A new active to make age spots disappear from sight
Gatuline® Spot-Light

INCI: Butylene Glycol (and) Actinidia Chinensis (Kiwi) Fruit Water (and) Alcohol (and) Sophora Flavescens Root Extract

Genesis

Sourcing

Extraction

Mechanism of action

Formulation & Applications

Clinical evaluation
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Age spots, known commonly as dark spots:
- Permanent hyperpigmented marks that appear on UV exposed areas of the skin - also known as solar lentigo
- Their appearance increases over time

Skin blemishes not associated with any medical conditions:
- Range in color from light to dark brown
- Located on particular on the hands, face, décolleté, shoulders, arms, forehead, and the scalp if bald
Dark spots represent the first sign of aging in Asian skin.

Approximately 1 in 5 Chinese women already have pigmentation spots by the age of 20 and they get worse over time.

AGE SPOTS ARRIVE ON A FLAWLESS, WRINKLE-FREE SKIN:
- They appear even more visible
- A source of distress for many Asian women

A RECENT STUDY SHOWED THAT FOR CHINESE WOMEN THE SPOTS ARE TWICE AS AGING AS WRINKLES ON THE SAME FACE
- Beyond age, reducing dark spots increases significantly their perception of “facial attractiveness”

80% OF WOMEN IN ASIA USE COSMETIC PRODUCTS TO TRY TO CORRECT PIGMENTATION IRREGULARITY

One of the main aging concerns named by European and American women after wrinkles and sagging

In France:
- 20% of women over age 25 suffer from age spots
- 90% after the age of 50

Terms used to describe these spots in Caucasian skin are undeniably related to aging
- “Cemetery flower”, “senile freckle”…
Caucasian skin & Age spots

**In the 60’s & 70’s**

With the democratization of summer breaks and sunbathing, tanned skin starts becoming fashion and socially desirable

- Overexposure to sun with few concerns about damages caused to the skin

**Today**

Women turning 50-60 years old present hyperpigmentation problems

- Awareness of the need to correct and prevent age spots appearance
Physiopathology of age spots: still currently not properly known

Despite the link with UV exposure, mechanisms involved in the development of hyperpigmented areas are elusive
- A subject of great interest among the scientific community leading to an increased knowledge level

Causes:
- Widely admitted: disruption of skin pigmentation, oxidation (ROS) and inflammation
- Recent studies: evidenced that solar lentigo could be induced by the dermal environment located beneath the hyperpigmented areas
Age spots: existing solutions

- All active ingredients on the market target the epidermal causes.
- Few ingredients offer additional anti-oxidation and anti-inflammatory effect.
- An even smaller amount of products target accumulated melanin.
- NONE prevent glycation and dermis degradation, newly identified as key to prevent age spot appearance.

Clinical efficacy is not fully satisfying.
For better treatment of age spots:

- Act in the epidermis
  - Melanogenesis, production and elimination of melanin

- Act in the dermis
  - Protect from photo-aging and MMPs degradation
  - Protect the extracellular matrix from glycation

- Act throughout the skin
  - Inhibit inflammation and prevent oxidative degradation

Gatuline® Spot-Light is the first ingredient that tackles ALL these causes of age spots
Gatuline® Spot-Light

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A unique blend for high efficacy

- **Kiwi fruit water**
  - Demonstrated anti-tyrosinase activity

- **Sophora flavescens root extract**
  - Skin lightening potential widely described in literature
SourcEING

Sophora flavescens in TCM

- Roots of Sophora flavescens: long history as Traditional Chinese Medicine
  - First described in Shennong Ben Cao, the oldest Chinese book mentioning medicinal plants
- Used for skin disease healing properties
Sophora flavescens: taxonomy & name

- **Latin name**: Sophora flavescens Aiton
- **Chinese name**: Kushen or Ku-Shen
- **Japanese name**: Kujin
- **English name**: Shrubby sophora or bitter ginseng

- **Fabaceae family**
  - Third largest plant family with 630 genera and over 18,860 species
  - Mimosa belongs to this family
**SOURCING**

**Sophora flavescens: botanical description**

- **Evergreen shrub**
  - Can grow up to 1.5 m

- **Flowers:**
  - Bloom between June and July
  - Beautifully light yellow with a corolla and a chalice form
  - Measure around 7 mm

- **Roots:**
  - Long with a cylinder form
  - Measure between 10 to 30 cm (diameter: 1-2 cm)
Sourcing

Sophora flavescens: phytochemical profile

- Rich in active molecules with documented biological efficacy
- Secondary metabolites, secreted by the plant to communicate and self-defend

- Flavanones:
  - Sophoraflavanone G
    - Proven efficacy (literature):
      » Tyrosinase inhibition
      » Anti-inflammatory effect
      » Anti-oxidation

- Alkaloids:
  - Matrine
    - Proven efficacy (literature):
      » MMPs inhibition
      » Anti-inflammatory effect
SOURCING

Reliable suppliers

- Guaranteed Asian origin (certificate available on demand)
  - Pool of suppliers to ensure continuous supply

- Only part of the plant is harvested:
  - No interference with natural growth

- Strict specifications:
  - Dry, clean and sort the roots
    - Specific color and size
  - Upon arrival on the Gattefossé site: in-house quality control tests are performed
Handpicked Italian kiwi fruit (origin guaranteed)

100% natural constitutive water
  - Used to maximize the skin lightening potential of Sophora flavescens
Gatuline® Spot-Light

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**EXTRACTION**

A targeted process

**Fresh kiwi**
- Juice extraction (grinding)
- Flash distillation

**Sophora root**
- Alcoholic extraction
- Addition of vegetable BG

**Flow Chart**

- Mixing
- Filtration
- Packaging
- Labelling
- Batch release

**Control Points**

- In-process control
- Final control
EXTRACTION

Guaranteed content in active molecules

- Flavanones (expr. in sophoraflavanone G): ≥ 35 mg/100 g
- Matrine: ≥ 15 mg/100 g

Gatuline® Spot-Light

QUALITY
MECHANISM OF ACTION

A double targeted action for higher efficacy

Throughout the skin
- Anti-oxidation
- Anti-inflammatory effect

In the epidermis
- Exfoliation
- Anti-tyrosinase activity
- Inhibition of melanogenesis

In the dermis
- Inhibition of MMPs enzymatic activities
- Anti-glycation activity

Degradation of the dermal environment, by MMPs and glycation, triggers release of melanogenic soluble factors from fibroblasts that stimulate the melanocyte function.
MECHANISM OF ACTION

Gatuline® Spot-Light

Throughout the skin

- Anti-oxidation
- Anti-inflammatory effect
**MECHANISM OF ACTION**

**Anti-oxidation**

- **DPPH radical**
  - 30 minutes incubation w/wo Gatuline® Spot-Light
  - Measure of the absorbance at 518 nm using UV spectrophotometer

> Up to 75% DDPH radical scavenging activity (dose effect)
MECHANISM OF ACTION

Anti-inflammatory effect

- Measure of pro-inflammatory mediators release by keratinocytes
  - Under PMA stimulation
  - ELISA dosage

Strong inhibition of pro-inflammatory mediators release, up to IL-6: 70% and IL-8: 63%

* p<0.05
*** p<0.001
MECHANISM OF ACTION

Gatuline® Spot-Light

In the epidermis

- Exfoliation
- Anti-tyrosinase activity
- Inhibition of melanogenesis
MECHANISM OF ACTION

Exfoliation

- Enhanced desquamation
  - Corneodesmosin enzymatic degradation by kalikrein related peptidase-5

- Up to +81% proteolysis of corneodesmosin due to enhanced enzymatic activity of KLK5
MECHANISM OF ACTION

Anti-tyrosinase activity

- Enzymatic inhibition of tyrosinase
  - 10 minutes incubation w/wo Gatuline® Spot-Light or kojic acid
  - Addition of L-dopa, 10 min incubation, and measure of absorbance at 490 nm with a spectrophotometer

More than 80% tyrosinase activity inhibition from 0.1% Gatuline® Spot-Light
MECHANISM OF ACTION

Inhibition of melanogenesis

- Melanin synthesis inhibition
  - B16 melanocytes
  - 72 hours incubation with NDP-MSH and w/wo Gatuline® Spot-Light
  - Quantification of total melanin content by measuring absorbance at 405 nm

- 58% melanin synthesis inhibition with 0.5% Gatuline® Spot-Light (dose effect)
MECHANISM OF ACTION

No cytotoxicity unlike kojic acid

- Cell viability assessment
  - B16 melanocytes

Unlike kojic acid, Gatuline® Spot-Light is absolutely not cytotoxic at the same concentrations
In a recent publication*, demonstration in vitro that Sophora extract combined with kiwi fruit water induces:

- Strong and significant inhibition of melanin production in normal human melanocytes
- Strong and significant decrease of melanin transfer to recipient keratinocytes

MECHANISM OF ACTION

Gatuline® Spot-Light

In the dermis

Inhibition of MMPs enzymatic activities
Anti-glycation activity
MECHANISM OF ACTION

Prevention against MMP degradation

- Inhibition of MMPs enzymatic activities
  - MMP-1 (collagenase-1), MMP-2 (gelatinase A), MMP-3 (stromelysin-2), MMP-9 (gelatinase B) and MMP-12 (macrophage elastase)
  - 30 minutes incubation w/wo Gatuline® Spot-Light and measure of the absorbance at 412 nm with a spectrophotometer

- Up to:
  - MMP-1: -27%
  - MMP-2: -61%
  - MMP-3: -59%
  - MMP-9: -33%
  - MMP-12: -26%

Strong inhibition of enzymatic activities of major MMPs
**MECHANISM OF ACTION**

**Anti-glycation**

- AGEs inhibition activity
  - BSA/glucose model
  - 7 days incubation w/wo Gatuline® Spot-Light and measure of the fluorescence ($\lambda_{ex}370\text{nm}/\lambda_{em}440\text{nm}$) with UV spectrophotometer

- **Up to 65% reduction of advanced glycation end products (dose effect)**
MECHANISM OF ACTION

Conclusion

Throughout the skin

**Anti-Inflammatory effect**
Inhibition of pro-inflammatory mediators release with 0.5% Gatuline® Spot-Light
- Interleukine-6: -70%
- Interleukine-8: -69%

**Anti-oxidation**
Up to 79% DDPH radical scavenging activity (dose effect)

Release of melanogenic soluble factors from photo-aged fibroblasts

In the epidermis

**Exfoliation**
Up to +81% proteolysis of comedosuction due to enhanced enzymatic activity of kallikrein-related peptidase 5

**Inhibition of melanogenesis**
58% melanin synthesis inhibition with 0.5% Gatuline® Spot-Light (B16 melanocytes, dose effect, higher efficacy than koic acid)

**Anti-tyrosinase activity**
More than 80% tyrosinase activity inhibition from 0.1% Gatuline® Spot-Light

In the dermis

**Inhibition of MMPs enzymatic activities**
- MMP-1: 27%
- MMP-2: 61%
- MMP-9: 33%
- MMP-12: 26%
- MMP-3: 69%

**Anti-glycation activity**
Up to 63% reduction of advanced glycation end products (dose effect)
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Extraction
Clinical study performed in Thailand

- Monocentric and double blind
- Comparative: active formula (3%) vs. placebo
- Between December and March

Inclusion criteria:

<table>
<thead>
<tr>
<th>Number of volunteers</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin</td>
<td>Asian</td>
</tr>
<tr>
<td>Phototype</td>
<td>II and III (mainly III) with ITA° &gt; 28°</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
<td>45 to 63 years old, with an average of 53.6 ± 5.3</td>
</tr>
</tbody>
</table>
| Skin characteristics  | All skin types  
                        | Volunteers with at least one age spot of epidermal origin on the cheek (checked with a Wood lamp) and visible to the naked eye (approximately 3 mm) on each half face and with a spotless area near the studied age spot |
CLINICAL EVALUATION

Methodology of application

- **Application zone:**
  - Cream A: split-face except the forehead
  - Cream B: other split-face except the forehead (randomization of the side of application)

- **Frequency:** twice a day (in the morning and in the evening)

- **Duration:** 3 months – last application: in the evening preceding each evaluation day

- **Conditions of application:** under normal conditions of use (as much as necessary); apply at home on cleansed skin, massaging gently until the cream is absorbed
Clinical Evaluation

Evaluations

- Clinical scoring vs. placebo
- Image analysis vs. placebo
  - Age spot: contours and size
  - Normal skin color
- Before/After pictures
- Use test questionnaire
CLINICAL EVALUATION

Clinical scoring

- Visibility of the age spot
  - Contrast between a spot and its immediate environment
  - 6-point photographic scale (0 to 5) based on Skin Aging Atlas, Asian Type, Vol. 2 (R. Bazin & F. Flamant)
CLINICAL EVALUATION

Clinical scoring

- Density of age spots
  - Number of spots per unit area on the cheek
  - 8-point photographic scale (0 to 7) based on Skin Aging Atlas, Asian Type, Vol. 2 (R. Bazin & F. Flamant)
CLINICAL EVALUATION

- Fewer, less visible age spots

Gatuline® Spot-Light induces a significant reduction of the visibility and density of age spots
CLINICAL EVALUATION

Image analysis: contours of the age spot

- Faded appearance

Gatuline® Spot-Light blurs the contours of the age spot
**Clinical Evaluation**

**Image analysis: size of the age spot**

- **Smaller size**

![Graph showing reduction in age spot perimeter with Gatuline® Spot-Light](image)

- **Gatuline® Spot-Light reduces significantly the perimeter of the age spot**
CLINICAL EVALUATION

Image analysis: normal skin color

- Lightens skin tone

△L*: luminance difference between treated and untreated normal skin

△ITA°: difference of the pigmentation degree between treated and untreated normal skin

Gatuline® Spot-Light lightens significantly normal skin tone

Gatuline® Spot-Light lightens significantly normal skin tone
Gatuline® Spot-Light shows a visible correcting action on age spots of different morphologies.
Visible efficacy

- Visualization at the heart of the age spot
High appraisal levels from users

After 56 days:
- 97% My skin looks brighter
- 90% The cream reduces the color of my dark spots
- 93% My age spots are less visible

After 84 days:
- 97% The product gives my skin a healthy glow
- 97% My skin is lightened

The skin looks brighter, younger, and age spots are minimized
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FORMULATION & APPLICATIONS

Formulation

- Use level: 3%
- Soluble in water and alcohol
- Insoluble in vegetal and mineral oils
- To be added to the aqueous phase at RT

Simple emulsion with 3% Gatuline® Spot-Light
Applications

- **Facial care and make-up**
  - Age spot targeted treatments
  - Skin perfectors, foundations and concealers
  - Brightening products
  - Alphabet creams
  - Global anti-aging lines

- **Body care**
  - Hand creams
  - Body lotions
Specifications:
- Yellow to brown liquid
- Preservative-free
- No toxicity
- Quality controls

Regulation:
- Worldwide approval
- China: listed on IECIC 2014-06
- REACH China compliant
- ECOCERT and COSMOS compliant
- NPA certified
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**Key features:**
- Natural active
- Corrects and minimizes age spots
- Acts on both epidermal and dermal causes of age spots
- High and visible efficacy

**Claims:**
- Reduces the visibility and number of age spots
- Fades the appearance of dark spots
- Lightens skin tone
- Safe and natural
- Anti-aging benefits