Isomerization of urocanic acid by ultraviolet radiation and its role in modulation of skin microbiome, antimicrobial peptides, and immune function.

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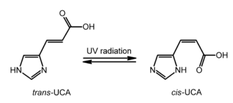
Introduction:

- Urocanic acid (UCA) is present locally in the stratum corneum of the skin in its trans isoform (*trans*-UCA)
- Upon ultraviolet-radiation (UV-R) *trans*-UCA is isomerized to *cis*-UCA. [1]



- *cis*-UCA is known to induce immune suppression via 5-HT$_2$A receptor, serotonin signaling and various other pathways. [2]
- Since skin microbiome is established all over the surface of the skin, we investigated the effects of *cis*-UCA on the skin microbiome and antimicrobial peptides (AMPs) expression and further looked into the immune modulation using mouse models. [3]

Results:

1. PUVA and UV-B isomerizes *trans*-UCA to *cis*-UCA.

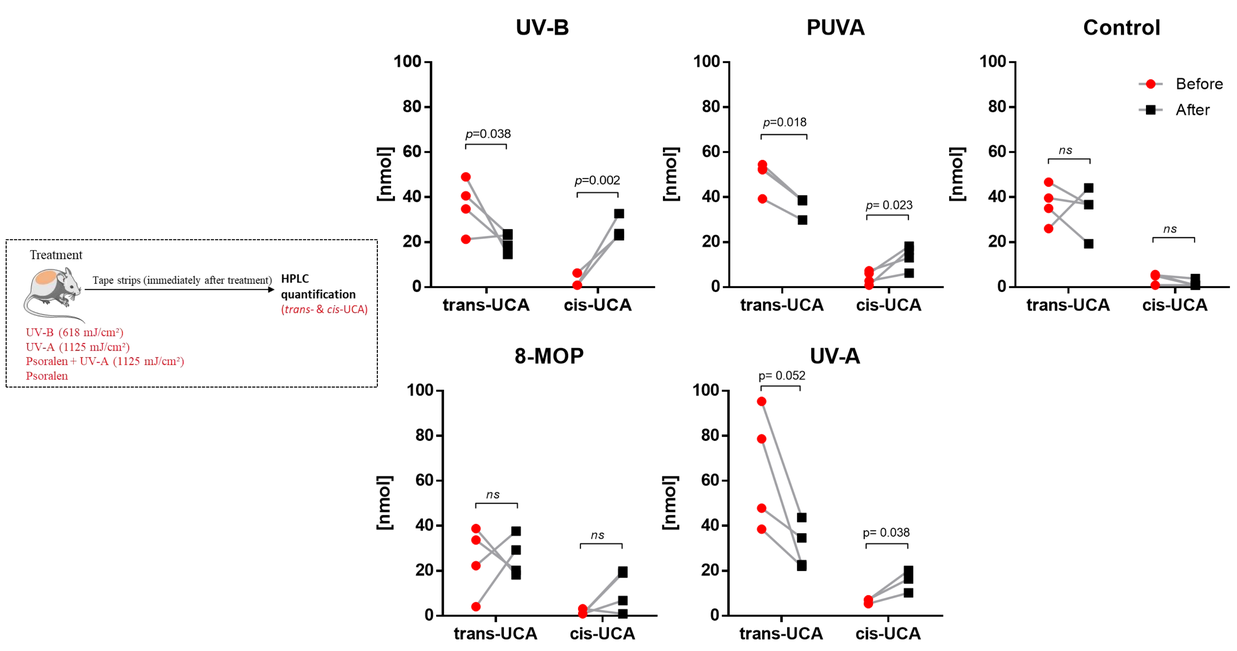


Fig 1: PUVA (1125 mJ/cm²) , UV-A (1125 mJ/cm²) and UV-B (618 mJ/cm²) significantly isomerizes *trans* to *cis*-UCA, but not or psoralen (8-MOP).

T-test (Holm-Sidak method, with alpha=0.5000%).

2. *cis*-UCA modulates microbes on the skin and AMP gene expression at 8h.

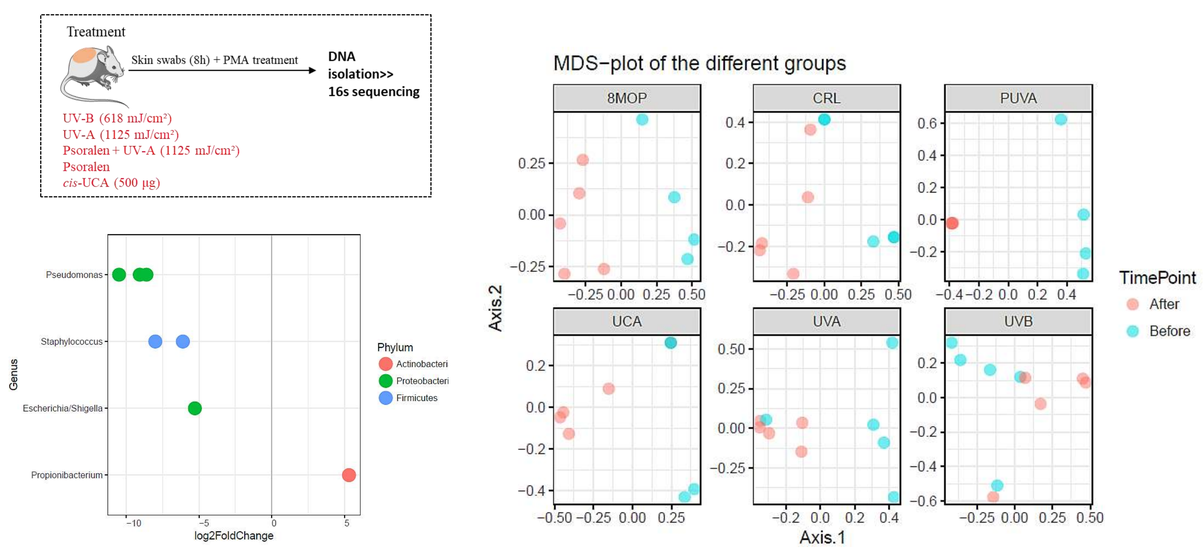


Fig 2 (a): Modulation of skin microbiome by *cis*-UCA (500 µg) and UV-R at 8h. MDS plots show a distinct separation between skin microbiome before and after treatment, notably for *cis*-UCA. Furthermore *cis*-UCA significantly increase abundance of *Propionibacterium*, and reduces *Pseudomonas, Staphylococcus* and *Escherichia/Shigella* species.

Fig 2 (b): *cis*-UCA (500 µg) increases gene expression of various AMPs at 8h. *cis*-UCA significantly increased gene expression of calcium binding proteins (S100A8 and S100A9), along with beta-defensins (mBD-1, -2 & -3).

ANOVA test (One-Way) with Tukey post hoc test. * p<0.05; **p<0.01; ***p<0.001

Results:

3. *cis*-UCA modulates microbes and AMPs on the skin at 24h .

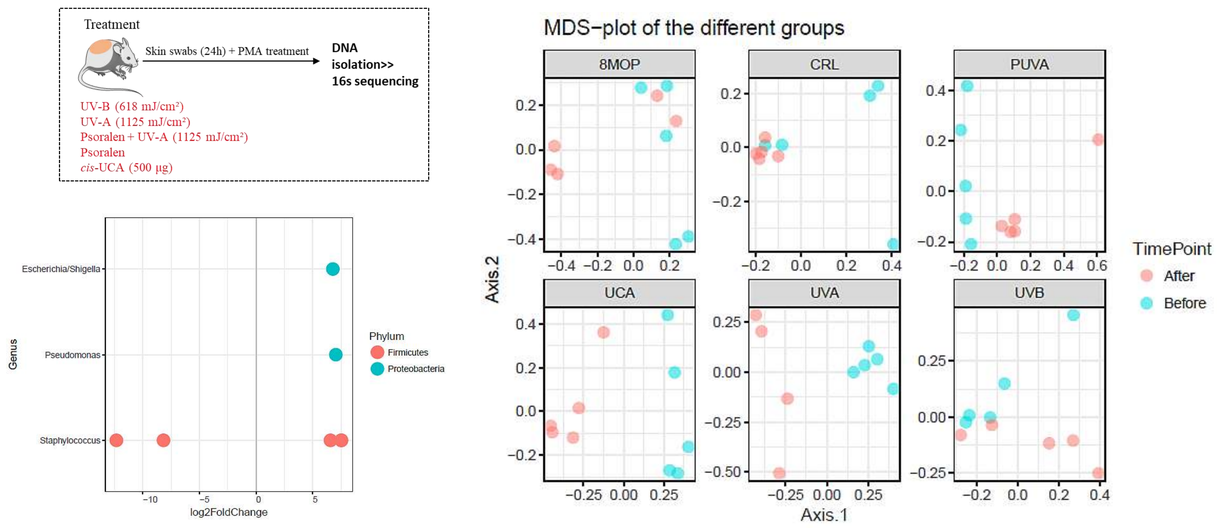


Fig 3 (a): Modulation of skin microbiome by *cis*-UCA (500 µg) and UV-R at 24h. MDS plots show a distinct separation between skin microbiome before and after treatment, notably for *cis*-UCA. Furthermore *cis*-UCA significantly increases abundance of *Pseudomonas, Escherichia/Shigella* species.

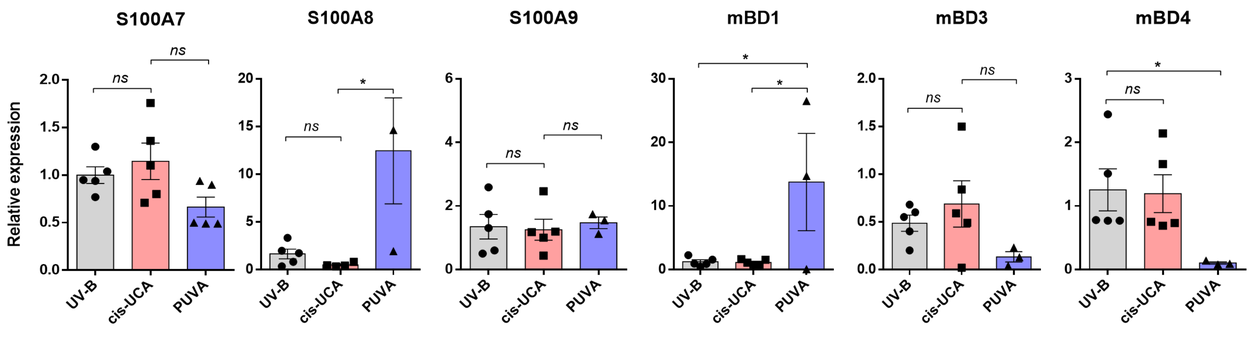


Fig 3 (b): AMPs gene signature significanlty differs at 24h. Expression of AMPs is reduced at 24h after cis-UCA (500 µg) , whereas PUVA causes extreme variations in gene expression.

ANOVA test (One-Way) with Tukey post hoc test. * p<0.05; **p<0.01; ***p<0.001

4. *cis*-UCA, PUVA and UV-B suppress immune reaction to contact allergen DNFB.

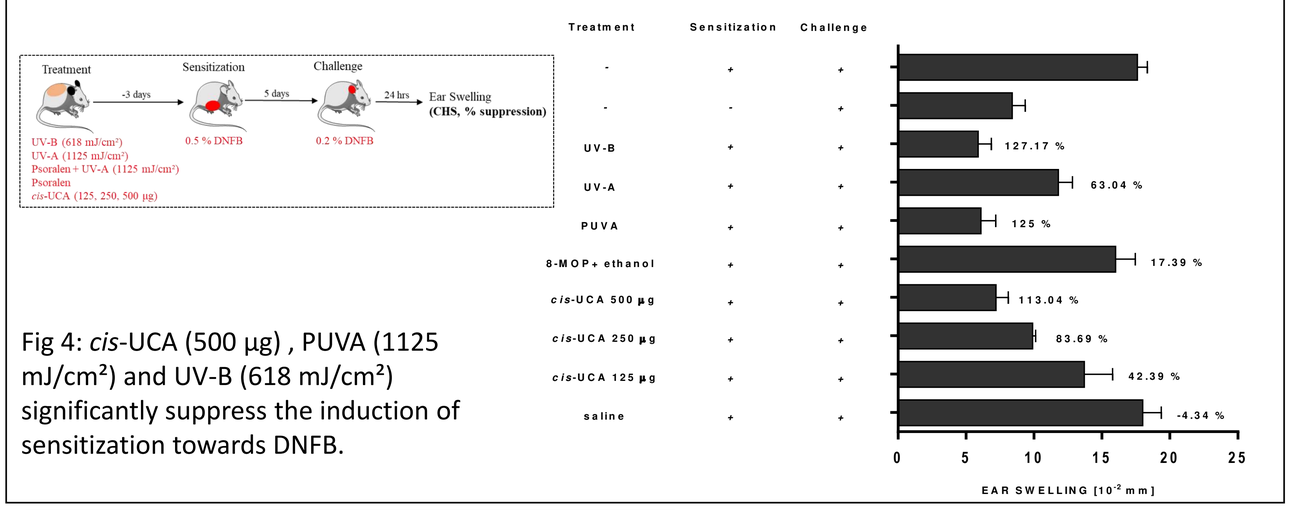
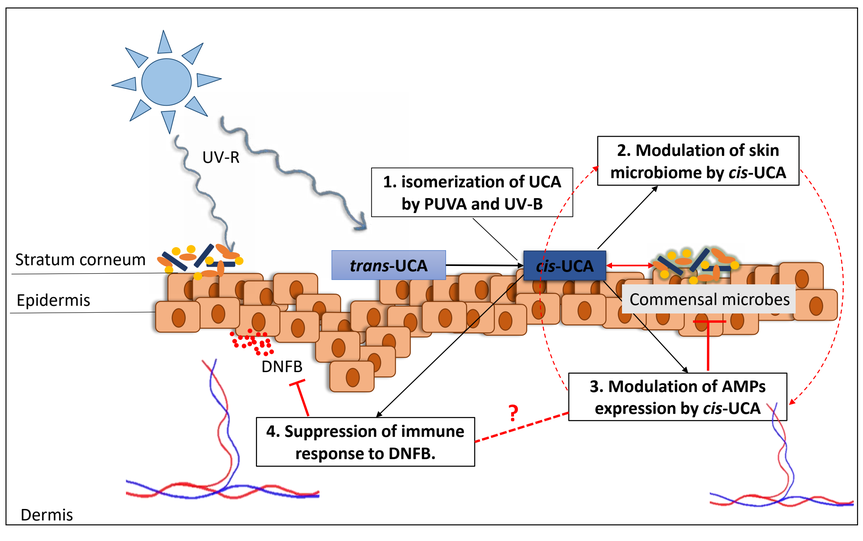


Fig 4: *cis*-UCA (500 µg) , PUVA (1125 mJ/cm²) and UV-B (618 mJ/cm²) significantly suppress the induction of sensitization towards DNFB.

Summary and Conclusion:



- ✓ PUVA, UV-A and UV-B significantly increase the formation of *cis*-UCA.
- ✓ Application of *cis*-UCA on the skin alters the microbial landscape and AMP gene expression of the skin.
- ✓ There is dose-dependent increase in immune suppression against the contact allergen DNFB, when the mice are pre-treated with UV-B, PUVA or *cis*-UCA (but not UV-A).
- ✓ Though UV-A significantly isomerizes *trans*-UCA, it shows no significant immune suppression to DNFB.
- ✓ *cis*-UCA may have a role in immune suppression through affecting skin microbiome and AMPs expression.

References:

[1] Neil K. Gibbs, Mary Norval, Urocanic Acid in the Skin: A Mixed Blessing?, Journal of Investigative Dermatology, Volume 131, Issue 1, 2011, Pages 14-17

[2] Jeffrey P. Walterscheid, Dat X. Nghiem, Nasser Kazimi, Leta K. Nutt, David J. McConkey, Mary Norval, and Stephen E. Ullrich. *Cis*-urocanic acid, a sunlight-induced immunosuppressive factor, activates immune suppression via the 5-HT$_{2A}$ receptor PNAS 2006 103 (46) 17420-17425

[3] Patra V, Byrne SN and Wolf P (2016) The Skin Microbiome: Is It Affected by UV-induced Immune Suppression? Front. Microbiol. 7:1235.

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