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Benvitimod ameliorates MC903-induced mouse atopic dermatitis-like lesions and regulates skin barrier proteins

Qiuyu Jia, Xiaojie Wang, Jianzhong Zhang

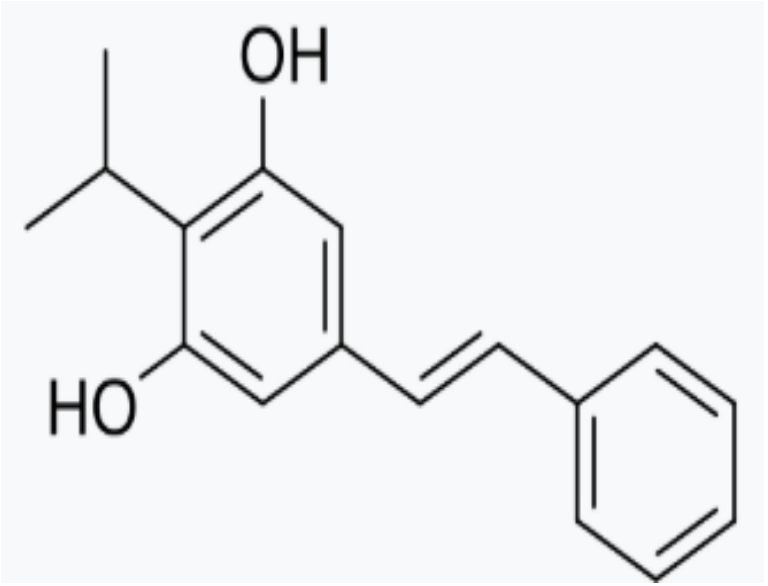
Department of Dermatology, Peking University People's Hospital

Background and Objective

- Benvitimod(tapinarof) is an aryl hydrocarbon receptor (AhR) modulator and has been approved for the treatment of atopic dermatitis in China and in the Unites States.

- The MOA of benvitimod is still not clear and need to be clarified.

- The purpose of this study is to investigate the effects of benvitimod on mouse dermatitis and on skin barrier protein.



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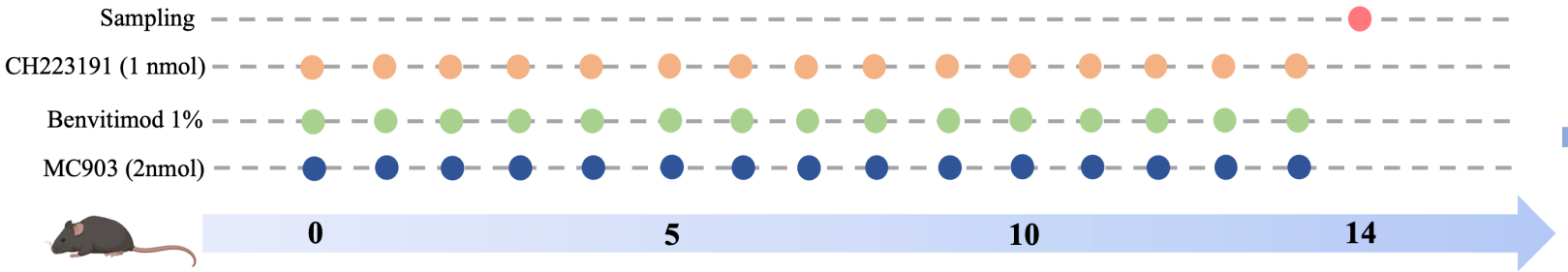
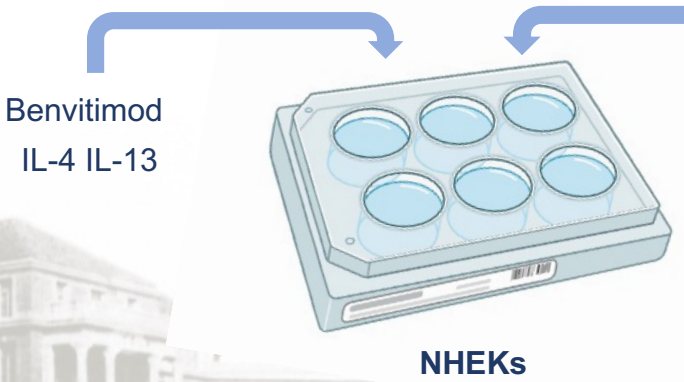
Materials and Methods

Part 1: Animal Experiment



- Histopathology
- ELISA
- qPCR
- Western blot

Part 2: In vitro Study (NHEK culture)



- qPCR
- Western blot

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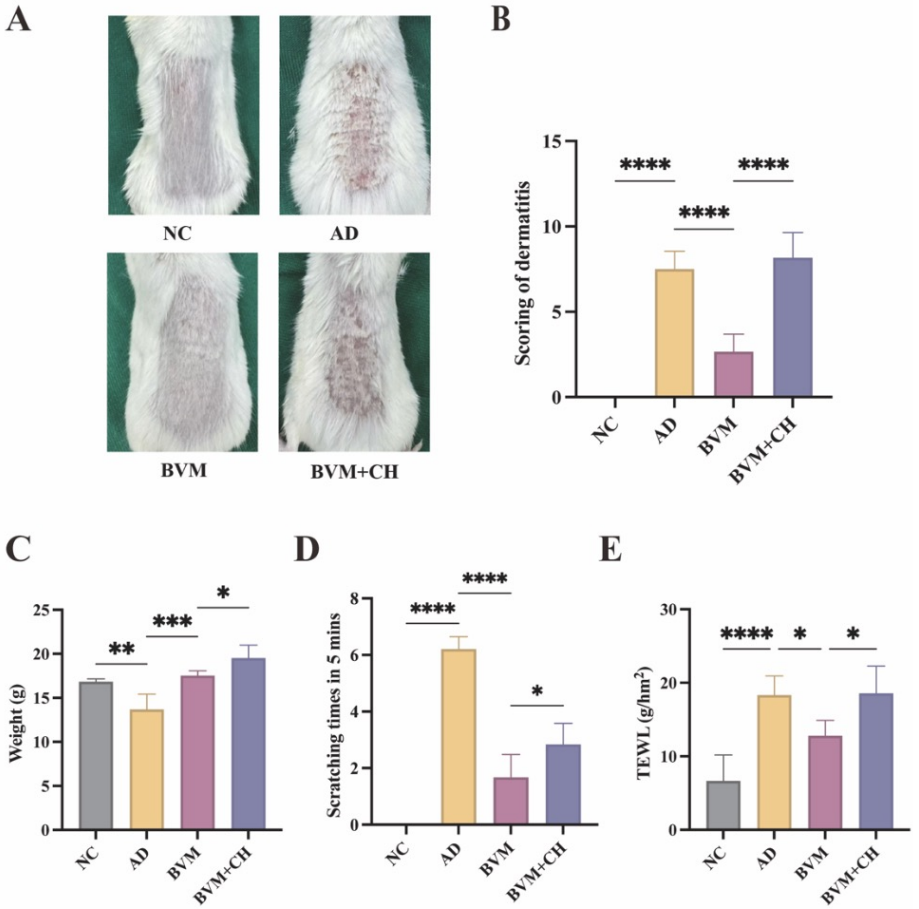
Results

1. Benvitimod treatment improved dermatitis in mouse AD model

- The **dermatitis score** was reduced by treatment with benvitimod.
- The **frequency of scratching** was decreased upon treatment with benvitimod.
- The **TEWL** was reduced by treatment with benvitimod.
- The above effects of benvitimod were all inhibited by AHR antagonist CH223191.



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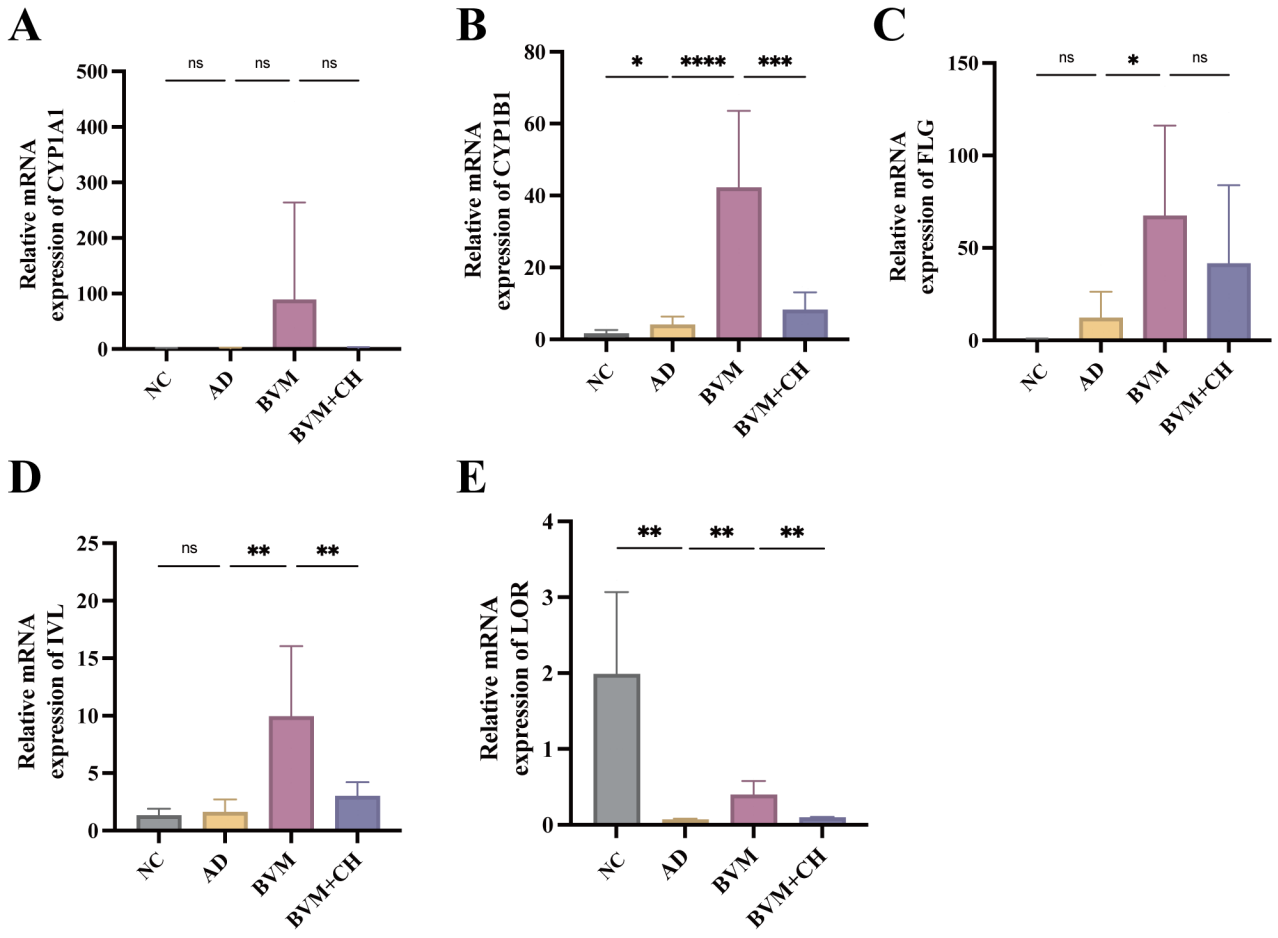
2. Benvitimod upregulated skin barrier molecule mRNA expressions in mouse AD model

- FLG, IVL and LOR mRNA levels were upregulated by treatment with benvitimod.
- At the same time, CYP1A1 and CYP1B1 were also upregulated.
- Pretreatment with CH223191 inhibited the upregulation of FLG, IVL, and LOR mRNA expression, suggesting that the effects of benvitimod is AHR-dependent.



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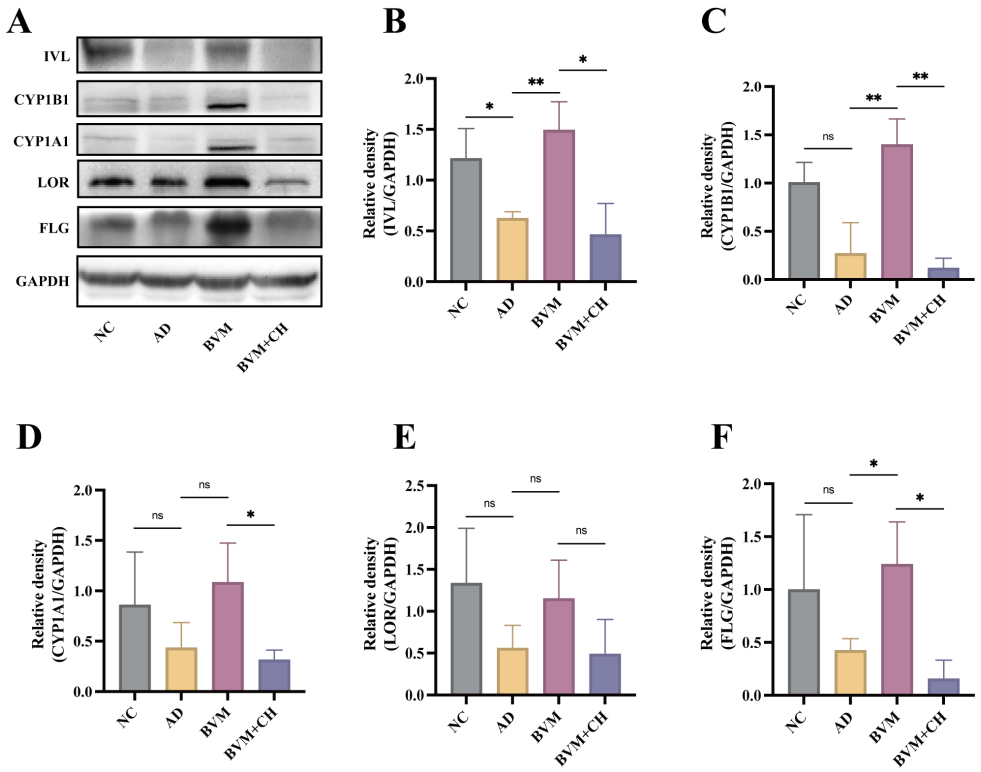
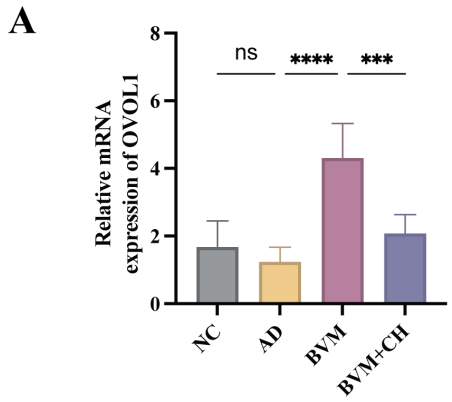
3. Benvitimod upregulated skin barrier protein expressions in mouse AD model

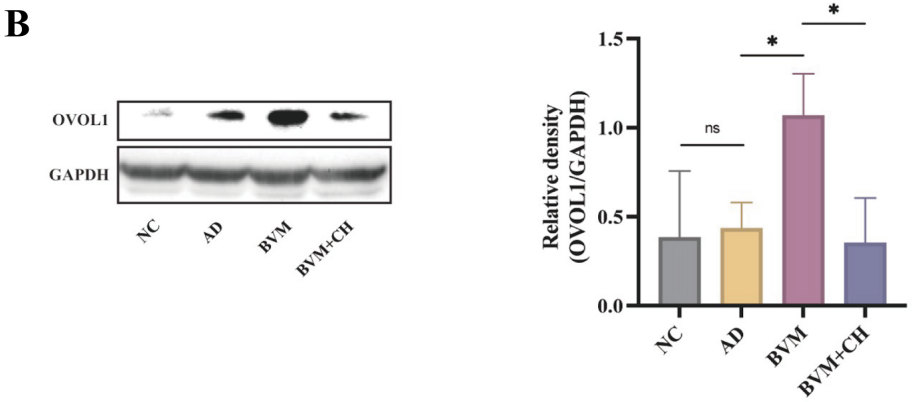
- The downregulation of FLG, IVL and LOR protein levels in mouse dermatitis were recovered by treatment with benvitimod.
- The CYP1A1 and CYP1B1 protein levels were also upregulated.
- These effects of benvitimod were all blocked by AHR antagonist CH223191.



4. Benvitimod upregulated OVOL1 expression in mouse AD model

- The OVOL1 mRNA and protein expressions were upregulated by benvitimod treatment.
- Again, These effects of benvitimod were blocked by AHR antagonist CH223191.





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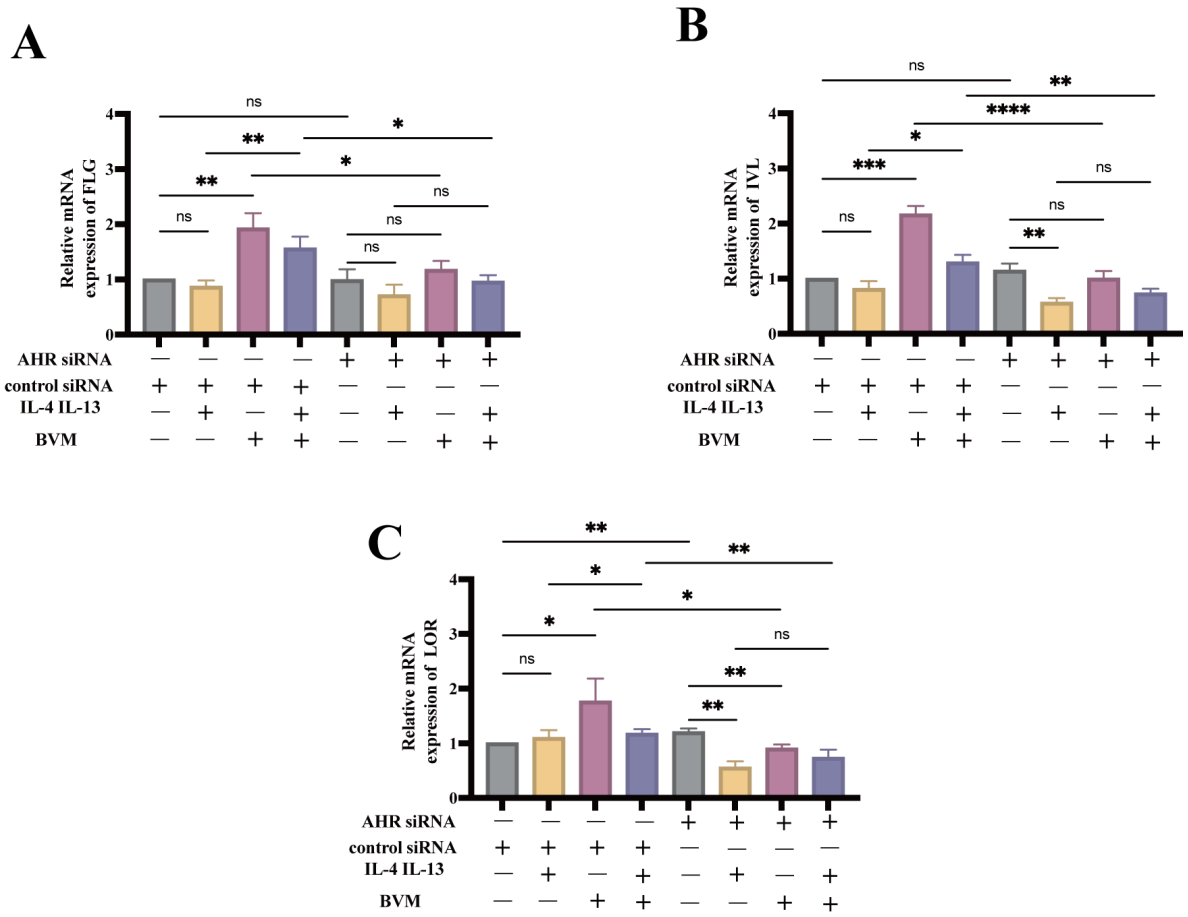
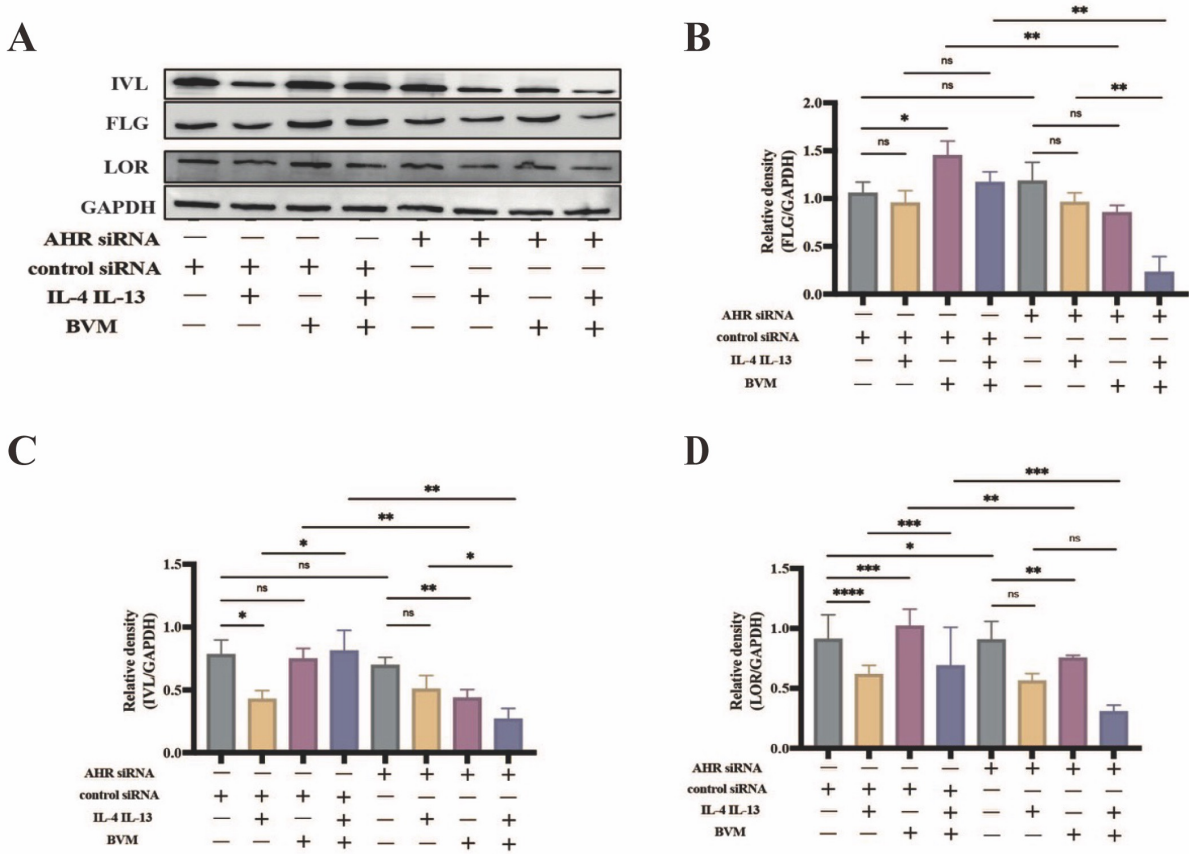
5. Results of *in vitro* Study: Effects of benvitimod on FLG, IVL and LOR mRNA expressions in NHEKs

- The FLG, IVL and LOR mRNA expressions were downregulated by IL-4 and IL-13.
- Addition of benvitimod to culture media recovered FLG, IVL and LOR mRNA levels.
- Transfection of AHR siRNA inhibited these effects of benvitimod.



6. Results of *in vitro* Study: Effects of benvitimod on FLG, IVL and LOR protein levels in NHEKs

- The FLG, IVL and LOR protein levels were also downregulated by IL-4 and IL-13.
- Again, benvitimod recovered the FLG, IVL and LOR protein levels.
- Transfection of AHR siRNA also inhibited upregulation of FLG, LOR and IVL protein levels



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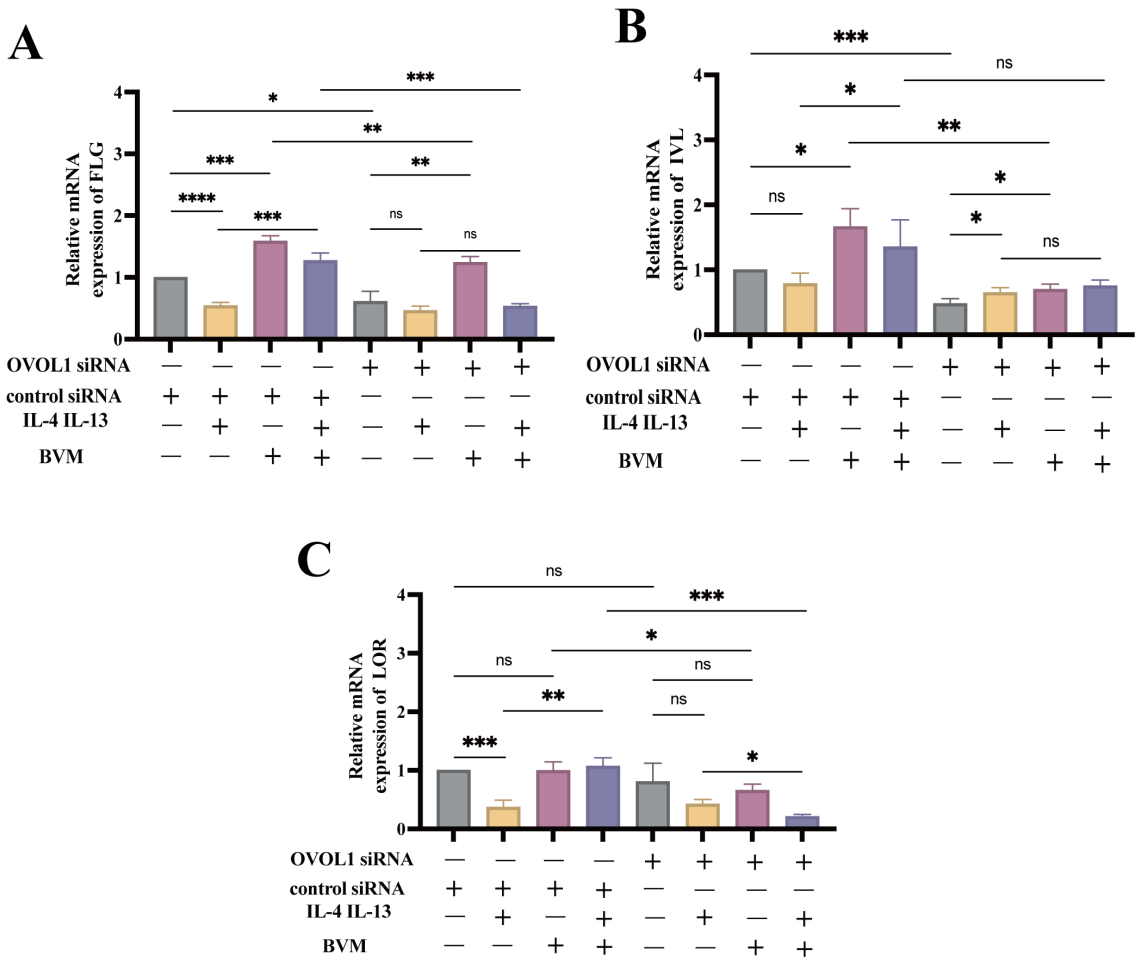
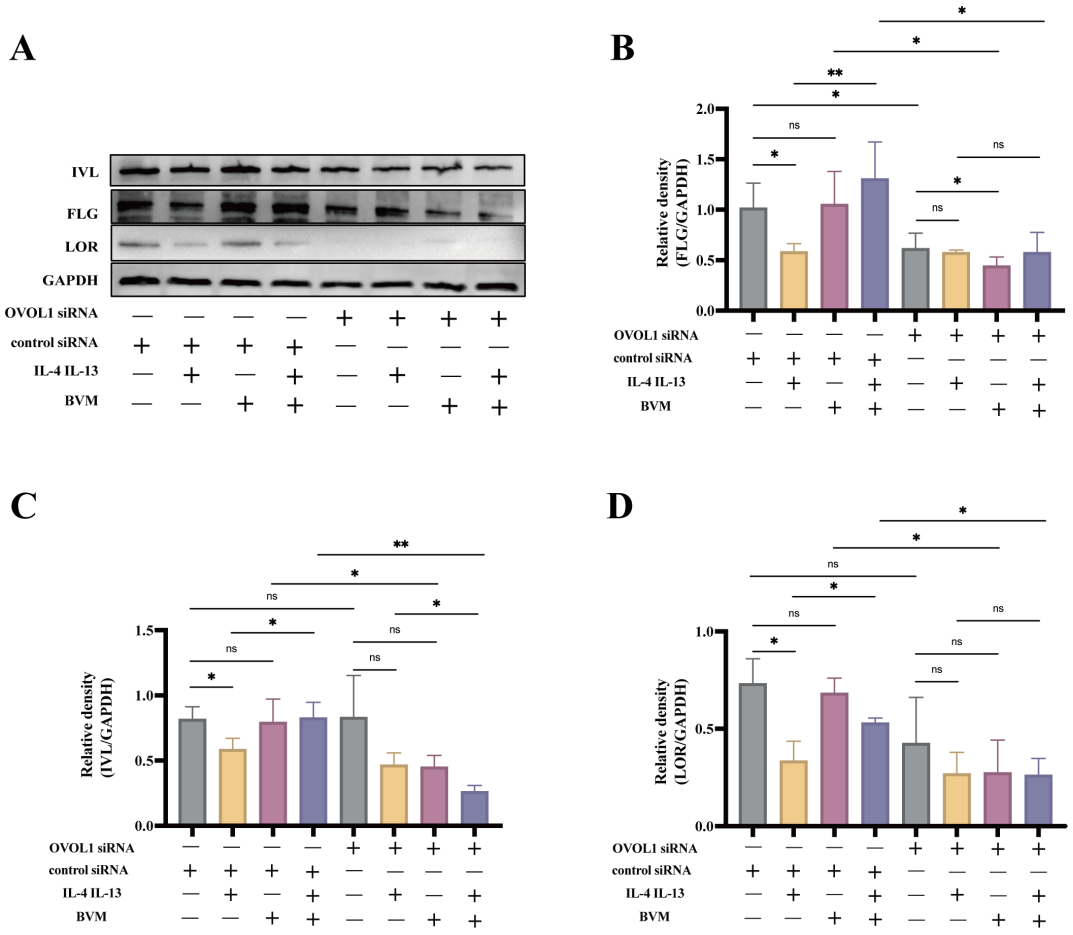
7. Results of *in vitro* Study: Knockdown of OVOL1 blocked the effects of benvitimod (mRNA levels)

- The FLG, IVL and LOR mRNA levels were upregulated by benvitimod in NHEKs.
- In NHEKs with OVOL1 gene knockdown, benvitimod failed to upregulate LOR and IVL mRNA expressions.



8. Results of *invitro* Study: Knockdown of OVOL1 blocked the effects of benvitimod (protein levels)

- The FLG, IVL and LOR protein levels were upregulated by benvitimod in NHEKs.
- These effect were abrogated in NHEKs transfected with OVOL1 siRNA, suggesting that the effects of benvitimod were OVOL1-dependent.



Conclusion

1. In animal experiments, topical treatment with benvitimod significantly improved MC903-induced mouse dermatitis.

2. In vitro study showed that benvitimod could inhibit downregulation of skin barrier molecule expressions induced by type two cytokines.

3. Inhibition of AHR or knockdown of OVOL1 gene blocked all effects of benvitimod, suggesting that the effects of benvitimod are mediated through AHR signaling pathway.

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Thank you !

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