confuse which statistic were applied to get the P-value? The website provided in the method cannot be accessed, meanwhile, no any detailed were mentioned for this result.

3, In Figure 4B, why there is no error bar for blank group?

4, The manuscript written should be revised deeply. Abstract is the most important section of the manuscript, however, in the main-body miR-17 and miR-99 were never mentioned, why they should be occurred in the abstract?

5, Finally, the most important extent work for this manuscript was the reason why Berberine could change the miRNA expression? Did Berberine change the methylation or histone modification of promoter region of miRNA-106/25 should be investigated.

6, All the abbreviation should be mentioned before usage, such as MM in the abstract

7, Supplementary Tables should be provided as Excel rather than Words within different sheets.