

Peer Review File

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**Reviewer A**

Comment 1: Key findings: Remove we analyzed and try to make more impersonal. Please correct this aspects throughout the entire work

**Reply 1: Thank you very much for your insightful advice.**

**Changes in the text: We have modified our text as advised (see Page 4, line 52).**

Comment 2: Line 55: “AD usually causes sudden persistent life-threatening pain” it is an unclear expression. It seems that pain is life threatening.

**Reply 2: Thank you very much for your insightful advice.**

**Changes in the text: We modified the words to make the expression clearer (see Page 4, line 58).**

Comment 3: Lines 56-59 are not in my opinion worth for introduction but should be in the beginning of the discussion. Please remove and provide references. Acute hypoperfusion of various organs is better with “end organ malperfusion” and provide some evidence.

**Reply 3: Thank you very much for your suggestion. we added relevant references (PMID: 27440162, 34599594)**

**Changes in the text: We have modified our text as advised and we added relevant references (see Page 5, line 59-62; Page 13, line 235-241).**

Comment 4: Lines 60-62 provides some references of these affirmations.

**Reply 4: Thank you very much for your suggestion. we added relevant references (PMID: 30086263, 18789403)**

**Changes in the text: We added relevant references (see Page 13, line 235-236).**

Comment 5: Lines 68-70 provide references.

**Reply 5: Thank you very much for your suggestion. we added relevant references (PMID: 29605031, 32748576)**

**Changes in the text: We added relevant references (see Page 5, line 70).**

Comment 6: Lines 72-75 is a summary of the results and findings of the paper and should be in the end of discussion, not here. Please remove

**Reply 6: Thank you very much for your suggestion.**

**Changes in the text: We removed this part (see Page 5, line 76-79).**

Comment 7: No major issues in Methods and Results. Just as a general factor, methods section is somehow too much technical and could be shortened is some extra details of the molecular biology procedures reported.

**Reply 7: Thank you very much for your suggestion.**

**Changes in the text: We have trimmed and modified the methods section**

**appropriately (see Page 7, line 105-109).**

Comment 8: Lines 229-240 reports mainly concepts that are already expressed in the introduction.

As suggested, you should shorten the introduction and provide information and references here. Then, I would like to have a little summary paragraph of few lines reporting what is new and what are the main findings of this paper right at the beginning of the introduction.

**Reply 8: Thank you very much for your insightful advice.**

**Changes in the text: we have modified our text as advised (see Page 12, line 232-240).**

Comment 9: Lines 266 -270 are quite useless in this discussion and or can be related to findings of the paper or should be erased.

**Reply 9: Thank you very much for your suggestion.**

**Changes in the text: we have modified our text as advised (see Page 14, line 274-278).**

Comment 10: Lines 282-288 needs to be shortened and please provide references of your statements.

**Reply 10: Thank you very much for your suggestion. we added relevant references (PMID: 34572082, 30086263)**

**Changes in the text: we have shortened our text as advised and added references (see Page 15, line 290-297).**

Comment 11: Lines 307-310: are those your findings, experiments or Literature results? No references on that aspect.

**Reply 11: These are Literature results. we added relevant references (PMID: 27283745)**

**Changes in the text: We have added references (see Page 16, line 318).**

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## **Reviewer B**

1. “four control, five AD” should be replaced with “four controls, five ADs”.

**Reply: Thank you very much for your insightful advice.**

**Changes in the text: We have modified our text as advised (see Page 6, line 100).**

2. DEG should be defined upon first use in the Main Text.

**Reply: Thank you very much for your insightful advice.**

**Changes in the text: We have modified our text as advised (see Page 7, line 133).**

3. When the manufacturer or a company is reported in the text, it should be accompanied by its city (location).

**Reply: Thank you very much for your insightful advice.**

**Changes in the text: We have modified our text as advised (see Page 7, line**

107-108, 117, 121).

4. “Zhang et al. reported that tamibarotene can reduce the damage response pathway and inflammatory pathway activation after inflammatory stimulation in smooth muscle cells by inhibiting the transcription factor KLF5(40).”

The author name should be checked for accuracy and consistency with the bibliography.

**Reply: Thank you very much for your insightful advice.**

**Changes in the text: We have modified our text as advised (see Page 16, line 320).**

5. “**Studies** have shown that serum and local osteopontin expression levels are significantly increased in AD patients. **Studies** have also shown that osteopontin affects the progression of the interlayer by enhancing matrix metalloprotein (MMP)-2 gene expression and activity in human vascular smooth muscle cells and affecting extracellular matrix secretion(30).”

Studies were mentioned, please confirm whether references or more than one reference are needed.

**Reply: Thank you very much for your suggestion.**

**Changes in the text: We have modified our text as advised (see Page 15, line 288-290).**

6. All the gene names used should be italicized.

**Reply: Thank you very much for your suggestion.**

**Changes in the text: We checked the full text and made corrections.**

7. The sign, \* under Statistical Analysis is not necessary.

**Reply: Thank you very much for your suggestion.**

**Changes in the text: We have modified our text as advised (see Page 9, line 170).**

8. All the abbreviations in the figure(s) and table(s) should be defined in the explanatory legend.

**Reply: Thank you very much for your suggestion.**

**Changes in the text: We have added the abbreviations in our text as advised (see Page 25-28).**

9. Table 3

\*”The top 10 protential drugs targeting AD.” - should potential be potential?

\*“Chimical Formula” - should Chimical be Chemical?

**Reply: Thank you very much for your suggestion.**

**Changes in the text: We have modified the words (see Page 21, line 446-447).**

10. Figure 1B

The white arrow needs an explanation in the legend.

**Reply: Thank you very much for your suggestion.**

**Changes in the text: We have added an explanation in the legend (see Page 25, line 473).**

11. Figure 2D

“positive regulation of **esponse** to external stimulus” - should **esponse** be response?

**Reply: Thank you very much for your insightful advice.**

**Changes in the text: It should be response. We have modified figure 2 (see Page 22, line 450).**