Dear Editor,

Thank you very much for decision letter along with the reviewer’s comments for our manuscript No.: ijms-414213

The reviewers requested modification, and more clarification. They also gave us several excellent suggestions which would strengthen our manuscript. We thank for reviewer’s constructive criticisms.

Please find some of our changes in revised MS. as highlighted in red in marked version.

Our point by point response to the comments of the reviewer is as follows:

Reviewer 2:

We have addressed the suggestions raised by the reviewer by performing a series of modifications

1. Line 48 “the presence of 2- alphaketoglutarate. Hydroxylated HIF-1α binds to von Hippele Lindau (VHL)” – correct spelling is “von Hippel Lindau”

Response 1: We thank the reviewer’s suggestions. We are very regret for our incautiousness. We have revised “von Hippele Lindau (VHL)” to “von Hippel Lindau (VHL)” (Page 2, Line 51).

2. Line 67 “was correlated with suppression of HIF-1α protein synthesis but not its degradation or” – change this to “but not its degradation”

Response 2: We thank the reviewer’s suggestions. We are very regret for our
incautiousness. We have revised “but bot not its degradation” to “but not its degradation” (Page 2, Line 70).

3. Line 342 “Based on our in vitro findings, HCT116 cells were injecting subcutaneously in mice and induced 343 tumor formation” – change this to “HCT116 cells were injected subcutaneously”

Response 3: We thank the reviewer’s suggestions. We are very regret for our incautiousness. We have revised “HCT116 cells were injecting subcutaneously in mice” to “HCT116 cells were injected subcutaneously” (Page 13, Line 347).

4. Line 355 “from five day. Tumor volume and mouse weight were measured using a equation and a disital” – correct to “an equation” and correct spelling “distal”

Response 4: We thank the reviewer’s suggestions. We are very regret for our incautiousness. We have revised “a equation” to “an equation” (Page 14, Line 360). We have revised “disital” to “digital” (Page 14, Line 360).

5. Line 372 “HIF-1α is a key stress-responsive transcription factor to low oxygen, the expression of HIF-1α 373 is associated with tumor progression and angiogenesis”- change this to “low oxygen; the expression…”

Response 5: We thank the reviewer’s suggestions. We are very regret for our incautiousness. We have revised “low oxygen, the expression…” to “low oxygen; the expression…” (Page 15, Line 377).

6. Line 387 “related to the activation of eIF4E. Importantly, eIF4E is a pivotal translation factor, it regulates the initiation of mRNA translation [24].” – change this to “factor; it regulates..”
Response 6: We thank the reviewer’s suggestions. We are very regret for our incautiousness. We have revised “factor, it regulates…” to “factor; it regulates…” (Page 15, Line 392).

7. Line 405 “The transcription of VEGF and EPO genes are mediated by HIF-1α, they are hypoxia-inducible 406 neuroprotective cytokines [30].” – change this to “mediated by HIF-1α; they are…”

Response 7: We thank the reviewer’s suggestions. We are very regret for our incautiousness. We have revised “mediated by HIF-1α, they are…” to “mediated by HIF-1α; they are…” (Page 16, Line 411).

8. Line 406 “In tumor tissues, VEGF is essential for tumor angiogenesis, it can induce the new blood vessels formation [31].” – change this to “angiogenesis; it can…”

Response 8: We thank the reviewer’s suggestions. We are very regret for our incautiousness. We have revised “angiogenesis, it can induce…” to “angiogenesis; it can…” (Page 16, Line 412).

9. Line 410 “EPO plays an important role in tumor angiogenesis in vivo, it can promote tumor cells survival and growth under hypoxic [34].” – change this to “in vivo; it can promote…”

Response 9: We thank the reviewer’s suggestions. We are very regret for our incautiousness. We have revised “in vivo, it can promote…” to “in vivo; it can promote…” (Page 16, Line 417).

10. Line 428 “suggests the0 potential use of vanillic acid cancer treatment, and
thus provides a basis for the” – correct the typo “the0”.

Response 10: We thank the reviewer’s suggestions. We are very regret for our incautiousness. We have revised “the0…” to “the…” (Page 16, Line 434).

We have re-checked the manuscript and found some inaccurate language and have made some modifications. Please review the changes in the revised MS. as highlighted in blue in marked version.

1. We are very regret for our incautiousness. We have revised “level” to “levels” (Page 1, Line 20).

2. We are very regret for our incautiousness. We have revised “declines” to “decline” (Page 2, Line 58).

3. We are very regret for our incautiousness. We have revised “isolated from the vanilla bean of Angelica sinensis as well as green tea” to “isolated from the Angelica sinensis and green tea” (Page 2, Line 64 to 65).

4. We are very regret for our incautiousness. We have revised “but does not” to “but not” (Page 9, Line 267).

5. We are very regret for our incautiousness. We have revised “HCT116 cells” to “HUVEC cells” (Page 11, Line 315).

6. We are very regret for our incautiousness. We have revised “HUVEC” to “HUVEC cells” (Page 11, Line 317).

7. We are very regret for our incautiousness. We have revised “Cell proliferation was also detected by an EdU incorporation assay. Following 12 h of treatment, vanillic
acid (30 µM) decreased the number of EdU-positive cells among hypoxia-exposed HCT116 cells (Fig. 6D). EdU staining demonstrated that vanillic acid treatment significantly suppressed DNA synthesis in HCT-116 cells compared with the positive control” to “Cell proliferation was also detected by a clonogenic assay. Following 12 h of treatment, vanillic acid (30 µM) decreased the number of hypoxia-exposed HCT116 cells. In other words, the clonogenicity of HCT116 cells was reduced in a dose-dependent manner (Fig. 6D)” (Page 12, Line 329 to 332).

8. We are very regret for our incautiousness. We have revised “inhibited HIF-1α mRNA, protein synthesis” to “inhibited HIF-1α protein synthesis” (Page 15, Line 388).

9. We are very regret for our incautiousness. We have revised “Because they were induced by HIF-1α, whether vanillic acid suppressed EPO and VEGF transcription in HCT116 cells was examined further” to “Since EPO was induced by HIF-1α, we further examined whether vanillic acid suppressed EPO and VEGF transcription in HCT116 cells” (Page 16, Line 417 to 419).