Botanical extracts for Personal Care applications in CHINA.

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NATUREX
Ultimate Botanical Benefits
Purified molecules from LICORICE:

Suitable for a Variety of Applications for Sensitive and Irritated skin
What are Licorice derivatives? (INCI names)

- (18 β) Glycyrrhetinic acid
- Stearyl Glycyrrhetinate
- Dipotassium Glycyrrhizate
- Ammonium Glycyrrhizate

- Market data
- Licorice
- Industrial
- Efficacy
- Toxicity
- Applications

Purified molecules from LICORICE:
Europe and Asia Pacific are two keys markets
Asia is the most active region with +65% new product launches in 2011* vs 2010 (-13% globally)
France remains leader with 14% share of launch from 2006 to 2011*, but Japan leads the way in 2011* with 21% of new product launches

Active Countries | % of Products Launched 2006-2011
---|---
France | 14.2%  
Italy | 10.2%  
Japan | 9.9%  
UK | 9.5%  
USA | 6.4%  
Greece | 5.6%  
Spain | 5.5%  
Netherlands | 4.7%  
Germany | 3.6%  
Brazil | 3.5%

Market data: 18 β Glycyrrhetinic acid

Product Launches

*Estimated data  
Source: Mintel, Nov 2011
5 important sub-categories

- **Face/Neck Care** (Cleansing gel, Product after shave balm, Face Cream, Anti-redness cream...)
- **Body Care** (Body milk, Skin lotion, Skin scrub, Ice spray...)
- **Deodorants**
- **Sun – Sun/Sunbed Exposure**
- **Sun – After Sun** are

Source: Mintel, Nov 2011
### Active Countries % of Products Launched 2006-2011

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Products Launched 2006-2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan</td>
<td>59.1%</td>
</tr>
<tr>
<td>USA</td>
<td>7.4%</td>
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<tr>
<td>Taiwan</td>
<td>3.1%</td>
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<tr>
<td>France</td>
<td>3.1%</td>
</tr>
<tr>
<td>Singapore</td>
<td>2.7%</td>
</tr>
<tr>
<td>South Korea</td>
<td>2.6%</td>
</tr>
<tr>
<td>Malaysia</td>
<td>2.3%</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>2.2%</td>
</tr>
<tr>
<td>Thailand</td>
<td>2.0%</td>
</tr>
<tr>
<td>Canada</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

Asia Pacific is the key market, accounted for 80% of new product launches from 2006 to 2011*, +9.6% growth in 2011* vs 2010.

Europe and North America are also 2 dynamic markets with >+100% growth in 2011* vs 2010.

Japan is monopole in this market, accounting for 59% share of launches from 2006 to 2011*.

*Estimated data

Source: Mintel, Nov 2011
5 important sub-categories

→ **Face/Neck Care** *(Cleansing gel, Product after shave balm, Face Cream, Anti-redness cream...)*

→ **Lip Colour**

→ **Lip Care**

→ **Sun – Sun/Sunbed Exposure**

→ **Body Care** *(Body milk, Skin lotion, Skin scrub, Ice spray...)*

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**Market data: Stearyl Glycyrrhetinate**

Share of launches from 2006 to 2011*

- Face/Neck Care: 32%
- Lip Colour Cosmetics - Lip Colour: 15%
- Lip Care: 14%
- Sun - Sun/Sunbed Exposure: 8%
- Body Care: 7%
- Sets: 4%
- Face Colour Cosmetics: 3%
- Eye Care: 2%
- Others: 1%

Source: Mintel, Nov 2011

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[Source: Mintel, Nov 2011]
Asia Pacific is the key market, accounted for 75% of new product launches from 2006 to 2011*, +18% growth in 2011* vs 2010.

Japan is monopole in this market with +15% growth in 2011* vs 2010.

### Active Countries

<table>
<thead>
<tr>
<th>Country</th>
<th>% of Products Launched 2006-2011</th>
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<tbody>
<tr>
<td>Japan</td>
<td>42.0%</td>
</tr>
<tr>
<td>USA</td>
<td>8.0%</td>
</tr>
<tr>
<td>South Korea</td>
<td>6.6%</td>
</tr>
<tr>
<td>Taiwan</td>
<td>4.0%</td>
</tr>
<tr>
<td>Singapore</td>
<td>3.9%</td>
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<td>China</td>
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<tr>
<td>Thailand</td>
<td>2.2%</td>
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</tbody>
</table>

*Estimated data

Source: Mintel, Nov 2011
2 important sub-categories

→ Face/Neck Care (Cleansing gel, Product after shave balm, Face Cream, Anti-redness cream...),

→ Sun – Sun/Sunbed Exposure

Market data:
Dipotassium Glycyrrhizate

Share of launches from 2006 to 2011*

*Estimated data  Source: Mintel, Nov 2011
Europe and Asia Pacific are two key markets. They are also two dynamic regions with +14% share of launch in 2011* vs 2010 for each. Despite the decrease in number of product launches in 2009 and 2010, USA remains leader with 15% share of launch from 2006 to 2011*, but Japan leads the way in 2011* with 10% of new product launches.

### Active Countries

<table>
<thead>
<tr>
<th>Active Countries</th>
<th>% of Products Launched 2006-2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>14.9%</td>
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<tr>
<td>Japan</td>
<td>11.6%</td>
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<tr>
<td>France</td>
<td>8.8%</td>
</tr>
<tr>
<td>UK</td>
<td>7.6%</td>
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<tr>
<td>Spain</td>
<td>5.7%</td>
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<td>3.0%</td>
</tr>
<tr>
<td>Mexico</td>
<td>2.9%</td>
</tr>
</tbody>
</table>

*Estimated data  
Source: Mintel, Nov 2011
3 important sub-categories

- Lip Care
- Lip Colour
- Face/Neck Care

73% launches are in lip area
= 80% share of sub-category launch

Market data: Ammonium Glycyrrhizate

Share of launches from 2006 to 2011*

- Lip Care: 40%
- Lip Colour Cosmetics - Lip Colour: 17%
- Face/Neck Care: 23%
- Multi-Use: 5%
- Eye Care: 4%
- Sets: 3%
- Others: 8%

*Estimated data Source: Mintel, Nov 2011
Want to know more about Licorice?

**Very well know**
- Licorice is a very well known botanical for food application as flavour

**Not very well known**
- Pure molecules can be purified at industrial GMP grade
- International trends are still increasing for cosmetic uses of licorice derivatives

Want to know more about this surprising botanical?
Licorice is a wild plant which grows in southern Europe (Spain/Italy), in Middle East, in Central Asia (Iran, Kazakhstan, Kyrgyzstan, Uzbekistan, Afghanistan, Turkmenistan) and in Western China.

- Roots are mainly collected in Central Asia and in Western China (the largest producer of licorice roots in the world - 40 000 T)
1903: Dr. Juan Vinyals, a young pharmacist, embraced his passion for botany and founded the laboratory that would carry his name.

2001: Cognis acquires the Laboratorios Vinyals and integrate them into Cognis Nutrition & Health Unit.

2009: Burgundy acquires botanicals extracts business from Cognis Nutrition & Health and its range of botanical derivatives as well as equipment.

2011: Naturex announces the acquisition of Burgundy Botanical Extracts, strengthening its offering in the pharmaceutical, and personal care markets.

⇒ Leading position in Licorice Extraction and Purification
Industrial Facilities

- GMP requirement
- norm ICH Q7A (pharma)
- API production
- Clean Rooms class 100,000
- In Spain and France
Phytochemistry of Licorice

Licorice Roots

Extraction with Hot water

Filtrations
Concentration Cristalization

Cake Water

Crude extract
Glycyrrhizic acid = Glycyrrhizin 30% purity

Glycyrrhizic acid
From Licorice roots: Purification gives 4 pure molecules

Phytochemistry of Licorice

Glycyrrhizic acid = Glycyrrhizin

Hydrolysis

18 β Glycyrrhetinic acid = enoxolone

Esterification

Di Potassium Glycyrrhizate

Ammonium Glycyrrhizate

Stearyl Glycyrrhétinate
EFFICACY of Licorice derivatives

⇒ Starting point:


Conclusions:
These results, obtained in four different kinds of tests, show that Glycyrrhetic acid is an active anti-inflammatory agent.

- 18-β Glycyrrhetic acid (enoxolone) is the most powerful anti-inflammatory active compound in licorice.
What is inflammation?

PROSTAGLANDINS (PG)
Fixation of PG on specific receptors is followed by redness and swelling

LEUKOTRIENS
Involved in the amplification of deleterious effects of inflammation

Leukotrienes
Involved in the amplification of deleterious effects of inflammation
What is anti-inflammation?

- Anti-inflammatory refers to the treatment that reduces inflammation: the cold (it causes vasoconstriction, decreases swelling and relieves pain), anti-inflammatory drugs, in oral, suppository, by inhalation, or Dermal application,

- Corticosteroids are a class of chemicals involved in a wide range of physiologic processes, in particular regulation of inflammation,

- Due to Side effects of steroids, other active compounds NSAIDs (= Non-steroidal anti-inflammatory drugs) appeared, but with also side effects,

- so other solution have to be found...
EFFICACY of Licorice derivatives

=> Evidences on metabolic pathways


- Derivatives of Glycyrrhetinic acid have shown their inhibitory activity against interleukin-1b (IL-1b)-induced prostaglandin E2 (PGE2) production in normal human dermal fibroblasts (NHDF). Tsukahara et al., (2005).
EFFICACY of Licorice derivatives

=> Evidences on topical applications

- Dipotassium Glycyrrhizate is an anti-inflammatory agent that is used to treat chronic dermatitis. Trotta et al. (2002).

- Licorice topical gel was effective in reducing the scores for erythema, oedema and itching over two weeks (p<0.05). Saeedi M, et al. (2003). => double-blind clinical trial in comparison with base gel on atopic dermatitis over two weeks (30 patients in each group).
EFFICACY of Licorice derivatives

- recent demonstration:

Ishida T et al., (2011) Inhibitory Effects of Glycyrrhetinic Acid on DNA Polymerase and Inflammatory Activities. Evidence-Based Complementary and Alternative Medicine, Vol 2012, Article ID 650514, 9 pages,

⇒ Inhibitory effect of Licorice derivatives on inflammation induced by TPA* or LPS*

*TPA = 12-O-tetradecanoylphorbol-13-acetate
*LPS : LipoPolySaccharides
**Efficacy of Licorice derivatives**

Inhibitory effect of Licorice derivatives on induced inflammation (TPA)

**Protocole:**
- Licorice derivatives (indicated concentrations) are applied on skin – 30 min
- Inflammation is induced with TPA*
- % of edema is measured as an inflammatory marker.

**Result:**
- Licorice derivatives reduce edema caused by TPA*, With a high dose-dependant activity.

Data are shown as the means ± SE (n=6).
Ishida T et al., (2011)

*TPA = 12-O-tetradecanoylphorbol-13-acetate
**Efficacy of Licorice derivatives**

Inhibitory effect of Licorice derivatives on induced inflammation (LPS)

- **Protocol:**
  - Cells are pre-treated with licorice derivatives (indicated concentrations) – 30 min
  - Inflammation is induced with LPS
  - TNF-α content is measured as an inflammatory marker.

- **Result:**
  - Cells in inflammatory conditions produced TNF-α.
  - Licorice derivatives inhibit the inflammation: the production of TNF-α is reduced.

TNF-α concentration in the cell medium is measured by ELISA
Data are shown as the means ± SE (n=5).

Ishida T et al., (2011)
EFFICACY of Licorice derivatives

=> Evidences for oral care applications

- Many clinical studies have shown interest of enoxolone in non specific gingivitis:


- And now principle of action is explained:


Enoxolone induces a significant decrease of oedema, vasodilatation, and IL8 excretion. The Enoxolone solution induced a decrease of IL-1α.
EFFICACY of Licorice derivatives

- Claims for Licorice derivatives:
  - Anti-inflammatory
  - Soothing
  - Smoothing
  - Relieving activity
  - Wound healing
  - Anti-itching

- Application
  - Soothing sensitive skin
  - Calming irritated skin after sun exposure
  - Repairing chapped lips
  - Flavoring oral care applications
licorice and licorice derivatives are Generally Recognized As Safe (GRAS) by the Food and Drug Administration (FDA)

CIR expert Panel concluded that these ingredients are safe in the current practices of use and concentration.

TOXICITY of Licorice derivatives

18-β Glycyrrhetinic acid (enoxolone)

Oral toxicity test
- **LD$_{50}$** is more than 610 mg/kg

Mutagenicity
- Ames test negative
- Cytogenetics assays negative
- Heritable translocation tests negative

Non skin irritant
- HET-CAM (6%)
- On shaved rabbit skin
- At concentration up to 6% in the formula

Non allergic contact sensitization
- At concentration up to 6% in the formula
  (clinical test : RIPT – 100 persons)

-Yamamura Y et al., (1992)
TOXICITY of Licorice derivatives

Dipotassium Glycyrrhizate

Acute oral toxicity
- LD50: 8 100 mg/kg body weight

Mutagenicity
- No reproductive or developmental toxicity in rats, mice, golden hamsters.

Non phototoxic agent or photosensitizer
- At concentration up to 5% in the formula

- Final report on the safety assessment of Glycyrrhetinic Acid and salts, Int J Toxicol. (2007);26 Suppl 2:79-112;
Ammonium Glycyrrhizate

Mutagenicity
- No genotoxicity in in-vivo and in-vitro cytogenetics assays (Ames)
- No reproductive or developmental toxicity in rats, mice, golden hamsters.

Non phototoxic agents or photosensitizers
- At concentration up to 5% in the formula

- Final report on the safety assessment of Glycyrrhetinic Acid and salts, Int J Toxicol. (2007);26 Suppl 2:79-112;
Products characteristics

- Botany Select GLA18
  - Cosmetic grade (H3064970)
  - Dermo-cosmetic grade (H3064725)
    Compliant with European Pharmacopeia (01/2008:1511),
    Produced under GMP requirement

- Botany Select GLAS18 (H3064975)

- Botany Select PGL (H3064985)

- Botany Select AGL
  - Cosmetic grade (H3064855)
  - Dermo-cosmetic grade (H3064710)
    compliant European Pharmacopeia (01/2008:1511)
    Produced under GMP requirement
APPLICATION of Licorice derivatives

18-β Glycyrrhetinic acid (enoxolone)

- Very often used up to 2% :
- Solubility : glycerol, ethanol
- Application :
  - oral care (toothpaste, mouth wash)
  - skin care (sensitive, fragile, irritable and inflamed skin, insects bites)
  - After sun care
  - After shave care

- Stearyl Glycyrrhretinate

- Frequently used up to 1% :
- Solubility : oil
- Application : emulsion, lip care
APPLICATION of Licorice derivatives

- **Dipotassium Glycyrrhizate**
  - Very often used up to 1% :
  - Solubility : water
  - Application :
    - Gel , lotion, cleansing water

- **Ammonium Glycyrrhizate**
  - Frequently used up to 1% :
  - Solubility : water
  - Application : lip care, toothpaste
    (sweet taste stronger than Saccharose)
### APPLICATION of Licorice derivatives

<table>
<thead>
<tr>
<th>Product name</th>
<th>Active molecule / INCI name</th>
<th>Solubility</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLAS</td>
<td>Stearyl Glycyrrhizinate</td>
<td>Vegetable and mineral oil, Butter, Ester. At high temperature.</td>
<td>Lipstick, Make-up, Oil phase of emulsion for skin care, Oil, Butter, Balm.</td>
</tr>
</tbody>
</table>

Most efficient

sweet taste
APPLICATION of Licorice derivatives

Demonstration products with GLA 18:

- Soothing face cream (with 0,3% GLA18)
- Damaged hand cream (with 0,5% GLA 18)
- After sun milk (with 0,3% GLA 18)
APPLICATION of Licorice derivatives

Demonstration products with GLAS 18:
- After-sun oil (with 0.3% GLAS18)
- Lip repair (with 0.3% GLAS 18)

Demonstration products with PGL:
- Soothing cleansing water (with 0.3% PGL)
- Calming jelly (with 0.5% PGL)
APPLICATION of Licorice derivatives

Demonstration set:

- Soothing face cream (with 0.3% GLA18)
- Flavoured Lip repair (with 0.5% AGL)
- Soothing cleansing water (with 0.3% PGL)
Purified molecules from LICORICE:

Suitable for a Variety of Applications for Sensitive and Irritated skin
Botanical extracts for Personal Care applications

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