Response to Reviewer 1 Comments

**Point 1:** The well written manuscript is concise and explains well the subject to be embroidered, however, some changes still need to be made and to complement the discussion. It is advisable to discuss the results with the findings of other researchers. On the other hand, it is a known compound of low yield of extraction from the natural source that also with a high commercial price which is already known its cytotoxic activity which lowers the novelty of the article.

**Response 1:** Thanks for the comments. According to the reviewer’s suggestion, we have added several findings of other researchers to complement the discussion. Please refer to line 282-283 and 368-373 in the updated manuscript. In addition, we had mobilized the whole team members to try our best to address the reviewer’s comments by careful revision using point-by-point fashion to improve the quality of our manuscript. Please refer to the revision as below.

**Point 2:** Introduction: Line 57 [11], \ What's that?

**Response 2:** Thanks for the kindly reminder. We have corrected the typing error. Please refer to line 58 in the updated manuscript.

**Point 3:** Materials: -No indication of how the compound was obtained (Ailanthone).

**Response 3:** Thanks for the comments. Ailanthone (Cat no. SA9130, purity: ≥98%) was purchased from Solarbio Life Sciences (Beijing, China). We have added this information in the Materials and Methods section. Please refer to line 83-84 in the updated manuscript.

**Point 3:** 2.2 Cell proliferation assay: -Indicate the concentrations used in the methodology. -how many repetitions were performed per assay? -which are the positive controls.

**Response 3:** Thanks for the comments. We have added the concentrations used in the method and the repetitions for this assay. Please refer to line 85-86 in the updated manuscript.

In addition, for the cytotoxicity of compounds, a solvent (DMSO) control group should be set up and the positive control wasn’t set up in many studies (Chen XY, et al., Oxid Med Cell Longev., 2019; Pan Z, et al., Oncol Rep., 2019; Liu L, et al., Front Endocrinol (Lausanne)., 2019). In our study, we also didn’t add the positive control in cell proliferation assay.
**Point 4**: 2.4, 2.5, 2.7 lack references on the basis of which studies the methodology was performed.

**Response 4**: Thanks for the kindly reminder. We have added the references for these assays in the methodology. Please refer to line 106, 112 and 124 in the updated manuscript.

**Point 5**: To include the structure of the Ailanthone and to compare in the discussion with another similar structure its effect opposite to melanoma.

**Response 5**: Thanks for the suggestions. To release the reviewer’s concern, we have added an image for the structure of ailanthone in the Introduction section. Please refer to line 68-69 in the updated manuscript. In addition, based on the chemical structure of ailanthone, we searched for the anti-tumor effects of other compounds with similar structure. It has been reported that one ailanthone derivative SUN2071 with 15 beta-acyloxy side chain showed significant tumor growth inhibition against melanoma B16 cells (Kato Taketoshi, et al., Anticancer Res., 1988). We have added this report in the Discussion section. Please refer to line 282-283 in the updated manuscript.