Designed for the

EFFECTIVE CONTROL OF
ERYTHEMATOUS TELEANGIEECTATIC
ROSACEA
**What are the key diagnostic features of rosacea**

**Primary features**
- Flushing (transient erythema)
- Non transient erythema (permanent redness)
- Telangiectasia (thread/ Spider veins)

**Secondary features**
- Burning or stinging
- Red plaques
- Dry skin
- Oedema
- Ocular manifestation
Three key features of rosacea are inflammation leading to damage, loss of vascular function, and hyper reactivity to VEGF resulting in excessive vascular production.
80% of the triggering of rosacea is exposure of UV sensitive skin in genetically predisposed individuals over time which leads to curte reactiosn becoming chronic, other trigger factors like Wine, heat, cold, spicy foods add to the UV effect and push the skin over the edge.
The activity was mainly based on the combined anti inflammatory effect and the possibility to down modulate angiokines and cytokines involved in rosacea.

MSM and silymarin have an overlapped and synergistic activity.
The synergistic effect of **SILYMARIN** and **MSM**

1. Photo-protection so on keratinocytes as on fibroblasts;
2. Down-regulation of vascular endothelial growth factor - VEGF;
3. Down regulation in the expression of PGE2;
4. Inhibition of the release of IL-1 and TNF;
5. Diminish the expression of CD80 and CD86 on monocytes;
6. Inhibition of UV-B induced $H_2O_2$ production;
7. Scavenging of ROS including hydroxyl radicals;
8. Reduction of the UVB-induced infiltrating leukocytes;
MAIN ACTIVITIES

MSM
- INHIBITION OF SUNLIGHT PHOTO DAMAGE
- PREVENTION OF MATRIX DAMAGE
- INHIBITION OF NEOANGIOGENESIS
- IMPROVEMENT OF THE INTEGRITY OF CUTANEOUS MICROVASCULATURE
- FREE RADICAL SCAVENGER ACTIVITY
- DE-SENSITIZING EFFECT

SILYMARIN

SkinMed
Combined effects of silymarin and methylsulfonylmethane in the management of rosacea: clinical and instrumental evaluation.


Berardesca, Enzo MD 1; Cameli, Norma MD 1; Cavallotti, Claudia MD 1; Levy, Jean Luc MD 2; Pierard, Gerald E MD 3; de Paoli Ambrosi, Gianfranco PhD 4

Abstract:
Objective: This study aims to evaluate a topical treatment based on silymarin/methylsulfonilmethane (S-MSM) to improve erythematous-telangiectactic rosacea.

Methods: Forty-six patients affected by stage I-III rosacea entered this double-blind, placebo controlled study. Subjects were treated for 1 month. Clinical and instrumental evaluations were done at baseline, after 10 and 20 days, and at the end of the study. Itching, stinging, erythema, and papules were investigated clinically as well as hydration and erythema instrumentally with capacitance and colour measurements.

Results: A statistically significant improvement was observed in many clinical and instrumental parameters investigated (P < 0.001). In particular, improvement of skin redness, papules, itching, hydration, and skin colour occurred.

Conclusions: The combination of silymarin and S-MSM can be useful in managing symptoms and condition of rosacea skin, especially in the rosacea subtype 1 erythematot-telangiectatic phase. The action can be considered multicentric and multiphase because of the direct modulating action on cytokines and angiokines normally involved and up regulated in the case of such skin condition.
Clinical Data

Abstract:

• Summary Objective

• This study aims to evaluate a topical treatment based on silymarin/methylsulfonylmethane (S-MSM) to improve erythematous-telangiectactic rosacea. Methods

• Forty-six patients affected by stage I-III rosacea entered this double-blind, placebo-controlled study. Subjects were treated for 1 month. Clinical and instrumental evaluations were done at baseline, after 10 and 20 days, and at the end of the study. Itching, stinging, erythema, and papules were investigated clinically as well as hydration and erythema instrumentally with capacitance and colour measurements. Results

• A statistically significant improvement was observed in many clinical and instrumental parameters investigated ($P < 0.001$). In particular, improvement of skin redness, papules, itching, hydration, and skin colour occurred. Conclusions

• The combination of silymarin and S-MSM can be useful in managing symptoms and condition of rosacea skin, especially in the rosacea subtype 1 erythematous-telangiectatic phase. The action can be considered multicentric and multiphase because of the direct modulating action on cytokines and angiokines normally involved and up-regulated in the case of such skin condition.

Affiliations:

• 1: San Gallicano Dermatological Institute, Rome, Italy 2: Marseille Laser Centre, France
• 3: Department of Dermatology, University Hospital of Liège, Liège, Belgium
• 4: General Topics, Worldwide Health Care Products, San Felice d/B, Italy
Study of the combined effect of **MSM** and **SILYMARIN** in the management of erythematotelangiectatic phase of **ROSACEA**

**Conclusions**

**MSM** and **SILYMARIN**

Exerts a synergistic effect in controlling the main steps of erythematotelangiectatic (Sub Type 1) Rosacea. Their activity showed a direct effect in controlling inflammation, angiogenesis and photo protection.
THE EVOLUTION IS OPEN®

ROSACURE

2015
What’s new

WE COMBINED THE PAST WITH THE FUTURE

BASED ON THE KNOW-HOW ACQUIRED OVER YEARS OF RESEARCH, AND EXTENDED BY OUR RECENT RESEARCH PROGRAM WE HAVE DISCOVERED A NEW, COMPLETE AND INNOVATIVE MECHANISM OF ACTION IN CONTROLLING ROSACEA

WE SYNCHRONIZED THE DOWN MODULATION OF THE PRO INFLAMMATORY CHEMICAL MEDIATORS OVER EXPRESSED IN ROSACEA USING MSM WITH THE ACTIVITY OF THE TrpV1 ANTAGONISTS
Is an unique world first antagonist of TrpV1 receptors in keratinocytes. 

There is further biochemical evidence a discussion on the following slides but in essence when nerve endings in the gut or elsewhere are triggered by something like hot peppers, then a nerve stimulus is sent to the central facial area. Causing receptors sites on skin cell keratinocytes to activate and release peptides which trigger a burning and stinging sensation. This can be triggered by many things such as spicy foods, wine, cheese, alcohol, red foods, tomatoes. Also heat and cold. It is known these pathways are hyper reactive in subjects prone to reddening and rosacea.
Polyglutamic Acid is a polymer of repeating units of glutamic acid. It is a safe ingredient that creates a physical smooth, elastic, self moisturizing and soft film resulting in improved sensory perception and protection of the outer layer of the skin. It reinforces the skin’s support structure and it stimulates the production of lipids and the renewal of epidermis.

This activity, according to EU regulations, justifies the status of medical device.

Ancillary ingredients integrate with this activity, making it possible to achieve a therapeutic skin benefit in those affected by erythematous teleangiectatic rosacea.
NEW FORMULA WITH AN INNOVATIVE APPROACH TO ROSACEA.

POLYGLUTAMIC ACID

forms an elastic barrier film on skin surface, ameliorating hydration and improving the barrier function of the skin.

MSM

Anti inflammatory effect, by reducing the effect of various cytokines and angiokines such as TNF 1 alpha, VEGF and Interleukin 1 alpha produced in the skin as part of the inflammatory and flushing process which rosacea prone subjects hyper respond to.

4-t-butylcyclohexanol

antagonist of TrpV1 receptors in keratinocytes
See further detail on following slides.
Polyglutamic Acid is a polymer made of repetitive units of glutamic acid, it is a safe ingredient that create a physical smooth, elastic, self moisturizing and soft film resulting in improved sensory perception and protection of the outer layer of the skin. It reinforce the skin’s support structure it stimulates the production of lipids and the renewal of epidermis.

**MSM**

**4-t-butylcyclohexanol**

**MSM**, and **4-t-butylcyclohexanol** combine to deliver excellent results in controlling the subjective symptoms like burning, itching and tingling, visibly and quickly ameliorating the objective symptoms like erythema (redness and swelling).
The transient receptor potential cation channel subfamily V member 1 (TrpV1), is a nonselective cation channel that may be activated by a wide variety of exogenous and endogenous physical and chemical stimuli.

The best-known activators of TrpV1 are heat greater than 43°C, and capsaicin, the pungent compound in hot chili peppers.

The activation of TrpV1 leads to a painful, burning sensation.

The TrpV1 receptors are expressed on keratinocytes in the lower and upper epidermis.

TrpV1 seems to be a major contributor to the enhanced thermal responsiveness observed after cutaneous inflammation.
Neurovascular aspects of skin neurogenic inflammation.

Aubdool AA, Brain SD.
Cardiovascular Division and Centre for Integrative Biomedicine, BHF King’s College London Cardiovascular Centre of Excellence, King’s College London, Waterloo Campus, London, UK.

Neurogenic inflammation is involved in skin inflammation. It is hypothesized that it is involved in the pathogenesis of the common chronic cutaneous vascular disorder rosacea, but the exact mechanism of action is currently unknown. Transient receptor potential vanilloid 1 (TRPV1) and ankyrin 1 (TRPA1) are widely expressed on primary sensory neuron endings and non-neuronal cells such as keratinocytes. Here we describe the potential for TRPV1 and TRPA1 receptors to be involved in the pathophysiology of rosacea due to their polymodal activation, including cold and hot temperature, pungent products from vegetable and spices, reactive oxygen species, and mechanical stimuli. We discuss the role of both receptors and the sensory neuropeptides that they release in inflammation and pain sensation and evidence suggesting that both TRPV1 and TRPA1 receptors may be promising therapeutic targets for the treatment of the inflammatory symptoms of rosacea.
Distribution and expression of non-neuronal transient receptor potential (TRPV) ion channels in rosacea.

Sulk M, Seeliger S, Aubert J, Schwab VD, Cevikbas F, Rivier M, Nowak P, Voegel JJ, Buddenkotte J, Steinhoff M.
Department of Dermatology, University Hospital Münster, Münster, Germany.

Rosacea is a frequent chronic inflammatory skin disease of unknown etiology. Because early rosacea reveals all characteristics of neurogenic inflammation, a central role of sensory nerves in its pathophysiology has been discussed. Neuroinflammatory mediators and their receptors involved in rosacea are poorly defined. Good candidates may be transient receptor potential (TRP) ion channels of vanilloid type (TRPV), which can be activated by many trigger factors of rosacea. Interestingly, TRPV2, TRPV3, and TRPV4 are expressed by both neuronal and non-neuronal cells. Here, we analyzed the expression and distribution of TRPV receptors in the various subtypes of rosacea on non-neuronal cells using immunohistochemistry, morphometry, double immunofluorescence, and quantitative real-time PCR (qRT-PCR) as compared with healthy skin and lupus erythematosus. Our results show that dermal immunolabeling of TRPV2 and TRPV3 and gene expression of TRPV1 is significantly increased in erythematotelangiectatic rosacea (ETR). Papulopustular rosacea (PPR) displayed an enhanced immunoreactivity for TRPV2, TRPV4, and also of TRPV2 gene expression. In phymatous rosacea (PhR)-affected skin, dermal immunostaining of TRPV3 and TRPV4 and gene expression of TRPV1 and TRPV3 was enhanced, whereas epidermal TRPV2 staining was decreased. Thus, dysregulation of TRPV channels also expressed by non-neuronal cells may be critically involved in the initiation and/or development of rosacea.

TRP ion channels may be targets for the treatment of rosacea.
MECHANISM OF ACTION
The down modulation of TNF-α induced by a silicon emulsion containing MSM 5% has been evaluated on reconstructed artificial human skin model comprising normal human epidermal keratinocytes, growing as an integrated three-dimensional cell culture model, perfectly mimicking the human skin in vitro. The model exhibits normal barrier functions (presence of a differentiated stratum corneum).

Data on file General Topics: ABICH - 2007
The down modulation of IL1-α induced by a silicon emulsion containing MSM 5% has been evaluated on reconstructed artificial human skin model comprising normal human epidermal keratinocytes, growing as an integrated three-dimensional cell culture model, perfectly mimicking the human skin in vitro. The model exhibits normal barrier functions (presence of a differentiated stratum corneum).

Data on file General Topics: ABICH - 2007
The down modulation of IL1-α RA induced by a silicon emulsion containing MSM 5% has been evaluated on reconstructed artificial human skin model comprising normal human epidermal keratinocytes, growing as an integrated three-dimensional cell culture model, perfectly mimicking the human skin in vitro. The model exhibits normal barrier functions (presence of a differentiated stratum corneum).

Data on file General Topics: ABICH - 2007
INFLAMMATORY PROCESS

TNF-α up-regulation

INFLAMMATORY PROCESS

TrpV1 activation

INFLAMMATORY PROCESS
One important mechanism of action of MSM is related to the inhibition of TNF-α release from keratinocytes combined with the activity of 4-t-butylcyclohexanol as an antagonist of the TrpV1 receptors. The TrpV1 receptors contribute to skin inflammation via a distinct mechanism of action.
1. Dietary triggers (e.g., hot peppers)

2. Triggers stimulates nerve signal which is transmitted to facial area

3. Nerve impulse causes receptor sites on keratinocytes in reddening area to activate

4. This leads to small peptides being released which exacerbate redness, swelling, stinging, burning

5. Further inflammatory chemicals are released into the skin either as a secondary consequence of 4. or through direct external stimulation from UV, wind etc

Rosacure contains 4-T-cyclobutylhexanol to inhibit peptide effect by blocking the receptor sites as under point 3. Also MSM (methyl sulphonyl methane) suppresses the release of inflammatory chemicals released as described under 5. Lastly Polyglutamic acid raises skin tolerance levels to external triggers.
CLINICAL DATA
## Activity on Evident Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Filming protective effect</th>
<th>Antioxidant effect</th>
<th>IL1 alpha. TNF alpha down modulation</th>
<th>IL1-alpha RA up regulation</th>
<th>VEGF alpha down modulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyglutamic acid</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSM</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

## Activity on Subjective Symptoms

<table>
<thead>
<tr>
<th></th>
<th>Tingling</th>
<th>Stinging</th>
<th>Burning</th>
<th>Sensory comfort: Immediate Relief</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-t-butylcyclohexanol</td>
<td>-50%</td>
<td>-60%</td>
<td>-70%</td>
<td>*****</td>
</tr>
</tbody>
</table>
The cytoprotective effect of MSM on keratinocytes after UVB exposure

In order to assess the protective action of the tested substance we evaluated both the vitality (MTT assay) and the morphology (microscope analysis) of the treated and UVB exposed keratinocytes. MTT assay quantifies cell vitality/death, the microscope analysis assesses the presence of a proper/affected cell morphology and supports the MTT assay in evaluating the cell number.
ANTI-ANGIOGENIC EFFECT OF Silymarin

Effect of silymarin on capillary tube formation (in vitro differentiation) on Matrigel. Representative phase contrast photomicrographs (1003 magnification) were taken at 6 h (A–D) and 17 h (E–H) after seeding.

Solvent  | Silymarin 50µg/ml  | Silymarin 50µg/ml  | Silymarin 50µg/ml
Vascular Protective and Restructuring Activity

Artificial wound Assay, shows level of repair on human vascular endothelial cells over time following wound

At Time zero

Untreated cells

Cells treated with Rosacure FAST

After 8 Hours

Untreated cells

Cells treated with Rosacure FAST

After 16 Hours

Untreated cells

Cells treated with Rosacure FAST

After 24 Hours

Untreated cells

Cells treated with Rosacure FAST
Desensitising Effect

CD 80 Expression (as a percentage of normal)

Expression of CD80 markers on monocytes shows level of immune response to NiSO4 trigger. rose Rosacure FAST shows an effective inhibitory effect thereby reducing sensitivity and reactivity of skin similar in effect to the prescription product dexamethasone.
Anti-inflammatory Activity

Rosacure Fast shows an inhibition in the release of IL-1alpha which demonstrates and correlates to a reduction in the bodies inflammatory response to reddening triggers. SLS is the surfactant used as the trigger.
IN VIVO PERCENTAGE OF REDUCTION OF ERYTHEMA INDUCED BY UVB RAYS

Bar chart showing the percentage of reduction of erythema induced by UVB rays.

- TOC: 21
- B8-M10: 63.4

SkinMed
Activity on Permanent Redness

After 10 days (T1) treatment, there was an 18.6% statistically significant reduction of redness intensity.

After 20 days (T2) there was a 28% statistically significant reduction in redness intensity.
AFTER 10 DAYS TREATMENT – TWICE A DAY
AFTER 10 DAYS TREATMENT - TWICE A DAY
SYNCHRONOSE

Before and After Photo using special imaging photography that shows underlying redness in the skin
Field Based Evaluation

Acne Support Group
Recruited 100 clinically confirmed rosacea sufferers from ASG.

All were long standing sufferers who were well used to testing new treatments and were long term sceptics still searching for a solution (the toughest consumer test)

All completed questionnaires on their red skin colour, symptoms, plaques, pustules, skin tone, irritation level.

All used the 4 product Rosacure set for 8 weeks, completing the questionnaire at 0, 4 and 8 weeks and then asked their buying intentions.
Overall Effectiveness of Synchrorose as evaluated by ASG members

Effectiveness on managing condition

- Poor to No effect: 13
- Some effect: 8
- Reasonable Effect: 11
- Good to Excellent Effect: 43
Effectiveness of Synchrorose in treating Acne Support Group members rosacea

<table>
<thead>
<tr>
<th>Effectiveness</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor to No effect</td>
<td>17%</td>
</tr>
<tr>
<td>Some effect</td>
<td>11%</td>
</tr>
<tr>
<td>Reasonable Effect</td>
<td>15%</td>
</tr>
<tr>
<td>Good to Excellent Effect</td>
<td>57%</td>
</tr>
</tbody>
</table>
Skin hydration after 30 days of treatment, b.d dosage, evaluated via corneometer

Data on file General Topics: Istituto San Gallicano, Rome – Prof. Enzo Berardesca - 2012

- t - 0: 42.41666667
- t - 30 days: 47.16666667
Skin erythema after 30 days, b.d dosage evaluated via mexameter

Data on file General Topics: Istituto San Gallicano, Rome – Prof. Enzo Berardesca - 2012
After 30 days of treatment – b.d. dosage
After 30 days of treatment – b.d. dosage
After 30 days of treatment – b.d. dosage
After 30 days of treatment – b.d. dosage
After 30 days of treatment – b.d. dosage
After 30 days of treatment – b.d. dosage
After 30 days of treatment – b.d. dosage
After 30 days of treatment – b.d. dosage
After 30 days of treatment – b.d. dosage
After 30 days of treatment – b.d. dosage
Gentle Cleansing Gel

**FUNCTIONS**
It is a innovative concept of cleansing, soothes the skin and exerts a very delicate cleansing action.

**HOW TO USE**
Apply day and night as a normal liquid soap, can be leaved on the skin, removing the excess with a cotton pad, or rinsed off with water.

**ACTIVE INGREDIENTS**
Polyglutamic acid, MSM, soya protein, hyaluronic acid.

**CONTAINER**
PE white flacon

**CONTENT**
200 ml
### Fast cream

**FUNCTIONS**
Delivers a marked anti-inflammatory effect, able to counteract erythema and diminish the sensations of burning and itching.

**HOW TO USE**
Apply two – three times per day, gently massaging until absorbed.

**ACTIVE INGREDIENTS**
Polyglutamic acid, 4-t-butylcyclohexanol, Methyl Sulfonyl Methane.

**CONTAINER**
PE co-extruded tube

**CONTENT**
30 ml
Intensive cream SPF 30

FUNCTIONS
It has a high protection against UVA and UVB radiation and it exerts an anti-inflammatory and calming effect.

HOW TO USE
Apply two – three times during the day, gently massaging until absorbed.

ACTIVE INGREDIENTS
Polyglutamic acid, 4-t-butylocyclohexanol, Methyl Sulfonyl Methane, sun filters.

CONTAINER
PE co-extruded tube

CONTENT
30 ml
# Intensive cream SPF 30 Teintée

## FUNCTIONS

It is a colored cream with high protection against UVA and UVB radiation and exerts an anti-inflammatory and calming effect.

## HOW TO USE

Apply two – three times during the day, gently massaging until absorbed.

## ACTIVE INGREDIENTS

Polyglutamic acid, 4-t-butylcyclohexanol, Methyl Sulfonyl Methane, sun filters.

## CONTAINER

PE co-extruded tube

## CONTENT

30 ml
LOGICALLY COMPREHENSIVE

INNOVATIVE

EFFECTIVE & SAFE