



Patent Pending

The Struggle against Cellulitis based on “Anti-Water Activity”

REDULITE

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1. OVERWEIGHT - CELLULITIS & WATER

Today overweight is a frequently manifest phenomenon the cause of which can be found in modified nutritional habits (overabundant offer of food), in the decrease of physical activity and in the mechanisation of our professional and domestic life.

Nevertheless, the populations of the western world are conscient of the problem posed by obesity with respect to health and esthetics: slimming diets, surgical intervention and appetite reducing drugs are very much in fashion.

It is clear that in this context (reduction of overweight, struggle against the concomittant cellulitis, improvement of cutaneous esthetics) cosmetic science is called upon to contribute its part even if it cannot replace the other approaches such as education, physical activity and dieting.

In women the surplus weight is initially concentrated on the thighs, then on the hips. One of the esthetic consequences that is manifest on the cutaneous level is the phenomenon called **cellulitis** or "orange peel skin".

Hernandez and Mercier-Fresnel describe cellulitis in their "Précis d'esthétique cosmétique" [1] as a *lipodistrophy*, i.e. a local fat accumulation associated with retention of water and toxins and a fibrous reaction of the surrounding conjunctive tissue.

These authors also describe the evolution of cellulitis in several stages :

- **the congestive stage** during which the adipocytes agglomerate, the collagen fibres become more dense,
- **the static stage** during which the increasingly dense collagen fibres compress the vessels and lead to retention of water, of toxins and to the formation of oedemas ;
- **the sclerotic stage** that is characterised by the accumulation of fat, of water, of toxins that together form the cellulite nodules. The tissue ages prematurely by progressive loss of collagen fibres, the skin adopts a granular, irregular aspect called "orange peel skin".

We thus note an interesting correlation between the adipose tissue (fat accumulation) and the water retention in the subcutaneous tissue.

Whereas the cosmetic approach to the struggle against cellulitis has concentrated mostly on the decrease of fat in the adipocytes through the stimulation of lipolysis and/or the inhibition of lipogenesis (see the SEDERMA brochures **CARNITILINE**, **VEXEL**, **CoAXEL**, **CYCLOLIPASE**), the question of the elimination of the other factors contributing to cellulitis has not received the same amount of attention.

With **REDULITE**

we present a new concept : **the fight against water**. This approach is based on the combination of a phytotherapeutic effect and a physical effect (osmosis) and must be understood as complementary to lipolytic treatment, to classical firming and collagenolytical care ; it does not replace them but completes the treatment efficiently.

The aim of **REDULITE** is to facilitate the elimination of interstitial water, to decrease the pressure exerted upon the tissue and thus to improve the macroscopic appearance of the skin, to reduce the neglected parameter of cellulitis, i.e. water retention.

2. DESCRIPTION OF REDULITE

REDULITE is a viscous transparent gel of the following composition

- elderberry extract
- glyceryl polyacrylate
- ethoxydiglycol.

The gel contains no preservatives and can be used in any type of cosmetic formula designed for anti-cellulite treatment, for body firming care etc...

This composition was chosen on the basis of the following considerations :

The Elderberry extract

Two varieties of elderberry (*Sambucus ebulus* L. and *Sambucus nigra* L.) are used since antiquity by popular medicine. Diverse virtues are attributed to the fruit, the roots and the flower extracts (infusions), but both plants are mostly employed for the diuretic effect [2,3]. Among the classical plants known for this purpose, elderberry is by far the most active [4].

The flowers of elderberry contain essential oils, tanins, sugars, a flavonic glucoside (derivative of quercetol). The mechanisms of diuretic action induced by the plant extracts are not well known, the phenomena are complex ; for example, the dose/efficacy relationship is not linear as it has been shown that an oral dose of 10mg/kg has strong diuretic activity, whereas 100mg/kg are inactive [4].

We have thus chosen to include an extract of elderberry with the aim of improving, by topical application, the evacuation of interstitial water. Indeed, Riecker describes in 1975 [5] certain extrarenal effects of diuretic agents, among which he mentions the elimination of oedemas, the decrease of arterial pressure, the displacement of interstitial (oedematous) fluids towards the vascularized system. Other authors have studied the possible relationship existing between diuretic agents and lipolysis and have found indirect effects (generation of free fatty acids) without being able to supply biochemical explanations [6,7].

Glyceryl polyacrylate

SEDERMA has acquired over the recent years a vast experience with gels based on glyceryl polyacrylate. These non drying gels of apparently simple chemical composition, but of complex physical behaviour, distinguish themselves particularly with respect to water. They possess an extremely high moisturizing power, they do not readily release the water contained within their molecular structure – even under severe drying conditions –, they absorb water from the atmosphere and through semi-permeable membranes (osmotic effect), they can be used for their microbicidal effect based on physical action, they stabilize emulsions.

On the basis of a number of isolated observations it seemed interesting to study the possible interaction of this kind of gel with the extra-tissular water in cellulitic skins.

This idea is less paradoxical than it may seem. The moisturizing of a very dry horny layer by a gel of this type can be explained by a better retention of water in the very superficial layers thanks to the osmotic power of the gel.

In the case of a generous application of the gel on the cellulite tissue one may be allowed to surmise that – together with the massaging effect – the osmotic power of the gel will mobilise the water molecules that are imprisoned in the extracellular volume. This mobilisation will facilitate the evacuation of water and of the previously mentioned toxins [1] by the blood and the lymphatic vessels, thus reducing the local pressure on the tissue ; therefore the nodules and the "orange peel" appearance of the skin caused by the cellulitis will be alleviated.

Ethoxydiglycol

This component is well known for its fluidising properties which help in the percutaneous penetration of all kinds of active ingredients. In the case of **REDULITE** we have included this substance in order to facilitate the access of the two active compounds, the elderberry extract and the osmotic Gel to the tissue concerned. At the same time, ethoxydiglycol improves the feel of the gel by decreasing its tackiness.

REDULITE is thus an original complex that combines physical activity (osmosis) with phytocosmetic activity (elderberry extract) in order to fight against cellulitis with a new weapon, the ANTI-WATER campaign.

The efficacy test (cf. following pages) shows that the initial hypothesis correlates well with the results obtained.

3. EFFICACY TESTS *in vivo*

STUDY CARRIED OUT BY LABORATOIRE SPINCONTROL, TOURS

Aim of the study

The test was designed to evaluate the anti-cellulite efficacy of a slimming emulsion containing 20% of **REDULITE** compared to a placebo. Methods used were ultrasound echography and a tape measure.

Principle of the techniques employed

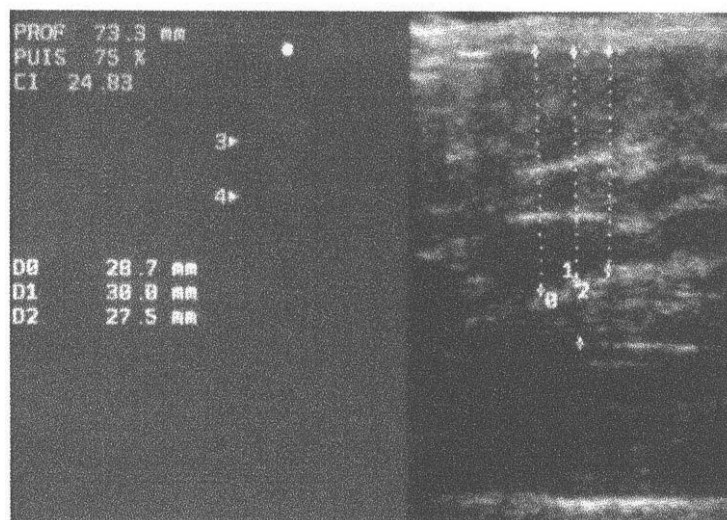
Mode B echography

Ultrasound imaging consists of establishing a cartography of impedance of the studied tissue with respect to ultrasound waves. After the emission of a wave packet by the probe, the received echos and the value of their intensity that is related to their absorption by the various tissues is recorded. It is then possible to construct an image in the plane of the wave packet.

The apparatus used in this study was an Echograph AU4 Idea of Esaote Biomedica.

Figure 1

Ultrasound image of cutaneous and subcutaneous tissue of the thigh



Tape measures

The measurement by centrimetric tape of the perimeter of the thigh on a previously marked spot turns out to be the reference method for the evaluation of slimming efficacy.

Indeed, for a small decrease in the adipose tissue thickness, the variation of the circumference of the thigh appears quite sensitive. (The experimental details of the measurements are given in the appendix).

Protocol of the study

The evaluation was carried out on a panel of 11 female volunteers aged between 18 and 48 years. Echographic measurement of the thickness of cellulite layer on the external face of the thighs was coupled with tape measurement of the perimeter at the same spot. Two persons were excluded from the panel for non-observance of the study protocol. The results of 9 participants were used for interpretation.

The study duration was 42 days for all volunteers ; the emulsions were applied daily for the first 28 days. Examinations were carried out before the first application of either product (emulsion containing **REDULITE** or placebo) at T0, then on day 14, on day 28 and 42 days after the beginning of the test.

The choice of the panelists was based on usual inclusion and exclusion criteria. However, an additional condition of admission was the weight/height ratio ($BMI = \text{Weight}/\text{Height}^2$) of 20 to 25 or a distinct cellulitic skin on the thighs for BMIs between 18 and 20.

The products were applied by massaging on the thighs, the active emulsion (containing 20% **REDULITE**) on the right thigh, the placebo on the left thigh.

Schedule

At T0	First day of product application : Weighing of the panelists Positioning of the cutaneous marks, of the anatomical location and of the elevation with respect to the floor (cf. appendix for details) Echographic measurement of the adipose tissue thickness, at 4 cm right and left of the cutaneous mark centrimetric tape measurement of the thigh at the same horizontal level
At T14	Weighing of the panelists Echographic and tape measurement of both thighs in identical fashion to T0
At T27	Evening : last application of product
At T28	Measurements under the same conditions as T14
At T42	Evaluation of the effects of remanence of the products : measurements identical to T14

Results

1) Slimming effect

The slimming effect is evaluated by the echographic measurement of the thickness of the adipose layer and the measurement of the global perimeter of the thighs.

Average echographic values (table A, figure 2)

The evolution of the raw echographic data shows a regular decrease of the cellulite tissue thickness over the whole duration of the study, on both thighs.

Table A
Echographic values (in mm)

REDULITE			Placebo		
T0	T28	T42	T0	T28	T42
41.9	42.7	41.9	41.2	40.3	39.8
49.2	43.2	41.4	47.8	42.8	41.1
44.9	40.8	40.2	42.1	40.5	40.1
31.7	26.6	25.8	34.3	29.7	29.4
34.3	30.7	30.5	33.7	32.7	32.2
55.8	52.2	49.1	44.6	42.9	41.5
35.5	30.4	27.3	39.6	31.7	28.7
21.0	23.2	21.7	31.8	32.5	31.7
47.3	43.4	43.4	42.4	43.3	43.5
* 40.2	37.0	35.7	39.7	37.4	36.5
** 3.5	3.2	3.2	1.8	1.9	1.9
T=3.39			T=2.4		
T=4.22			T=2.6		
highly significant difference (p<0.01 ; n=9)			significant difference (p<0.05 ; n=9)		

* : mean, ** : SEM

NB : the decrease of the thickness of the thigh treated with **REDULITE** is highly significant.

The loss in thickness over the 42 day period of the study is 3.3 mm on the left thigh (placebo) and 4.5 mm on the right thigh (treated).

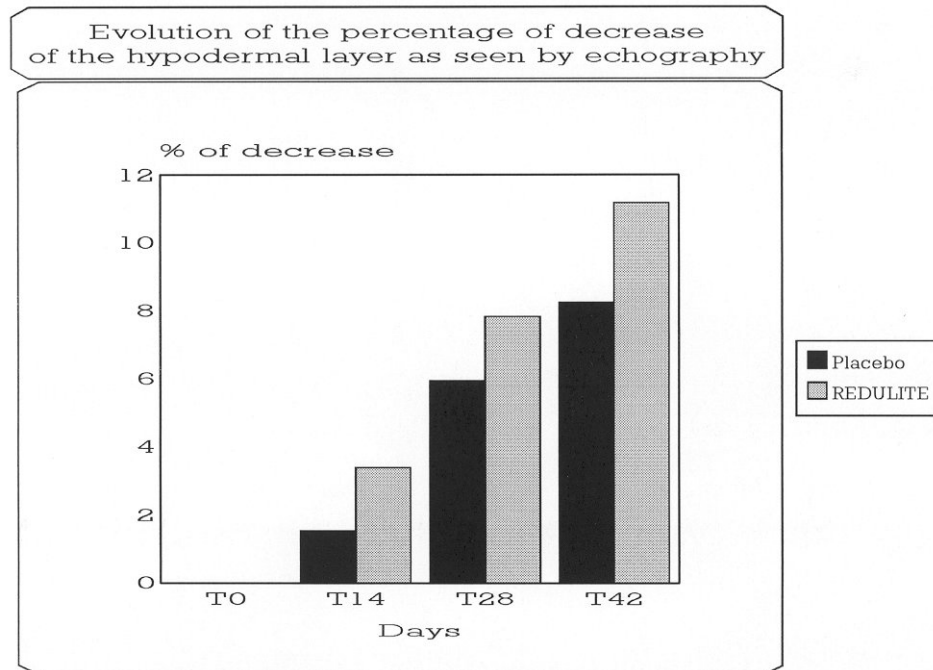


Fig. 2

Expressed as a percentage, the decrease measured by echography reaches 11% for the right thigh, treated with **REDULITE**.

The difference with respect to the placebo is particularly interesting between T28 and T42, thus after the end of the product application. This result could be explained by considerable remanence of the effects of the **REDULITE** containing cream (table B, fig. 3).

Table B

**Evolution of the percentage of decrease
of the adipose layer
Echographic measurements on 9 panelists over 42 days**

Days	REDULITE	Placebo
T0	0.0	0.0
T14	3.4	1.5
T28	7.8	5.9

===== End of treatment

T42	11.2	8.2
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Difference of the percentage of decrease
between REDULITE treated thigh and placebo
treated thigh as seen by echography

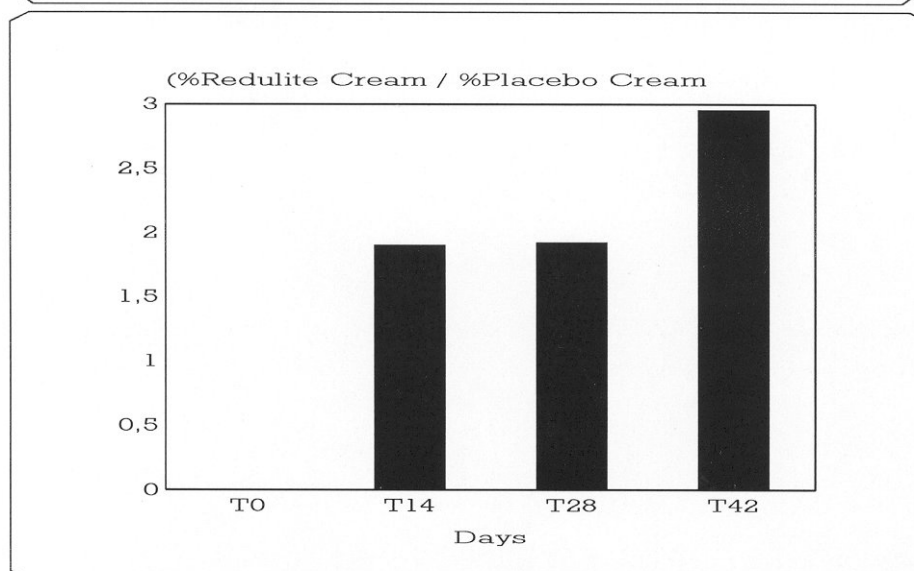


Fig. 3

Mean centrimetric values

The tape measurement values confirm the results of echography. One notes a more pronounced decrease on the **(REDULITE)** treated thigh as compared to the control thigh (placebo). The loss in circumference of the treated thigh is double (1 cm) the one obtained with the placebo (0.5cm).

Table C
mean centrimetric values on 9 panelists

Day	REDULITE	Placebo
T0	58.7	58.1
T14	58.2	57.8
T28	58.12	57.7
T42	57.7	57.6

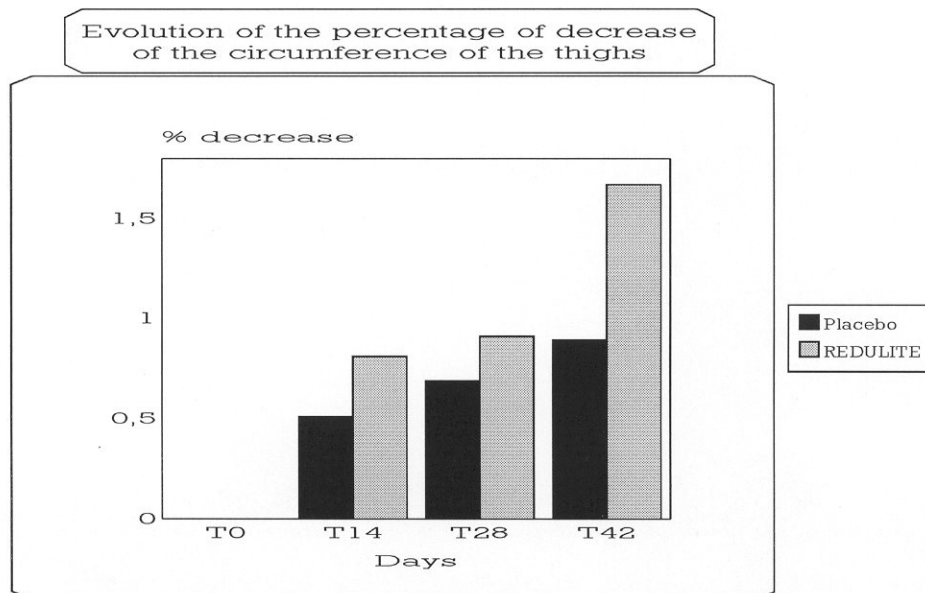


Fig. 4

These two types of measurements confirm the distinct difference between the massaging effect (placebo) and the efficacy of REDULITE, the more so as between T28 and T42 there was no more massaging.

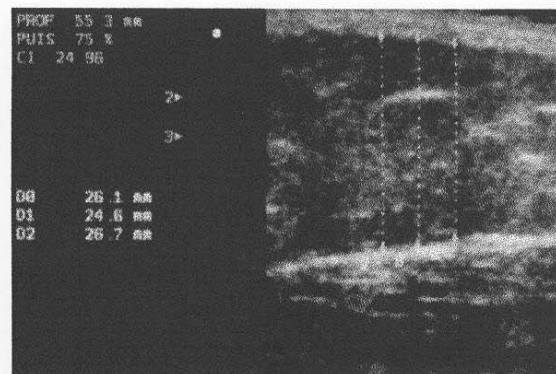
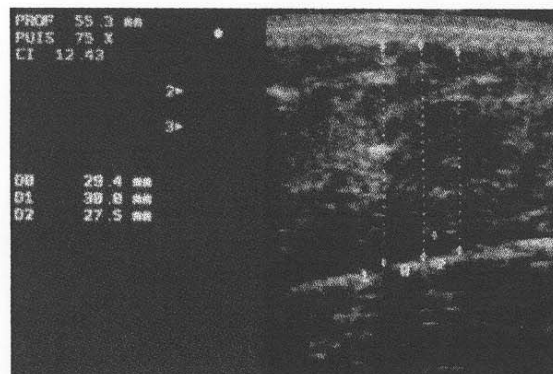
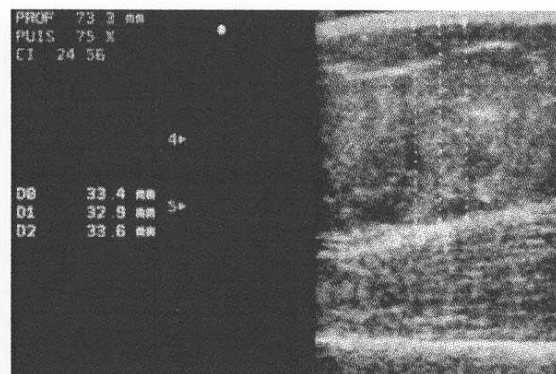
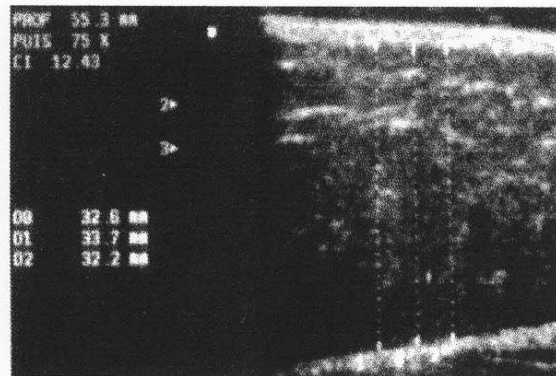
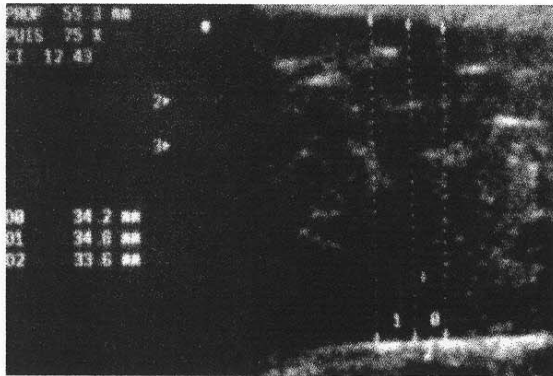
2) Anti-Water Activity

The following pictures represent images obtained by echographic ultrasound measurements on three panelists. One distinguishes clearly the epidermis/dermis layer from the hypodermal layer. In addition to the decrease of the thickness of this layer (representative of the entire study) one should retain the qualitative difference of the images of the adipose layer before and after the treatment.

The interpretation of echographic images in terms of tissue identification is presently only at its beginnings [7].

Nevertheless, the images B (T42, after the treatment) show a more homogenous, more regular, better structured tissue than the images A (before the beginning of the treatment).

ICONOGRAPHY



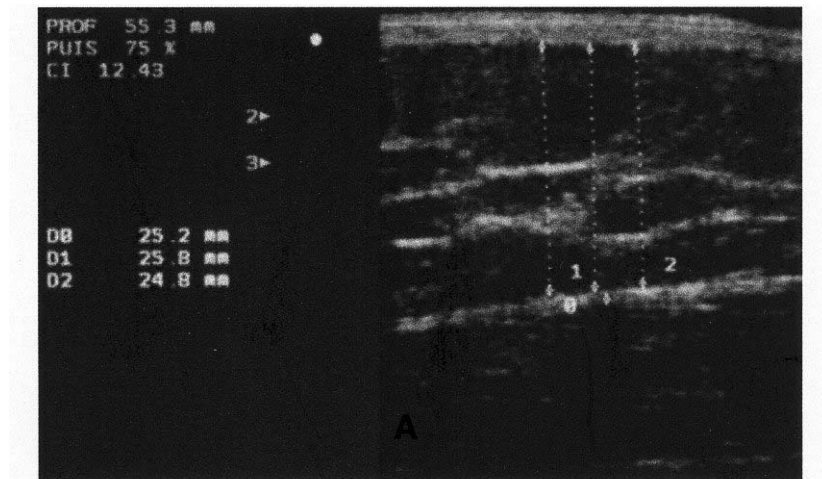
A

B

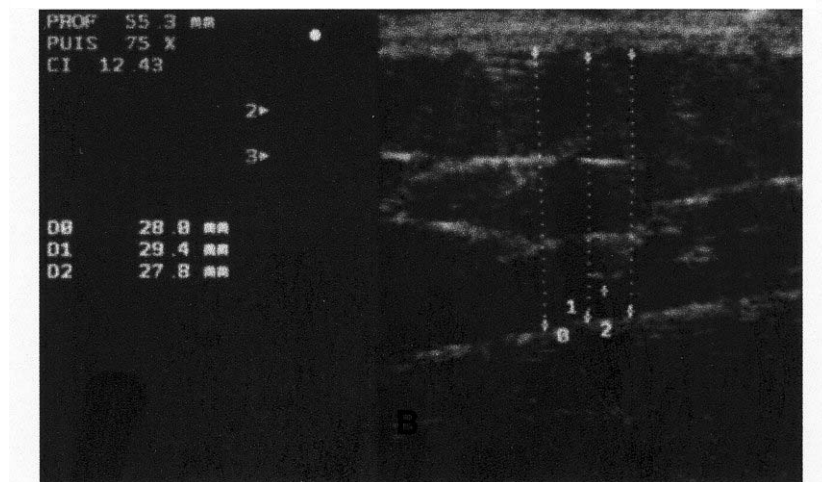
ECHOGRAPHIC IMAGES

BEFORE (A) AND AFTER (B) TREATMENT WITH REDULITE

These qualitative differences are not found to the same degree on the placebo site.



A



B

It is thus tempting to interpret these results in terms of **anti-water activity** which would be coherent with the properties of **REDULITE** described in chapter 2.

4. CONCLUSION AND COSMETIC INTEREST

REDULITE presents a new concept in the struggle against cellulitis.

Based on a synergistic combination of phytocosmetic activity of the diuretic extract of elderberry (*Sambucus nigra* L.) and the physical osmotic activity of the glyceryl polyacrylate gel, REDULITE attacks the problem of the retention of interstitial water in hypodermal adipose tissue by facilitating drainage, mobilisation of water and better evacuation thus leading to improvement of the tissue structure.

The *in vivo* study by echography has shown that the "slimming" effect of REDULITE – albeit highly significant and real – is relatively small as compared to the placebo effect, during the 28 days of application. The difference, and thus the original activity of REDULITE, resides in the remanence which might be due to improved restructuring of the hypodermal tissue thus allowing for improved evacuation of water, toxins and lipolytic metabolites.

REDULITE is thus an indispensable, new complement for slimming, firming and classical anti-cellulite treatments that employ lipolytic agents. It is furthermore easily incorporated into all types of corresponding products (gels, emulsions, lotions).

We recommend the use of REDULITE between 15 and 25%, these high percentages result from the osmotic character of the gel that becomes operative only above a certain threshold

5. PHYSICO-CHEMICAL CHARACTERISTICS

Average analytical values

Aspect	:	viscous gel
Color	:	yellowish
Odor	:	characteristic
pH at 10% in water	:	≈ 6
Refractive index (25°C)	:	≈ 1.423
Water content (K. Fischer)	:	$\approx 29.5 \%$
Total germ count	:	< 100 germs/g

BIBLIOGRAPHY

- [1] M. Hernandez et M. Mercier-Fresnel (1992)
in : *Précis d'esthétique cosmétique*, 3.e éd., Editions Maloine, Paris, 236-237

- [2] V. Petkov et V. Markovska (1981)
Plant. Med. Phytomer. 15, 172-182

- [3] D. Beaux et J. Fleurentin (1991)
Thèse de doctorat, Université de Metz

- [4] F. Mortier (1990)
in : *Ethnopharmacologie, Sources, Methodes, Objectifs*, Editions de l'ORSTOM, pp. 199-209

- [5] G. Riecker (1970)
Int. J. clin. Pharmacol. 4, 106-110

- [6] W. Heptner et al. (1971)
Acta diabet. lat. 8, 278-287

- [7] P. Torsti et P. Neuvonen (1967)
Ann. med. exp. Fenn. 45, 403-406

- [8] B. Dreux et al. (1990)
Chirurg. 61, 880-886 (1990)

APPENDIX

EVALUATION OF THE EFFICACY OF SLIMMING PRODUCTS BY ECHOGRAPHY B (ULTRASOUND IMAGING) AND TAPE MEASUREMENT OF THE THIGHS

(Study carried out by Laboratoire SPINCONTROL, 11 rue Marcel
DASSAULT, Le Technopôle, 37200 Tours)

Aim of the study

The test was designed to evaluate the anti-cellulite efficacy of a slimming emulsion containing 20% of **REDULITE** compared to a placebo. Methods used were ultrasound echography and a tape measure.

Principle of the techniques employed*Mode B echography*

Ultrasound imaging consists of establishing a cartography of impedance of the studied tissue with respect to ultrasound waves. After the emission of a wave packet by the probe, the received echos and the value of their intensity that is related to their absorption by the various tissues is recorded. It is then possible to construct an image in the plane of the wave packet.

The apparatus used in this study was an Echograph AU4 Idea of Esaote Biomedica.

The spatial resolution of the images obtained is directly related to the frequency of the emitted ultrasound waves. For the study we employed a high frequency probe (14 MHz). The introspective depth of this emission value lies between 18 and 70 mm for respective resolutions of 80 to 300µm.

Tape measures

The measurement by centrimetric tape of the perimeter of the thigh on a previously marked spot turns out to be the reference method for the evaluation of slimming efficacy. Indeed, for a small decrease in the adipose tissue thickness, the variation of the circumference of the thigh appears quite sensitive.

Localisation and marking of the sites of measurement

The localisation of the sites of measurement and its marking at different points in time of the study must be identical for both techniques and must be perfectly reproducible so that the obtained results could be compared.

Three markings are simultaneously carried out and determined individually for each panelist.

The first is a cutaneous mark at the site of measurement on both thighs. This mark is destined for the tape measurement.

The second spot identification consists in measuring for each volunteer the height above floor of this cutaneous mark. This allows us to define the vertical positioning of the echographich probe or the centrimetric measurement of the circumference of the thigh at the various points in time. This marking is carried out on both thighs at the same height.

The third coordinate corresponds to the position of the cutaneous mark on a horizontal plane with respect to the axis connecting the antero-superiour iliac (hip-bone) spine and the summit of the kneecap. Although less precise, this marking allows us to reposition the point of measurement in case of accidental obliteration of the cutaneous mark.

During the positioning of these various markings and in order to avoid compression phenomena, the panelist is standing upright, feet maintained separated by 20 cm with the help of a wedge.

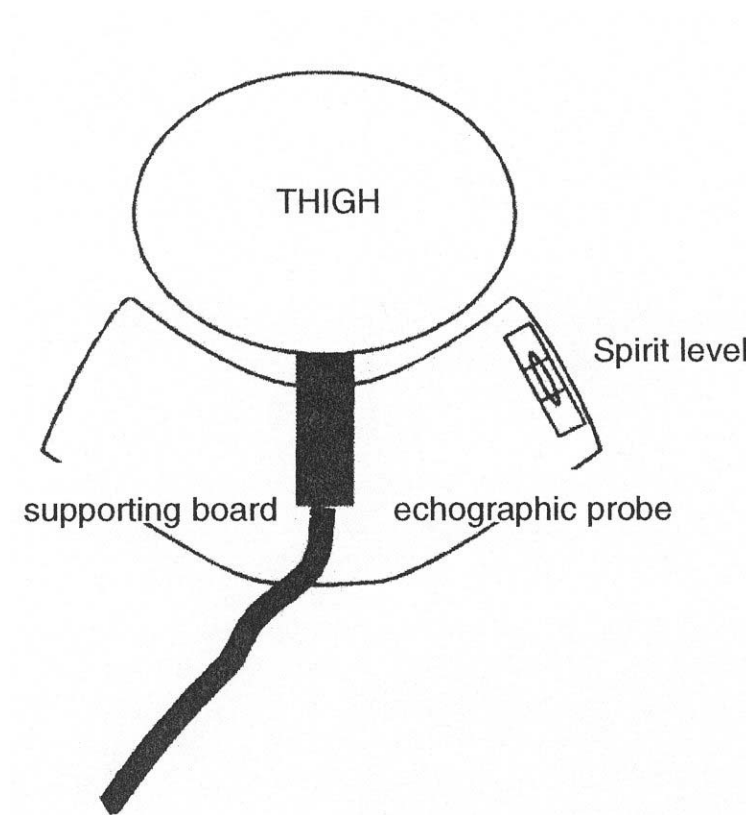
Echographic measurements

The site of measurement is given by the cutaneous mark and by the height at which the probe is positioned. For such a vertical localisation and in order to avoid movement or compression of the tissue during the measurement, the echographic probe is placed on a stable, height adjustable board, independent of the investigator.

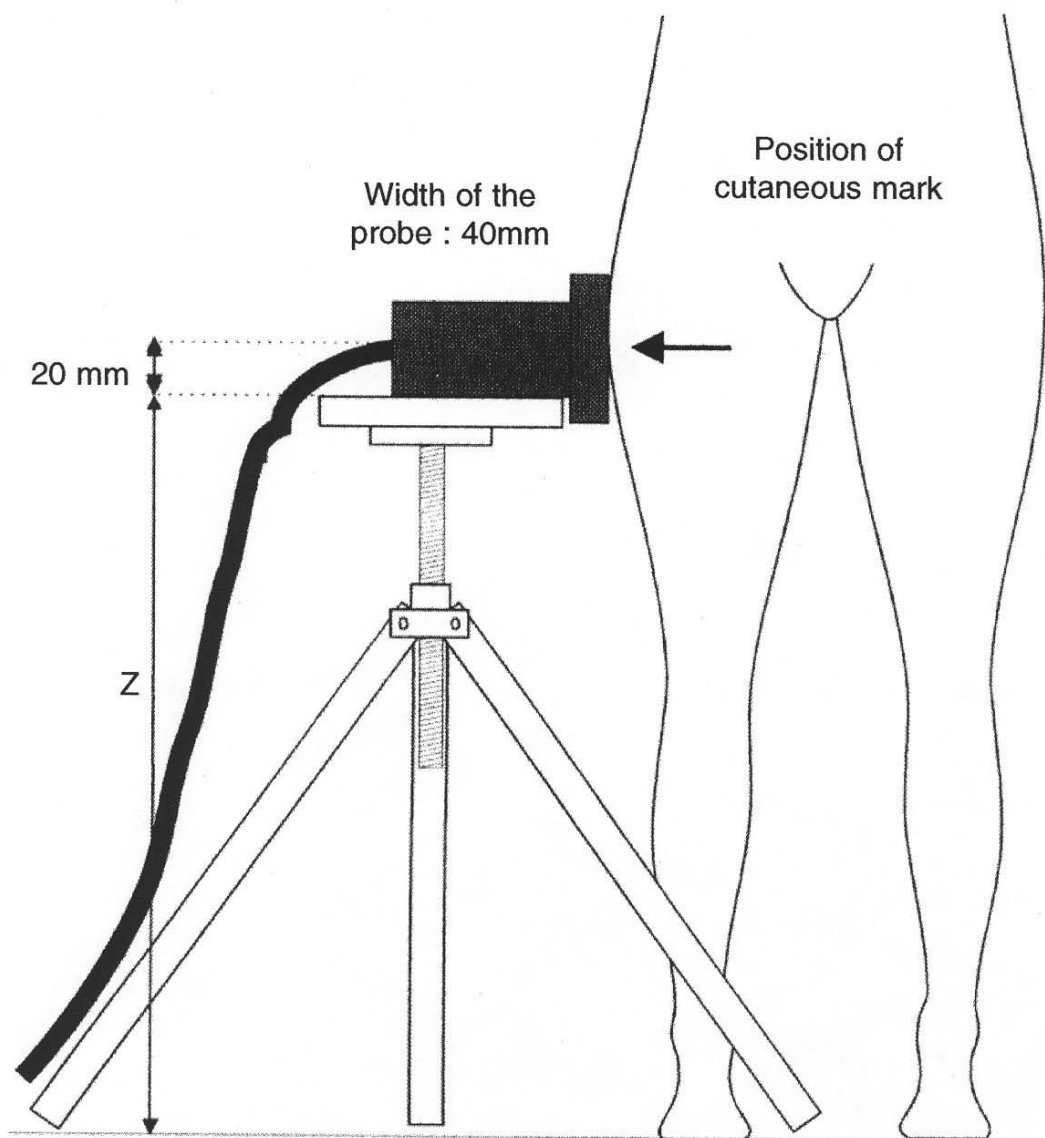
Two measurements are obtained on either side of the mark. For both locations 5 consecutive recordings are made.

Centrimetric tape measurements

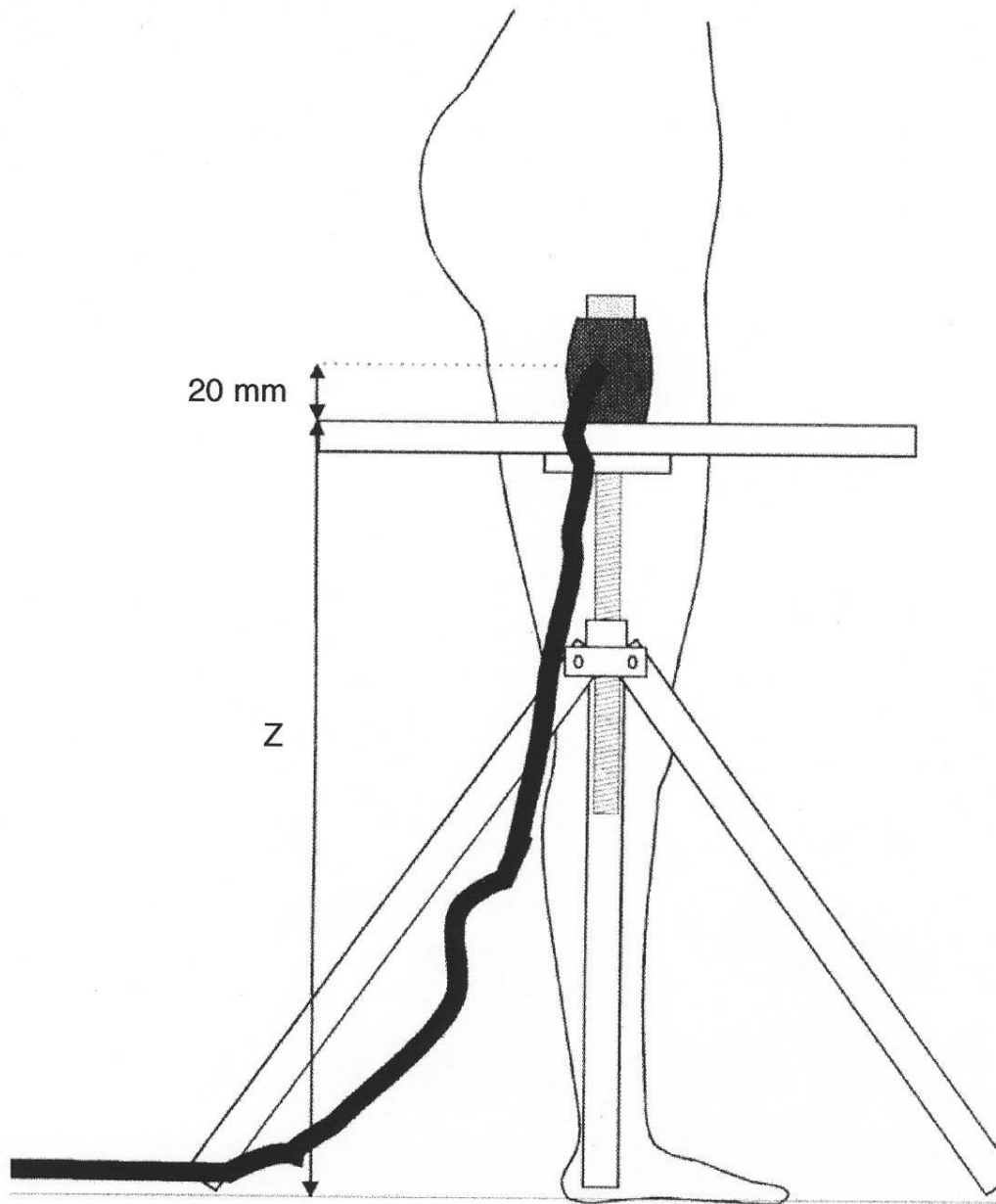
The measurement of the circumference of each thigh is carried out with the same apparatus as used for the echography in order to assure correct vertical positioning. After marking a horizontal line with a pencil on the perimeter of the thigh, the measurement is obtained with a supple adhesive tape that is applied precisely and without compression directly beneath this line.



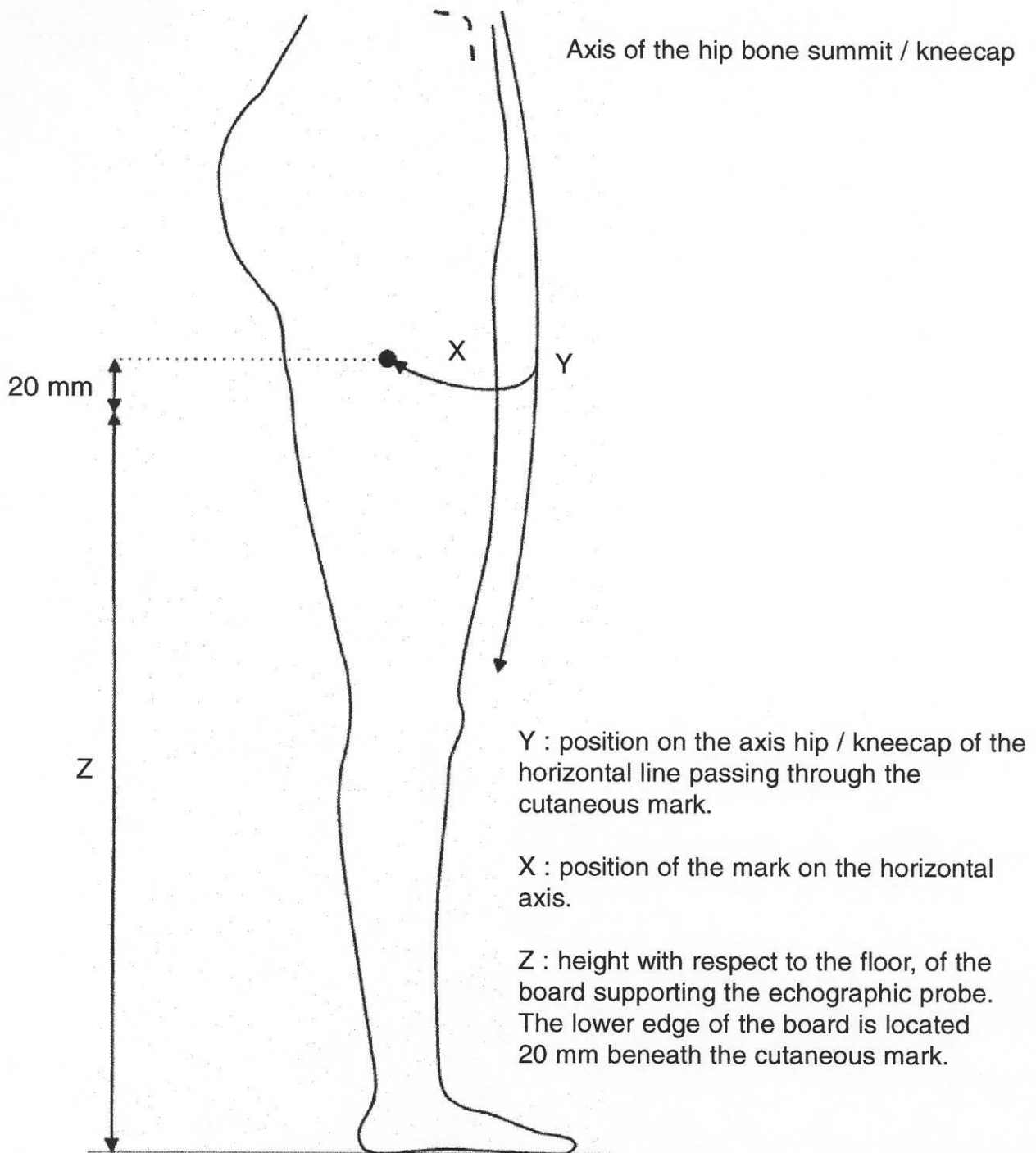
View from above
of the measuring device



Frontal view of the
measuring device



Lateral view of
the measuring device



Anatomical positioning