Reviewer 1

Major revision

1. The author cannot suggest a mechanism of NOB on bladder cancer cells without performing at least cytotoxic assay on a normal cell line.

Respond: Thanks for reviewer’s suggestion. The concentrations of NOB in this study have been examined in normal skin cell lines (HaCaT cells). The results exhibit that the toxicity of Nobiletin is lower in normal cells than in bladder cancer cells obviously.

2. Student’s test is not suitable to statistical analysis. You should use for example the ANOVA for analysis of variance, followed by Tukey’s test.

Responds: Thanks for reviewer’s suggestion. We have modified the correct description in 4.10. Statistical Analysis
Minor revisions

1. In the section “Materials and Methods” it is not indicated the vehicle in which the NOB is dissolved.

   Respond: Thanks for reviewer’s suggestion. We have modified mistake and expand description in line 348. Nobiletin dissolved in DMSO.

2. The English language needs to be improved.

   Respond: Thanks for reviewer’s suggestion. This manuscript has been improved by a native speaker.

3. If it is possible the bibliography should be integrated with some more recent articles.

   Respond: Thanks for reviewer’s suggestion. We have supplement some reference in the manuscript. Reference 19-22.


