

A Polyphenol for reducing visible signs of rosacea

Naringenin chalcone is known to have potent anti-allergic and anti-inflammatory properties. Based on this information, Mibelle Biochemistry have developed a modified CM-Naringenin-Chalcone

This is a new compound with improved stability and water solubility. The new molecule has been studied for its beneficial effects on skin conditions with signs of rosacea. Recent research reveals that an overproduction of the antimicrobial peptide cathelicidin LL37 in keratinocytes plays a major role in the development of this inflammatory skin disorder. LL-37 induces the release of pro-inflammatory mediators, which lead to inflammatory reactions in the skin.

In an in-vitro study CM-Naringenin-Chalcone was shown to reduce the release of LL-37 induced pro-inflammatory cytokines in human keratinocytes. A placebo-controlled clinical study performed on female Caucasian volunteers with mild rosacea confirmed a measurable reduction in capillary blood flow and a visible diminution of rosacea redness after 56 days of treatment.

CM-Naringenin-Chalcone is a promising new cosmetic active ingredient appropriate to treat irritated skin such as in rosacea.

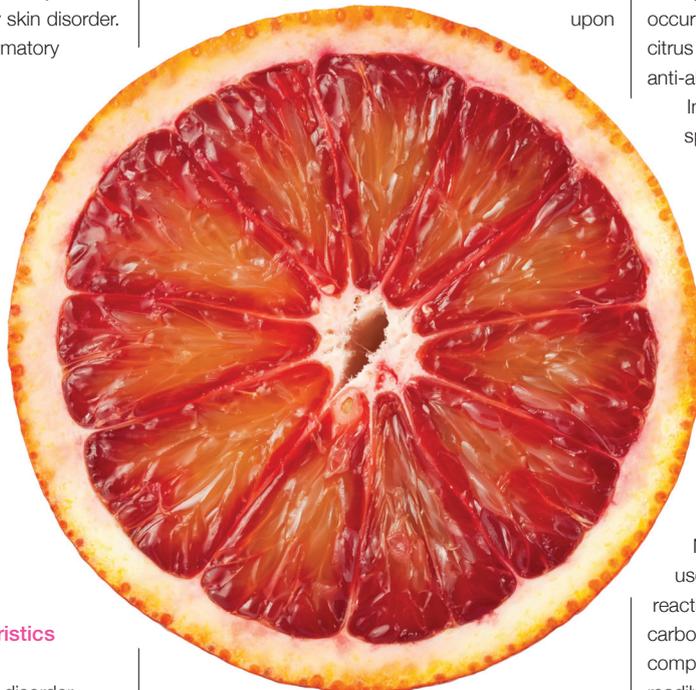
Facial erythema (redness) and visible blood vessels are characteristics of rosacea

Rosacea is a chronic inflammatory skin disorder generally occurring in the face. It is characterised by erythema, visible blood vessels, papules and pustules, combined with frequent burning and itching sensations. Many known factors that trigger rosacea include exposure to sun, high temperatures, emotional stress or spicy food. However, the pathophysiology of this skin disorder is complex. Recent research has revealed that the antimicrobial peptide cathelicidin LL37 plays a major role in the development of rosacea.

High levels of cathelicidin found in skin of individuals with rosacea

Antimicrobial peptides like cathelicidin LL37

correspond to one of the primary mechanisms activated in the early stages of the skin's immune defense. While epidermal keratinocytes in healthy skin express low amounts of cathelicidin LL37, these levels strongly increase upon



infection or disruption of the skin barrier. One important role of cathelicidin LL37 is to combat microbial invasion. In addition to the antimicrobial function, cathelicidin LL37 acts as a signalling molecule within the cutaneous innate immune system. LL37 induces the chemotaxis of immune cells and angiogenesis but also leads to an increase in the expression of pro-inflammatory ligands such as cytokines and chemokines. In normal skin this effect is part of a controlled action of the immune system. In rosacea, however, an abnormally high level of cathelicidin LL37 is reported. Associated with the constant presence of this peptide is a continuous inflammatory activity. The

consequences are chronic inflammation and vascular changes -typical signs of rosacea.

Characteristics of naturally occurring naringenin chalcone

Naringenin chalcone is a polyphenol naturally occurring in plants e.g. in the peel of tomato and citrus fruits. Recent studies have reported its potent anti-allergic and anti-inflammatory properties.

In nature, the naringenin chalcone spontaneously isomerizes to the flavanone naringenin. Naringenin, however, exhibits only weak anti-allergic activity. The chemical equilibrium between the chalcone and the flavanone is pH dependent, which makes it unsuitable for cosmetic formulations. Moreover, naringenin chalcone has a low solubility in aqueous solutions. Therefore, Mibelle Biochemistry's first goal was to modify the naringenin chalcone structure in order to block cyclisation and to improve water solubility.

Synthesis of CM-Naringenin-Chalcone

Naringenin, isolated from orange peels, was used as starting material. In several chemical reaction steps naringenin is converted to tetra-carboxy-methyl-naringenin-chalcone. The new compound exhibits improved pH-stability and is readily soluble in water. CM-Naringenin-Chalcone is a good example demonstrating how a natural compound can be improved for application as an active ingredient in cosmetics.

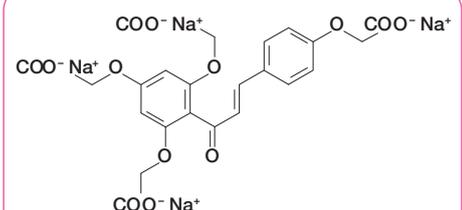
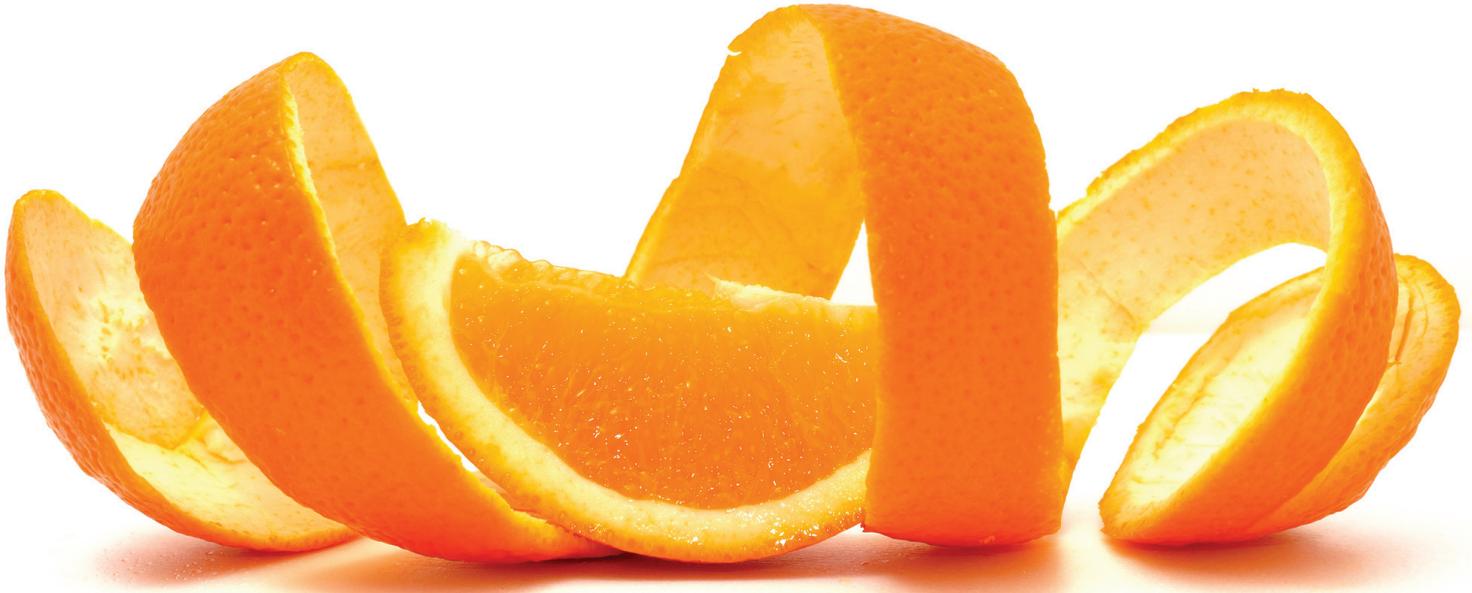


Figure 1: Chemical Structure of CM-Naringenin-Chalcone (sodium salt)



Anti-Inflammatory Study

The anti-inflammatory effect of CM-Naringenin-Chalcone was tested in an in-vitro assay on normal, human keratinocytes. Upon incubation with a stress cocktail containing cathelicidin LL-37 the keratinocytes start to express and release inflammatory mediators, such as CXCL1, IL-23A, IL-18, IL-1A and TNF. The addition of 0.033% CM-Naringenin-Chalcone to the stressed keratinocytes however, greatly decreases the amount of released cytokines:

- By approx. 70% in terms of CXCL1 and IL-18
- By approx. 50% in terms of IL-1A and TNF

This experiment clearly demonstrates that CM-Naringenin-Chalcone exhibits anti-inflammatory

properties by inhibiting the expression of inflammatory cytokines in keratinocytes.

Visible reduction of facial redness

Individuals with rosacea report flushing episodes, caused by a measurable increase in blood flow. Therefore, the efficacy of CM-Naringenin-Chalcone to reduce capillary blood flow and facial redness was evaluated in a double-blind placebo-controlled half-face study with 11 female volunteers aged from 30 to 63 with visible rosacea on the cheekbones.

An emulsion containing 0.1% CM-Naringenin-Chalcone and the corresponding placebo were applied twice a day for 56 days, one to each side of the face. Blood flow was monitored by means of the DRT4® Laser Doppler device (Moor Instruments, UK),

skin redness was evaluated by trained dermatologist.

A 56 day treatment with CM-Naringenin-Chalcone reveals a:

- Significant reduction of capillary blood flow by 57% compared to placebo
- Visible reduction of skin redness compared to untreated skin area

CM-Naringenin-Chalcone was demonstrated to successfully reduce the release of pro-inflammatory mediators by keratinocytes and to diminish persistent facial redness. These results suggest the new molecule is perfectly suitable for sensitive and irritated skin.

Mibelle Biochemistry, Stand 1G50

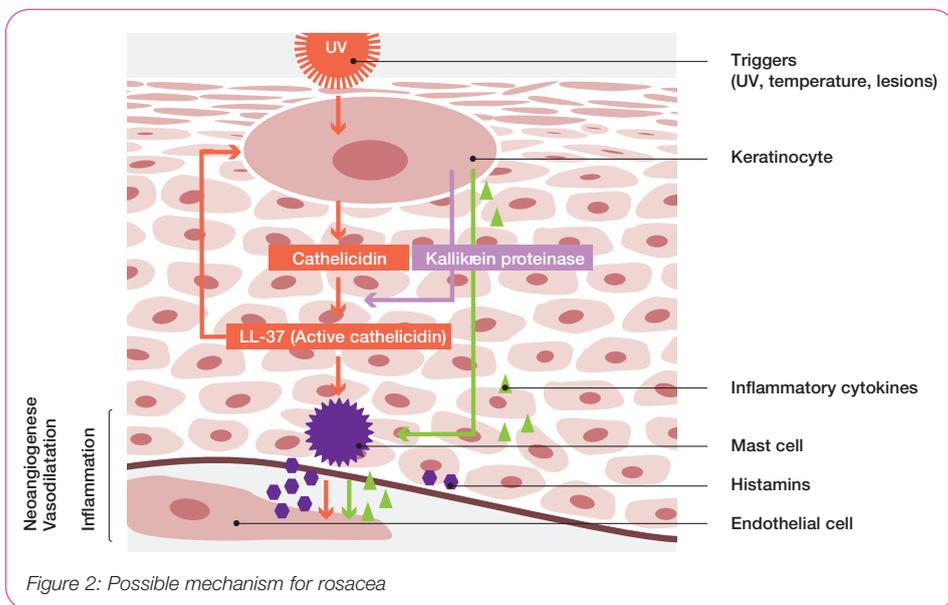


Figure 2: Possible mechanism for rosacea



Figure 3: Decrease in facial redness