



CM-Naringenin-Chalcone  
Shown to visibly reduce  
signs of rosacea



# CM-Naringenin-Chalcone

## Shown to visibly reduce signs of rosacea

### A Polyphenol for Reducing Visible Signs of Rosacea

Carboxy-Methyl (CM)-Naringenin-Chalcone is a single substance derived from the polyphenol naringenin chalcone, which naturally occurs in the peel of citrus fruits and tomato skin.

Naringenin chalcone was reported in the literature to have potent anti-allergic and anti-inflammatory properties. Based on this information Mibelle Biochemistry developed a modified CM-Naringenin-Chalcone, a new compound with improved stability and water solubility. The new molecule was 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. Furthermore, 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.

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

### CM-Naringenin-Chalcone

- Visibly reduces redness in sensitive skin
- Protects and comforts stressed skin
- Down-regulates pro-inflammatory mediators

### Applications

- Skin care for sensitive skin
- Anti-redness formulation
- Calming formulations for irritated skin

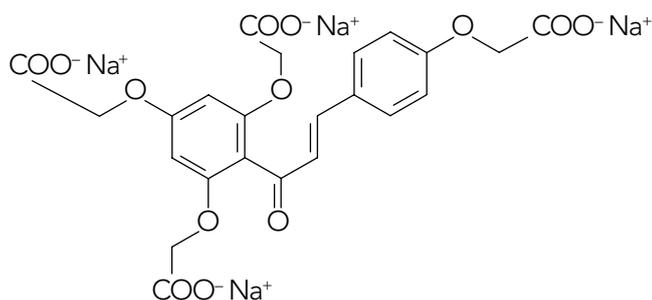
### Formulating with CM-Naringenin-Chalcone

- Recommended use level: 0.1 %
- Incorporation: CM-Naringenin-Chalcone can be formulated in emulsions (O/W, W/O) and gels. For cold processes, dissolve CM-Naringenin-Chalcone in the aqueous phase. In cold/hot processes add pre-dissolved during the cooling phase below 40°C.
- Thermostability: Homogenization and temperatures of up to 60°C over a short time do not affect the stability of CM-Naringenin-Chalcone. Water-solubility is strongly pH dependent (decreasing < pH 5)
- Remarks: Shield the product from light where possible.

### INCI (EU/PCPC) Declaration

Tetrasodium Tetracarboxymethyl Naringenin-chalcone (and) Aqua/Water

### CM-Naringenin-Chalcone



# Skin inflammation in rosacea

## Expression of high levels of cathelicidin LL37 in rosacea skin

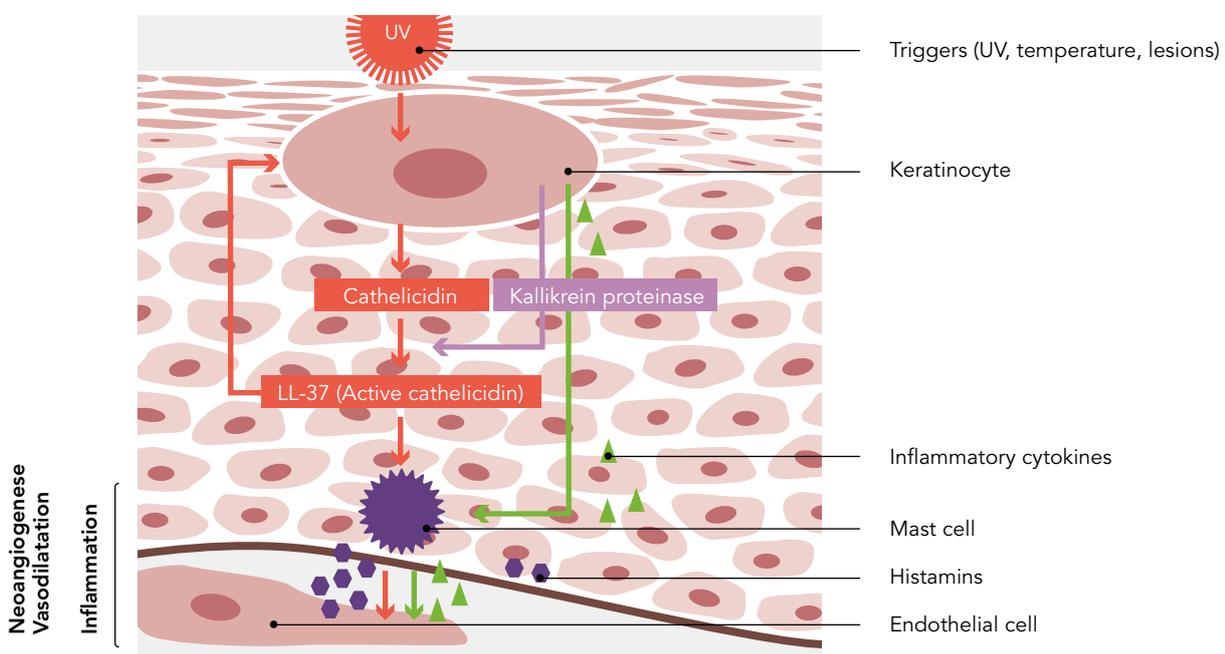
### Facial Erythema (Redness) and Visible Blood Vessels are Characteristics of Rosacea

Rosacea is a chronic inflammatory skin disorder generally occurring in the face. It is characterized by erythema, visible blood vessels, papules and pustules, combined with frequent burning and itching sensation. Many factors that trigger rosacea are known, among those are 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.

### Possible Mechanism for Rosacea



# Naringenin-Chalcone

## A polyphenol from the peel of oranges with anti-inflammatory properties

### 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.

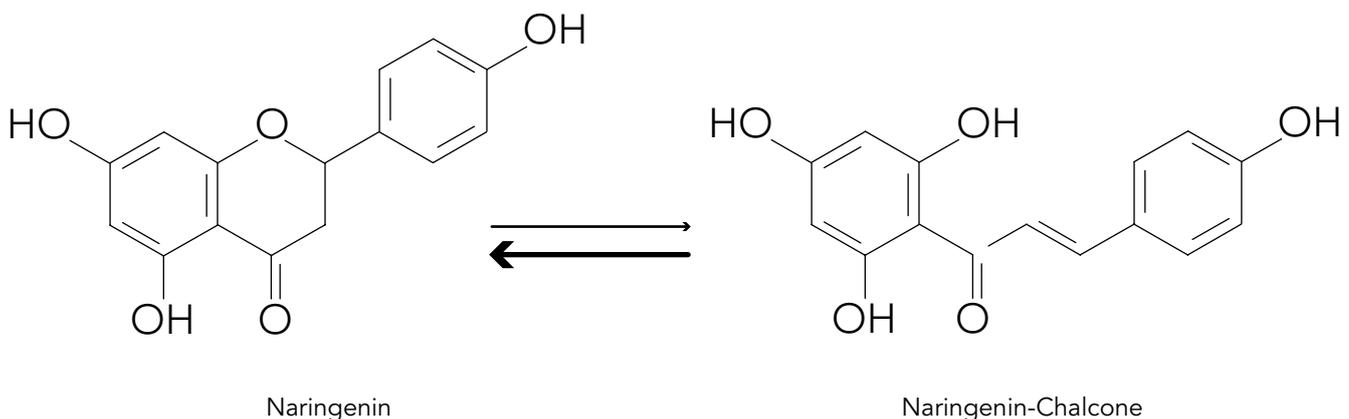
In nature, the naringenin chalcone spontaneously isomerizes to the flavanone naringenin. Naringenin, however, exhibits only weak anti-allergic activity. The chemical equilibrium between the chalcone and the flavanone is pH dependent, which makes it poorly suitable for cosmetic formulations. Moreover, 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 water solubility.

CM-Naringenin-Chalcone is a good example demonstrating how a natural compound can be improved for application as an active ingredient in cosmetics.

### Natural Equilibrium between the Flavanone Naringenin and Naringenin Chalcone



# CM-Naringenin-Chalcone

## Study results



### Anti-Inflammatory Study

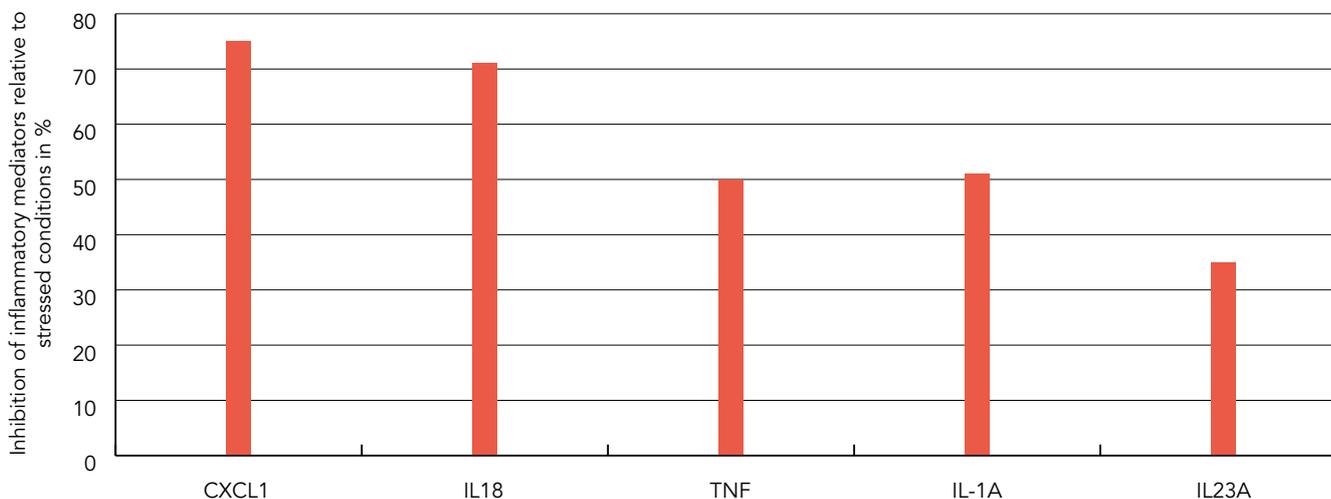
The anti-inflammatory effect of CM-Naringenin-Chalcone was tested in an in-vitro assay on normal, human keratinocytes. Upon incubation with a stressor cocktail containing cathelicidin LL-37 the keratinocytes start to express and release inflammatory mediators, such as CXCL1, IL-23A, IL-18, IL-1A and 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 stressed keratinocytes.

### Anti-Inflammatory Effect of CM-Naringenin-Chalcone in Stressed Keratinocytes

+ 0.033 % CM-Naringenin-Chalcone





### 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 daily for 56 days, one to each side of the face. Blood flow was monitored by means of the DRT4<sup>®</sup> Laser Doppler device (Moor Instruments, UK), skin redness was evaluated by trained dermatologist.

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

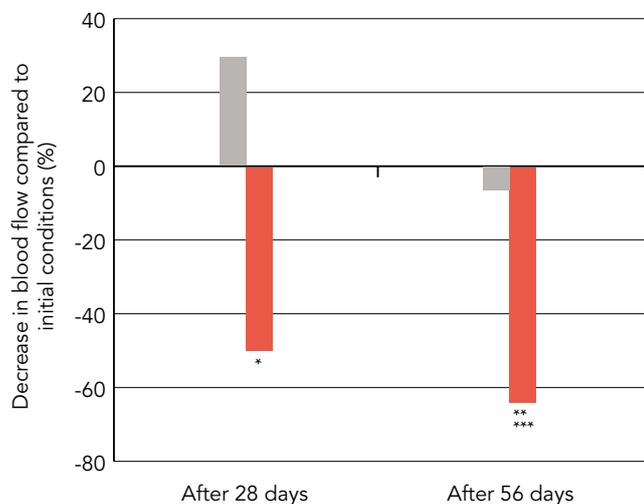
- Significant reduction of capillary blood flow by 57 % compared to placebo.

- Visible reduction of skin redness compared to untreated skin area.

To summarize, 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 perfectly suitable for sensitive and irritated skin.

### Decrease in Blood Flow

■ Placebo ■ Cream with CM-Naringenin-Chalcone (0.1 %)



\*p = 0.007 versus day 0  
\*\*p = 0.002 versus day 0  
\*\*\*p < 0.05 versus placebo

# CM-Naringenin-Chalcone

## Study results



In a clinical study performed on 11 volunteers with rosacea skin, CM-Naringenin-Chalcone, clearly diminishes capillary blood flow and thereby the appearance of facial redness.

### Decrease in Facial Redness

D0



D56



# CM-Naringenin-Chalcone

## Guide formulation

### Cellular defense cream (water in silicone)

Trade Name	INCI Name	% w/w	Function
XIAMETER® PMX-200 SILICONE FLUID 1.5CS	Dimethicone	5.00	Skin Feel
FLORAESTERS 20	Jjoba Esters	3.50	Natural ester
SeraSense GB10	Cyclopentasiloxane (and) Dimethiconol	5.00	Skin Feel
SeraSilk EL 61	Dimethicone & Dimethicone/Vinyl Dimethicone Crosspolymer	5.00	Skin Feel
Perfume Compound AR323859	Perfume	0.30	Fragrance
Euxyl PE9010	Phenoxyethanol & Ethylhexyl Glycerin	1.10	Preservative
Formulation Aid 5225C	Cyclopentasiloxane (and) PEG/PPG-18/18 Dimethicone	10.00	Emulsifier
Water	Aqua	64.00	Solvent
Glycerin	Glycerin	5.00	Humectant
Salt Pure Vacuum Dried	Sodium Chloride	1.00	Emulsion stabiliser
CM-Naringenin-Chalcone	Tetrasodium Tetracarboxymethyl Naringenin-chalcone	0.10	Active
		100.00	

### Method of Manufacture

#### 1. Into the main vessel add:

XIAMETER® PMX-200 SILICONE FLUID 1.5CS	Start the mixer on a moderate speed.
FLORAESTERS 20	Mix until uniform and homogenous.
SeraSense GB10	Mix until uniform and homogenous.
SeraSil EL61	Mix uniform and homogenous.
Perfume	Mix until uniform and homogenous.
Euxyl PE9010	Mix until uniform and homogenous. Continue to mix with moderate mixing avoiding aeration.

#### 2. Into a separate premix vessel add:

Aqua (as cold as possible)	Start the mixer on a moderate speed.
Glycerin	Mix until uniform and homogenous.
Salt PVD (Sodium Chloride)	Mix until all the solids have dissolved.
CM-Naringenin-Chalcone	Mix until all the solids have dissolved.
	Increase the mixer speed in the main vessel to fast. Very slowly add the premix into the main vessel (over an hour period). The emulsion may not form properly if the water phase is added too quickly.

#### Product specifications:

pH	N/A
Viscosity	80'000–200'000 cps (RVT TBAR Spindle E, speed 2.5, 1 minute)
Colour	pale yellow
Odour	Floral
Appearance	Viscous emulsion

# CM-Naringenin-Chalcone

## Guide formulation

### Anti-redness cream (oil in water)

Trade Name	INCI Name	% w/w	Function
Purified Water	Aqua (1)	74.77	Solvent
Versene™ NA2	Disodium EDTA	0.05	Chelating Agent
NovoXan™ 80T	Xanthan gum	0.10	Thickener
Ultrez™ 20	C10–30 alkyl acrylate crosspolymer	0.10	Thickener
Glycerin	Glycerin	2.00	Humectant
Euxyl PE9010	Phenoxyethanol & Ethylhexyl Glycerin	1.10	Preservative
TEGO® Care 165	Glyceryl Stearate & PEG 100 Stearate	2.00	Emulsifier
Polwax GP200	Cetearyl Alcohol & Cetearth-20	1.00	Emulsifier
CETIOL® SN	Cetearyl Isononanoate	4.50	Emollient
CETIOL® 868	Ethylhexyl Stearate	3.00	Emollient
ESSACHEM™ O	Octyldodecyl Olivat	1.50	Light, fast absorbing ester
ESSACHEM™ BW	Behenyl Olivat	3.00	Emollient ester, Spreadability
LANETTE® S3	Cetearyl Alcohol	1.50	Co-Emulsifier
Sodium Hydroxide (36% Solution)	Sodium Hydroxide	0.08	Neutraliser
Perfume Compound AR323859	Perfume	0.20	Fragrance
Purified Water	Aqua (2)	5.00	Solvent
CM-Naringenin-Chalcone	Tetrasodium Tetracarboxymethyl Naringenin-chalcone	0.10	Active
		100.00	

## Method of Manufacture

### 1. Into the main vessel add:

Aqua (1)	Start the mixer on a fast speed.
Disodium EDTA	Mix until fully dissolved.
Xanthan Gum	Slowly sprinkle the Xanthan Gum into the vortex of the main vessel. Mix until fully dispersed. Switch off the stirrer.
Ultrez 20	Add slowly. Leave for 30min until the polymer becomes fully hydrated. Start the mixer on low speed.
Glycerin	Mix until fully dispersed and uniform.
Euxyl PE9010	Mix until fully dispersed and uniform.

### 2. Into a premix vessel add:

Glyceryl Stearate & PEG 100 Stearate	
Cetearyl Alcohol & Cetareth-20	
Cetearyl Isononanoate	
Ethylhexyl Stearate	
Octyldodecyl Olivat	
Behenyl Olivat	
Cetearyl Alcohol	Heat both vessels to 80 °C. Add the content of the premix vessel into the main vessel. Homogenize for 5 minutes.

### 3. Add to the main vessel:

Sodium Hydroxide (36% solution)	Homogenize for a further minute, then stop the homogenizer and start the mixer on low speed. Commence cooling to 23 °C.
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### 4. When the bulk is 40 °C or below add:

Perfume	
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### 5. Into a premix vessel add:

Aqua (2)	
CM-Naringenin-Chalcone	Mix until no solids remain.

### 6. Add the content of the premix vessel into the main vessel:

Increase the mixer speed to ensure the premix is fully incorporated into the main bulk. Continue to cool to 23 °C.

### Product specifications:

pH	5.5–6.3
Viscosity	200'000–300'000 cps (RVT TBAR Spindle E, speed 2.5, 1 minute)
Colour	pale yellow
Odour	Floral
Appearance	Viscous emulsion

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### Applications

- Skin care for sensitive skin
- Anti-redness formulation
- Calming formulations for irritated skin

### Marketing benefits

- Tested on sensitive and itchy skin such as rosacea
- New molecule with potent anti-inflammatory properties

### Innovating for your success

Mibelle Biochemistry designs and develops innovative, high-quality actives based on naturally derived compounds and profound scientific know-how. Inspired by nature – Realized by science.

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