

Peer Review File

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Reviewer Comments (Round 1)

Major review

Comment 1: To “Monolayer wound healing assay” did authors use mitomycin C? The treatment with mitomycin C is to ensure that cells were migrating and not proliferating.

Reply 1: We have modified our text as advised (see Page 5, line 110). Mitomycin-C has both antineoplastic and antiproliferative properties^[1]. Mitomycin C induces the expression of VEGF111b, a splicing variant of VEGF-A, VEGF111b inhibits viability and proliferation of ovarian cancer cells in vitro^[2]. However, considering that mitomycin C may affect cell migration^[3,4], we chose to use serum-free medium to inhibit cell proliferation.

Changes in the text: To change “fresh” (lines 128.) to “serum free”.

1、 Lee BJ, Jeong JH, Wang SG, Lee JC, Goh EK, Kim HW. Effect of botulinum toxin type a on a rat surgical wound model. *Clin Exp Otorhinolaryngol.* 2009 Mar;2(1):20-7. doi: 10.3342/ceo.2009.2.1.20. Epub 2009 Mar 26. PMID: 19434287; PMCID: PMC2671832.

2、 Li, X., Gu, F., Niu, C. et al. VEGF111b, a C-terminal splice variant of VEGF-A and induced by mitomycin C, inhibits ovarian cancer growth. *J Transl Med* 13, 164 (2015).

3、 Chen TC, Ho WT, Lai CH, et al. Mitomycin C modulates intracellular matrix metalloproteinase-9 expression and affects corneal fibroblast migration. *Eur J Pharmacol.* 2019 Dec 15;865:172752.

4、 Shen CY, Chen LH, Lin YF, et al. Mitomycin C treatment induces resistance and enhanced migration via phosphorylated Akt in aggressive lung cancer cells. *Oncotarget.* 2016;7(48):79995-80007.

Comment 2: Results (pag.7, lines 152-155): “..Interestingly, low concentrations of methyl vanilate (0-200 $\mu\text{mol/L}$) did not inhibit HOSEpiC cell proliferation (Figure 1B). These results suggest that low-dose methyl vanilate can effectively inhibit the proliferation of SKOV3 cells and does not affect the proliferation of HOSEpiC cells.” Accordingly of figure 1 (pag. 15), low concentrations of methyl vanillate little decreased the viability of SKOV3 cells. I invite authors to double check this sentence.

Reply 2: We have modified our text as advised (see Page 9, line 181-185).

Changes in the text: To change “Interestingly, low concentrations of methyl vanilate (0-200 $\mu\text{mol/L}$) did not inhibit HOSEpiC cell proliferation (Figure 1B). These results suggest that low-dose methyl vanilate can effectively inhibit the proliferation of SKOV3 cells and does not affect the proliferation of HOSEpiC cells.” to “Interestingly, there was no statistically significant difference in the inhibitory effect of low concentrations of methyl vanillate (0-200 $\mu\text{mol/L}$) on HOSEpiC cell proliferation. Conversely, high concentrations of methyl vanillate (400-1600 $\mu\text{mol/L}$) have a similar inhibitory effect on HOSEpiC cell proliferation as SKOV3 cells (Figure 1B). ”.

Comment 3: Conclusion of abstract is better than general conclusion. I suggest to authors to review that.

Reply 3: We have modified our text as advised (see Page 2, line 42-45).

Changes in the text: To change “The development and application of new compounds targeting migration-related molecular pathways can effectively assist the treatment of ovarian cancer. This study revealed the crucial roles and the potential mechanisms of methyl vanillic in ovarian cancer treatment.” to “Methyl vanillate plays an important role in the progression of ovarian cancer by inhibiting cell proliferation and migration and EMT, which may be caused by the inhibition of ZEB2/Snail signaling pathway. Therefore, methyl vanillate may be a promising therapeutic drug for ovarian cancer.” .

Minor review

Comment1: To change “methyl vanilate” (lines 101, 110, 115, etc.) to “methyl vanillate”.

Reply1: We have modified our text as advised (lines 119,129,136,186,191).

Changes in the text: To change “methyl vanilate” to “methyl vanillate” .

Comment2: Figure 2: Double check figures C and D. Are these percentage?

Reply 2: Thanks for your advice. The percentage of C and D (Figure 2)has been rechecked by us.

Changes in the text: *****

Comment 3: Figure 3: Scale bars is not clear or visible.

Reply 3: We have modified our text as advised (Figure 3).

Changes in the text: Scale bars are added to each image.

Comment 4: Figure 5. Is there not scale bar?

Reply 4: We have modified our text as advised (Figure 3).

Changes in the text: Scale bars are added to each image.

Reviewer Comments (Round 2)

Comment 1:About Figure 2C: Group 0 (24h), to SKOV3, have 0.6% to wound healing. Is it correct?

Reply 1: We have checked and corrected our text (see Figure 2C).

Changes in the text: *****

Comment 2: It is suggested that authors double-check (Conclusion, lines: 318-319): "The anticancer effect of methyl vanilla in ovarian cancer can be weakened by EMT inhibition of ZEB2/Snail."

Reply 2: We have checked and corrected our text (see Page13, line 274-276).

Changes in the text: To change “The anticancer effect of methyl vanilla in ovarian cancer can be weakened by EMT inhibition of ZEB2/Snail.” to “Methyl vanillate plays an important role in inhibiting EMT and cell proliferation and migration of ovarian cancer, which may be caused by the inhibition of ZEB2/Snail signaling pathway. ”.