

New focus on natural moisturisation

The fundamental role of urea in maintaining the skin's moisturisation is well known.¹

Concentrated in the *stratum corneum*, where it represents 7% of the natural moisturising factor (or NMF),² it is naturally present in normal skin, but its concentration falls rapidly by 50% in dry skin and 85% in skin suffering from dermatosis.

This drop in urea content is irretrievably accompanied by a depletion of NMF and therefore loss of moisturisation.³ The skin becomes wrinkled and loses its suppleness and radiance.

In 2007, Codif International's laboratories discovered urea channels for the first time in human skin. Urea channels, revealed in keratinocytes, are transporters of ammonium ions,⁴ indispensable precursors in the synthesis of urea. Their cutaneous expression constitutes a major discovery. In fact, they may be at the centre of urea metabolism, facilitating its expression in the epidermis to reconstitute the stock of urea forming the NMF.

Urea channels therefore appear to be essential components in the skin's natural moisturisation mechanism.

While a number of studies have tried to identify the best vehicle to use for helping urea penetrate into the epidermis, the discovery of urea channels may revolutionise the concept of moisturisation.

In fact, by acting on the synthesis of urea channels, the skin's moisturisation is



Salicornia herbacea (marsh samphire).

no longer aided by external means but by internal stimulation of the synthesis of urea, directly at the epidermal core.

In a biomimetic process, Codif International was inspired by the properties of *Salicornia*. This hardy perennial can be found in coastal regions and has developed extraordinary capacities for adaptation, linked to the presence of transporters of water and ammonium

ABSTRACT

Urea channels, recently discovered in the epidermis, may play a fundamental role in the transport of the ammonium ion, no longer enriching the natural moisturising factor (NMF) in urea by means of external sources but through internal stimulation and/or through regulation of the flow of urea through the epidermis.

ions that play a primary role in protection against dehydration and the strong salt content to which it is subjected daily.⁵

Localisation of these transporters, also called gamma-TIP (Tonoplast Intrinsic Protein), changes according to the salinity of the environment.⁶

The gamma-TIP of *Salicornia herbacea* has been studied: it is a water channel involved in salt tolerance and whose



Figure 1: Microscopic observations of urea channels labelling in reconstituted human epidermis, in the presence of a placebo emulsion (A) and of an emulsion containing 1% Hydrasalinol (B).

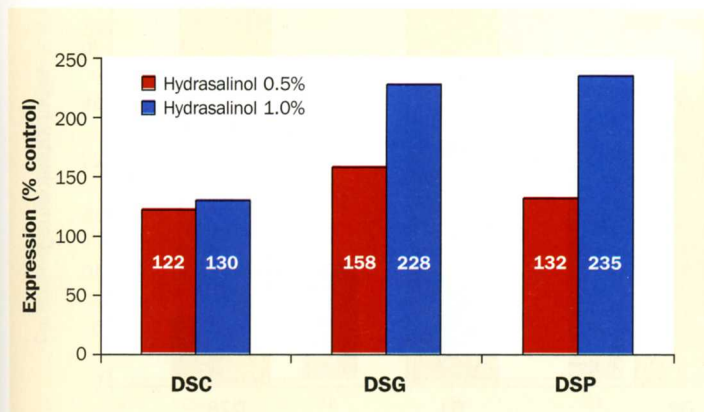


Figure 2: The effect of Hydrasalinol at concentrations of 0.5% and 1% on the expression of Desmocollin (DSC), Desmogleine (DSG) and Desmoplakin (DSP) in reconstituted human skin.

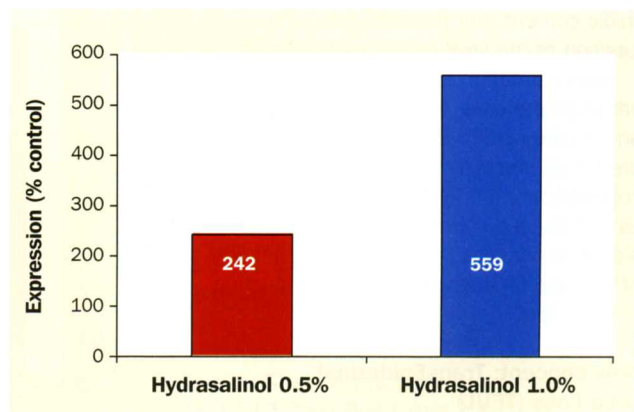


Figure 3: Effect of Hydrasalinol 0.5% and 1% on the synthesis of filaggrin in reconstituted human skin.

sequence presents a strong analogy with that of human urea channels.⁷ This last observation led to prediction of the capacity of an extract of *Salicornia herbacea* in stimulating synthesis of urea channels in the epidermis and therefore in reinforcing the NMF's urea content.

Therefore, Codif International developed a *Salicornia* oil, Hydrasalinol, and tested its moisturising properties via stimulation of urea channels and synthesis of epidermal urea.

Results

Effect of Hydrasalinol on production of urea channels in human skin

Thanks to immuno-labelling techniques (Fig. 1), it was discovered that Hydrasalinol used at a concentration of 1% stimulates synthesis of urea channels by 198%.

Moreover, an additional test using the mini chip technique showed that when Hydrasalinol is used in a 25% concentration it increases the synthesis of the related mRNA.

The theory according to which a *Salicornia* extract may stimulate synthesis of urea channels was therefore verified. These results favour enrichment of the NMF in urea content.

Supplementary benefits for moisturisation agents

Apart from its remarkable efficiency in synthesising urea channels, Hydrasalinol also presents other related properties that are highly beneficial for skin moisturisation.

In fact, it was demonstrated that the oil has a capacity to increase synthesis of adhesion proteins, from 0.5% (Fig. 2), as well as the synthesis of filaggrin whose hydrolytic products, histidine and glutamine, are then converted into urocanic acid and carboxylic-pyrrolidone, the principle constituents of NMF (Fig. 3).

Similarly, Hydrasalinol stimulates the metabolic enzymes of the epidermal lipids, involved in synthesis of ceramides and sphingolipids, major constituents of the lipidic cement that provides the barrier function of the *stratum corneum* (Fig. 4).

These simultaneous actions on the adhesion proteins, the synthesis of filaggrin and on the epidermal lipids led us to predict reinforcement of corneocyte cohesion and the lipid barrier as well as enrichment of the NMF. All of these elements favour a higher barrier protection of the epidermis and therefore a reduction in water loss.

New concept: TransEpidermal Urea Loss (TEUL)

Given that dehydrated skin or that suffering from dermatosis contains very little urea, it is interesting to study the skin's capacity to

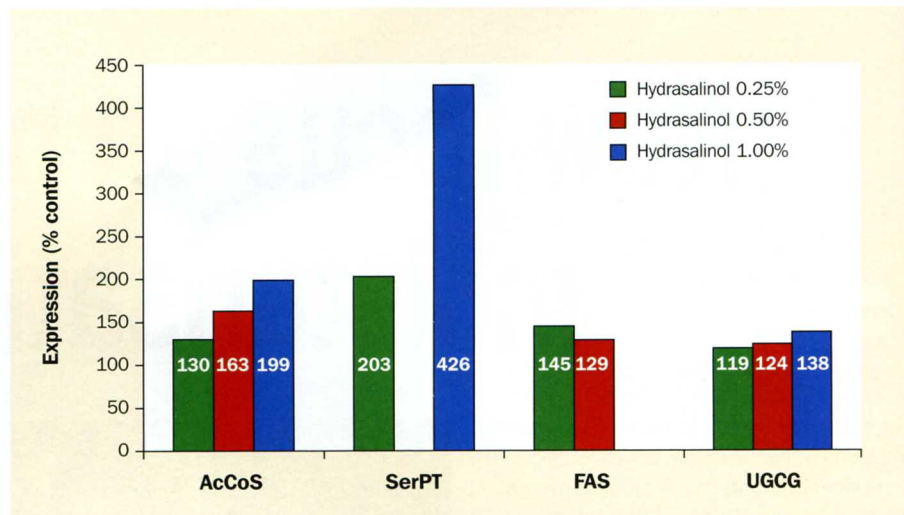


Figure 4: Effect of three concentrations of Hydrasalinol: 0.25%, 0.5% and 1% on the expression of Acetyl CoA synthetase (AcCoS), Serine palmitoyltransferase (SerPT), Fatty acid synthase (FAS), and Ceramide glucosyltransferase (UGCG), in reconstituted human skin.

retain urea. In fact, retained urea would permit an enrichment of NMF and therefore maintenance of moisturisation.

In this context, a new method has been developed consisting in the sampling of corneocytes with a Teflon probe (Fig. 5), followed by measurement of the quantity



Figure 5: Sampling of corneocytes on a surface area of 3.14 cm² with the aid of a Teflon probe for 30 seconds, followed by urea dosage.

of extractable urea. This is a non-invasive process, permitting quantification of the urea on the point of being lost.

In a first phase, evaluation of this parameter on dry untreated skin shows an increase over time of the amount of extractable urea, regardless of the corneometric measurements and TransEpidermal Water Loss (TEWL) (Fig. 6).

Then a second experiment measured the effect of treatment with galenic cosmetics such as vegetable oil and a placebo emulsion on the variation in quantity of extractable urea in the skin (Fig. 7). After 28 days of treatment, the vegetable oil enabled stabilisation of the quantity of extractable urea while with the placebo emulsion there was a 75% decrease in the amount of urea on the point of being lost.

This last observation shows that the quantity of extractable urea in the skin

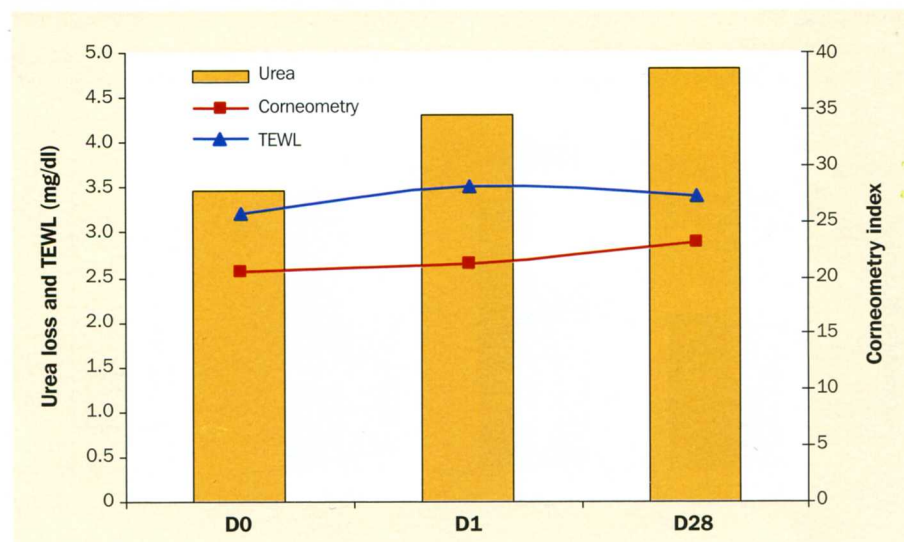


Figure 6: Evolution of extractable urea, corneometry index and TransEpidermal Water Loss (TEWL) on dry untreated skin over 28 days.

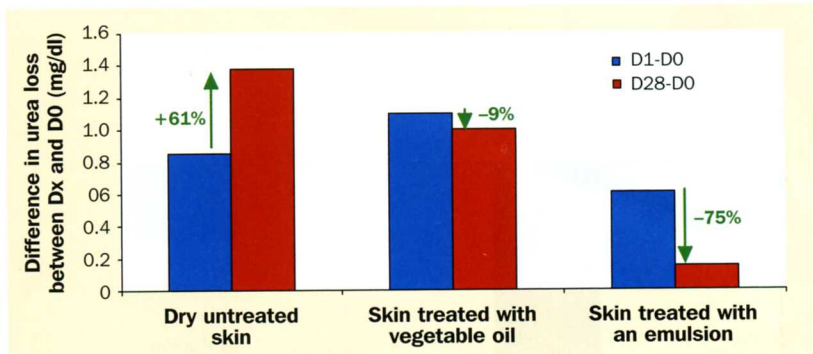


Figure 7: Variation in extractable urea content of dry untreated skin, skin treated with vegetable oil and skin treated with a placebo emulsion.

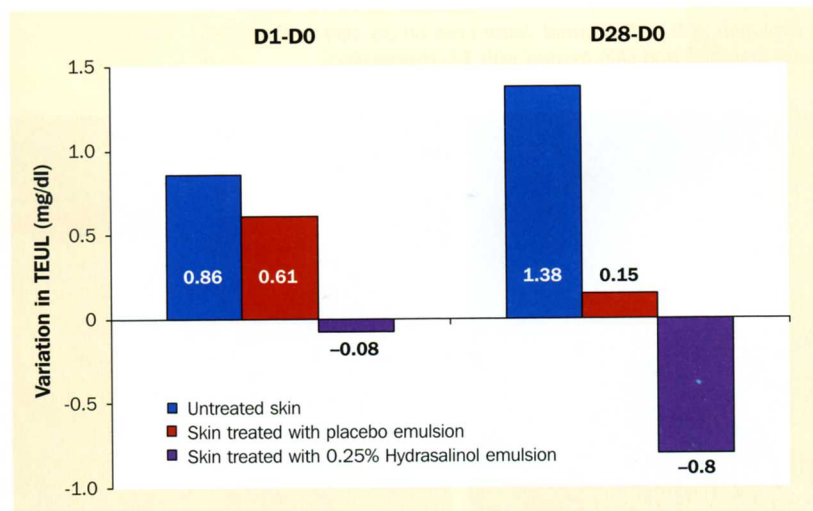


Figure 8: Variation in TransEpidermal Urea Loss in dry untreated skin, skin treated with a placebo emulsion and skin treated with an emulsion containing 0.25% of Hydrasalinol.

is directly related to the level of epidermal dehydration. Thus, the monitoring of the quantity of extractable urea in the skin could provide information on a product's moisturising properties.

And here we have the full value of this test that in itself constitutes a new method, both independent and

complementary, to the tests currently used to assess the effect of a product on skin hydration.

These results therefore introduce a new notion: TransEpidermal Urea Loss (TEUL) equivalent to TransEpidermal Water Loss (TEWL) for water.

Thus, similarly to TEWL, the monitoring of TransEpidermal Urea

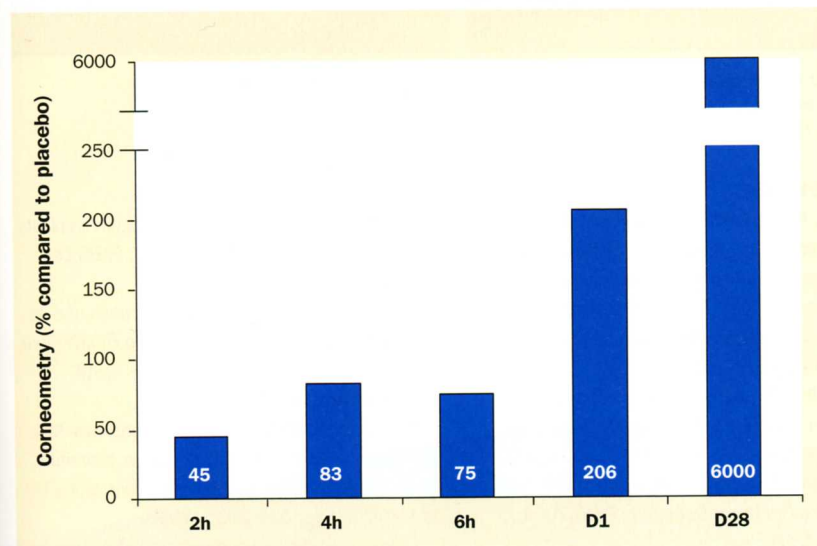


Figure 9: Evaluation of moisture content by corneometry on dry skin treated with an emulsion containing 1% Hydrasalinol.

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