

Role of the eucalyptus-derived ingredient eucalyptol in reducing unpleasant sensory irritation from cooling sensations – Investigations by Mandom

- For a very comfortable cooling sensation -

Mandom Corporation (Head Office: Osaka, President Executive Officer: Motonobu Nishimura, hereafter “Mandom”) has been studying the various factors consumers attribute to sensing comfort, and aim to improve both, usability and function of cosmetics (quasi-drugs).

As part of this initiative and through joint research with Professor Makoto Tominaga of the Okazaki Institute for Integrative Bioscience, Mandom previously established an alternative evaluation method using TRP (Transient Receptor Potential) channels (see “Reference material <Sensory irritation mechanism>”) to study sensory irritation in skin. This discovery enabled quantitative evaluation of irritation.

Here, using TRP channels, we identified the comfortable cooling effects due to eucalyptol, the eucalyptus-derived ingredient that does not cause unpleasant sensory irritation. We also discovered that it possesses the ability to reduce the unpleasant sensory irritation caused by other freshening ingredients.

Mandom is keen to continue exploring this approach, and use the findings in the application development of cooling sensations in future products.

Furthermore, we presented the results of this study at the “Congress of the Japan Neuroscience Society” held from September 14 to 17, 2011, and “The 21st Congress of the International Federation of Societies of Cosmetic Chemists (IFSCC)” held from December 12 to 14, 2011, Bangkok, Thailand.

1. Unpleasant sensory irritation from strong cooling sensations

In recent years, many refreshing cosmetics claim to be “refreshing” and “cool” based on assessments against heat, intense weather, energy reduction, etc. To provide such “refreshing” and “cool” feeling, these products are supplemented with freshening ingredients such as ℓ -menthol, or by providing cool sensation by lowering the body temperature based on ethanol vaporization which appears as heat loss.

The typical freshening ingredient ℓ -menthol is added to many refreshing cosmetics for this purpose. Other alternate freshening ingredients have been developed, but ℓ -menthol is indispensable given its superior ability to generate a stronger cooling sensation. However, if a large amount of ℓ -menthol is added, it causes a burning sensation, eventually leading to an unpleasant sensory irritation.

Mandom has surveyed several freshening ingredients that can develop a comfortable cooling sensation with minimal discomfort to consumers.

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2. The comfortable and sensory irritation-free freshening ingredient eucalyptol

Burning and cooling sensations felt at the same time due to ℓ -menthol seem to involve TRPA1, which is the same receptor in TRP channel and involved in the spicy ingredient in wasabi and pepper. Hence, if ℓ -menthol is added at high concentrations, TRPA1 is activated, which causes the unpleasant sensory irritation. In addition, TRPM8 is also involved in generating cooling sensations. At Mandom, we are seeking an ingredient that provides only a cooling sensation with no or minimal sensory irritation, and employing these two channels. By doing so, the ratio of TRPM8 activation and TRPA1 activation due to ℓ -menthol serves as a reference, and this ratio serves as a comfort index.

$$\text{Comfort index} \quad (\ell\text{-menthol}=1) \quad = \quad \frac{\text{TRPM8 activation}}{\text{TRPA1 activation}}$$

If this ratio is high, it indicates a strong cooling sensation with little unpleasant sensory irritation. Based on this comfort index, we screened various ingredients. Based on these results, we discovered eucalyptol, a natural, eucalyptus-derived ingredient (Fig. 1).

As we analyzed eucalyptol in detail, we found that it does not activate TRPA1, but activates only TRPM8. We also found that apart from TRPA1, eucalyptol does not activate TRPV1 and TRPV2, which are known sensors involved in unpleasant sensory irritation upon activation (Fig. 2). In other words, eucalyptol may be considered an ingredient that provides only a cooling sensation and no unpleasant sensory irritation.

3. Reduction of unpleasant sensory irritation by eucalyptol

Further analysis led Mandom to report the discovery for the first time that eucalyptol can inhibit TRPA1 activity (Fig. 3). Mandom from in-house studies validated the cooling sensations due to addition of ℓ -menthol, and activation of TRPA1 resulting in an unpleasant sensory irritation. When eucalyptol is added, it appears to reduce the unpleasant sensory irritation caused by ℓ -menthol (Fig. 4). We therefore, speculate that even though the addition of ℓ -menthol results in providing a stronger cooling sensation, it also means a proportional increase in unpleasant sensory irritation, such as a burning sensation. Adding eucalyptol may reduce such unpleasant sensory irritation, while also providing a stronger cooling sensation.

4. Realizing comfortable coolness

Assuming that the effect of ℓ -menthol simultaneously activating TRPA1 and TRPM8 represents a “rapid” cooling sensation. The ability of eucalyptol activating only the TRPM8 but not TRPA1 may result in a “mild” cooling sensation. So, by adjusting the balance of ℓ -menthol and eucalyptol, it may be **possible to control not only the intensity of cooling sensations but also that of sensory irritation.** Thus, we explored the possibility of developing and providing satisfactory products that address customer needs regarding cooling sensations preferences.

In the future, we shall actively use the newly identified freshening ingredient, eucalyptol, in our product development line-up.

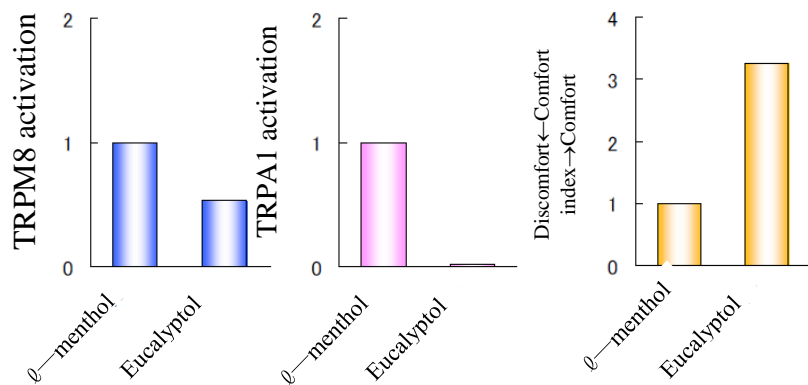


Fig. 1. TRPM8 and TRPA1 activation by eucalyptol for comfortable cooling

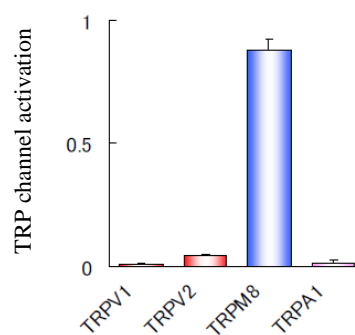


Fig. 2. Selective activation of eucalyptol on TRPM8

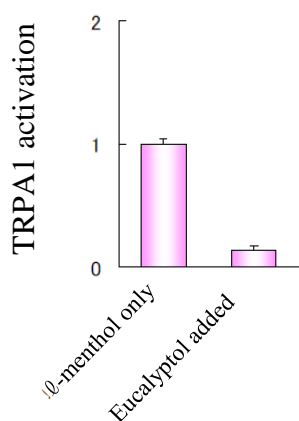


Fig. 3. TRPA1 inactivation by eucalyptol

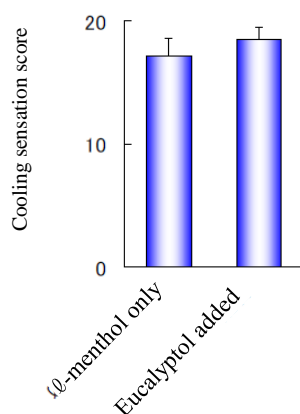
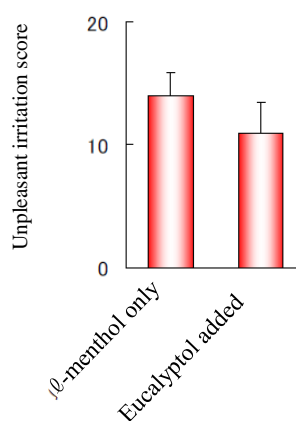


Fig. 4. Cooling sensation and reduction of unpleasant sensory irritation in the neck by eucalyptol



*Reference material

<Sensory irritation mechanism>

According to recent studies, “sensors” called “TRP channels” perceive chemical substances and temperature to convert them into electrical signals in the skin nerve cells. These signals contribute to the transmission of sensory irritation. The TRP channels found to be associated with the unpleasant “tingling” and “stinging” sensations felt when using cosmetics in Mandom’s researches.

TRP channels are involved in the “cooling sensation” involving refreshing cosmetics, and they activate TRPM8, a cold sensor. Addition of menthol to many refreshing cosmetics, activates TRPM8 and causes the cooling sensation. Furthermore, l-menthol at excess levels cause unpleasant sensory irritation. Though this sensory irritation involves TRP channels, it is caused by the reaction of TRPA1, which is also activated by the main ingredient in wasabi. TRPA1 therefore, contributes to the peculiar “tingling” and “stinging” sensation from alkali in hair coloring, and preservatives and polyalcohols in cosmetics.