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Review Article

Cellulite and its treatment

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Synopsis

The presence of cellulite is an aesthetically unacceptable cosmetic problem for most post-adolescent women. It is largely observed in the gluteal-fermoral regions with its 'orange-peel' or 'cottage cheese' appearance. It is not specific to overweight women although increased adipogenicity will exacerbate the condition. It is a complex problem involving the microcirculatory system and lymphatics, the extracellular matrix and the presence of excess subcutaneous fat that bulges into the dermis. It has been described as a normal condition that maximizes subcutaneous fat retention to ensure adequate caloric availability for pregnancy and lactation. Differences in the fibrous septae architecture that compartmentalize the adipose tissue have recently been reported in women with cellulite compared with men. Weight loss has been reported to improve the cellulite severity by surface topography measures although in obese subject's skin dimpling does not seem to change appreciably. However, histological analysis suggests that fat globules retract out of the dermis with weight loss. Cellulite has been treated with massage which decreases tissue oedema but it is also likely to have its effects at the cellular level by stimulating fibroblast (and keratinocyte) activity while decreasing adipocyte activity. In addition to massage, effective topical creams with a variety of agents were used to ameliorate the condition. Nevertheless, only a few studies are reported in the scientific literature. Xanthines, botanicals, fragrances and ligands for the retinoid and peroxisomal proliferator-activated receptors appear to be giving some benefit. Reducing adipogenesis and increasing thermogenesis appear to be primary routes and also improving the microcirculation and collagen synthesis. Many agents are being investigated for weight management in the supplement industry [hydroxycitrate, epigallocatechin gallate, conjugated linoleic acid (CLA), etc.] and some of these agents seem to be beneficial for the treatment of cellulite. In fact, CLA was proven to ameliorate the signs of cellulite. One product, Cellasene, containing a variety of botanicals and polyunsaturated fatty acids also appears to provide some relief from these symptoms. Although more work is needed, clearly these treatments do improve the appearance of skin in subjects with cellulite. It is quite possible, however, that synergies between both oral and topical routes may be the best intervention to ameliorate the signs and symptoms of cellulite.

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Résumé

La présence de cellulite est un problème cosmétique esthétique inacceptable pour la plupart des femmes post-adolescentes. On l'observe couramment dans la région glutéale fémorale sous forme de 'peau d'orange'. Il n'est pas spécifique d'un surpoids chez la femme, bien qu'une augmentation d'adiposité exacerbe le phénomène. C'est un problème complexe mettant en jeu le système micro circulatoire et lymphatique, la matrice extracellulaire et la présence

d'un excès de graisse sous-cutanée dans le derme. Elle a été décrite comme une condition normale qui maximise la rétention sous-cutanée de graisse pour assurer une disponibilité calorique adéquate lors de la grossesse et de la lactation. Des différences dans l'architecture fibreuse du 'septae' qui compartimente le tissus adipeux ont récemment été rapportées après comparaison de la peau de femmes souffrant de cellulite et celle d'hommes. On a observé, après étude topographique de surface, qu'une perte de poids aggrave la cellulite, alors que chez des sujets obèses la surface de la peau ne semble pas changer notablement. Cependant, une étude histologique suggère que les globules de graisses se rétractent lors d'une perte de poids. On traite la cellulite avec des massages qui diminuent l'œdème des tissus et qui ont également des effets au niveau cellulaire par stimulation des fibroblastes (et des kératinocytes) et diminution de l'activité des adipocytes. En complément des massages, on applique de façon topique des crèmes contenant différents agents. Néanmoins, il existe peu d'études scientifiques sur ce sujet. Des xanthines, des dérivés botaniques, des parfums et des ligands des récepteurs du proliférateur activé du rétinoide et du peroxysome semblent donner de bons résultats. La réduction de l'adipogénèse et l'augmentation de la dermogénèse paraissent être les premières causes de ces résultats, tout comme l'amélioration de la micro circulation et la synthèse du collagène. De nombreux agents ont été étudiés pour le contrôle du poids dans l'industrie des compléments alimentaires (hydroxycitrate galate d'épichalocatéchine, ECG, acide linoléique conjugué CLA, etc.) et quelques-uns de ces agents semblent être bénéfiques au traitement de la cellulite. En fait, on a montré que le CLA conduisait à quelques améliorations des manifestations de la cellulite. Un produit - le CELLASENE - contenant divers dérivés botaniques et des acides gras poly insaturés apparait également efficace vis-à-vis de ces symptômes. Bien que davantage de travail soit nécessaire, il es clair que ces traitements améliorent l'aspect de la peau chez des sujets souffrant de cellulite. Il est tout à fait possible, cependant, que des synergies entre la voie orale et la voie topique puissent être la meilleure façon d'améliorer les signes et les symptômes de la cellulite.

Introduction

Cellulite is a cosmetically unacceptable problem that most women experience at some point in their lifetime. It occurs mainly on the lower limbs, pelvic region (gluteal-fermoral regions) and abdomen and is characterized by an 'orange peel' or 'cottage cheese' appearance [1]. Approximately 85% of women over the age of 20 have some degree of cellulite [2, 3]. It has been described by Goldman [4] as a normal physiological state in post-adolescent women which maximizes adipose retention to ensure adequate caloric availability for pregnancy and lactation. This disorder should not be confused with obesity where only adipocytes hypertrophy and hyperplasia occurs. Although this also occurs in subjects with cellulite, there are also several structural alterations in the dermis and microcirculatory alterations exist. Increased interstitial fluid protein concentrations and interstial pressure have been reported and a reduced blood flux into the tissue culminating in decreased skin temperature on affected sites. Typical manifestations of the problem can be seen in Figs 1 and 2. Figure 1 shows the cellulite grade used by Rossi and Vergnanini [5] at rest and after gluteal contraction, whereas Fig. 2 shows the photonumerical scale used by Perin *et al.* [6] after a standardized compression of the thigh area.

The anatomy of cellulite can be clearly seen from the studies of Pierard *et al.* [7]. The superficial fat lobules (papillae adiposae) that protrude into the dermis can be clearly seen in Fig. 3a in autopsy section of the skin (see Fig. 3b for schematic fat projections into the dermis). Recently, magnetic resonance imaging and spectroscopy have been applied *in vivo* to understand the condition better. First, Querleux *et al.* [8] at L'Oreal Recherche quantified deep indentations of adipose tissue into the dermis and a great increase in the thickness of the inner fat layer in women with cellulite. As can be seen in Fig. 4 deep adipose indentations are clearly visualized and the Camper's fascia can been seen to separate the adipose tissue in two layers. The dermal thickness was similar between women with and without cellulite but the subcutaneous adipose thickness layer was five times thicker in women with cellulite (24.81 mm vs. 4.31 mm as can be seen in Fig. 5). Equally importantly, they described a higher percentage of fibrous septae perpendicular to the skin surface (Figs 6 and 7). Mirrashed *et al.* [9] and colleagues at Procter and Gamble made similar observations on the extrusion of underlying adipose tissue into the dermis and found that the percentage of adipose tissue vs. connective tissue in a given volume

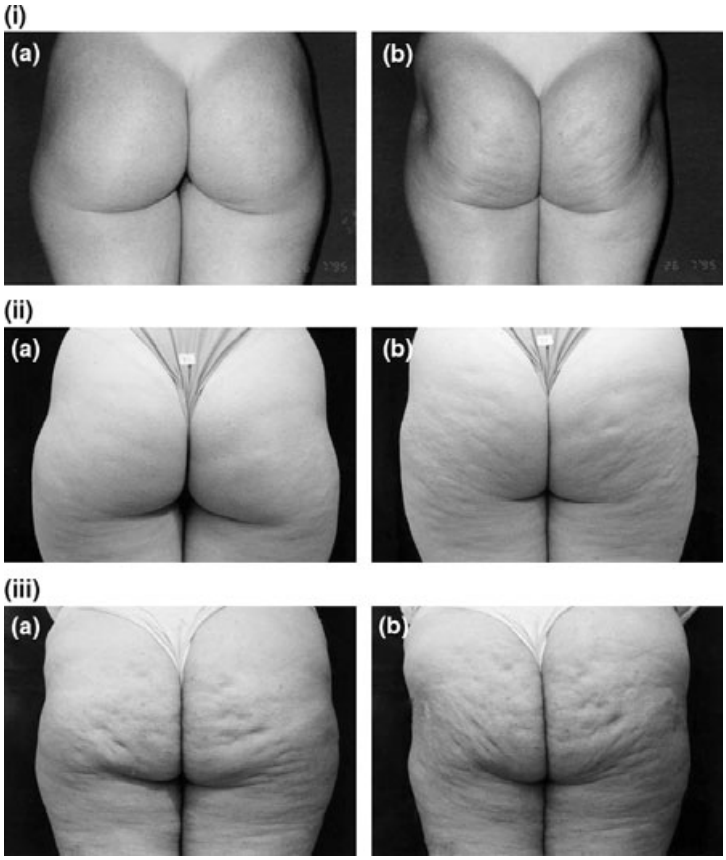

Figure 1 Cellulite grade at grade II (i), grade III (ii) and grade 4 (iii) at rest (a) and after gluteal contraction (b). From Rossi and Vergnanini [5].

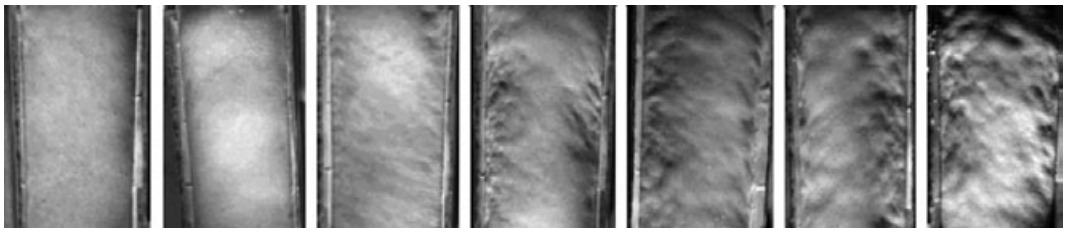

Figure 2 Photonumerical scale representative of the different grades of cellulite on compressed thighs: from no cellulite (left) to very severe signs of cellulite (right). From Perin *et al.* [6].

of hypodermis and that the percentage of hypodermic invaginations correlate with cellulite grade (Fig. 8). Most recently, in pilot studies, Callaghan [10] used *in vivo* confocal microscopy to evaluate the condition. Compared with male skin, striae were seen penetrating within the epidermis. The collagen had a dense appearance and stretched in one direction and the epidermis was thin. Clearly cellulite is a condition of altered connective tissue matrix as well as increased adipogenicity.

A variety of treatments have been proposed for the treatment of cellulite with weight loss being the most frequently employed. Skin massage treatments are used and a variety of topical agents as well as oral supplements.

Targets for cellulite treatment

Rossi and Vergnanini [5] reviewed various targets that need to be corrected in cellulite and will be described below. In their analysis, fibroblasts, activated by oestrogen, increase Glycosaminoglycan (GAG) synthesis which then leads to increased interstitial osmotic pressure and fluid retention. This consequently compresses blood vessels provoking tissue hypoxia. Local inflammatory cytokines

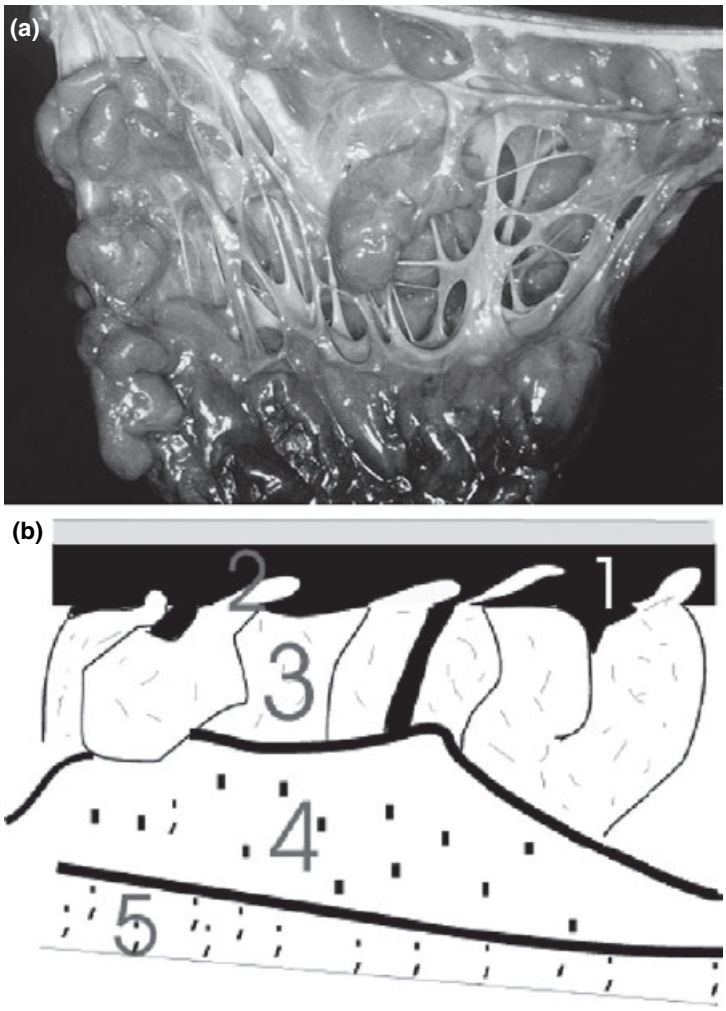

Figure 3 (a) Autopsy of amputated leg. Complex network of hypodermal fibrous strands in cellulite. Their thickness is uneven. There is no real septum partitioning the fat lobules. From Pierard *et al.* [7]. (b) A schematic diagram of skin structure showing five zones. The grey layer is the surface of the skin: the epidermis. Zone 1 is the dermis. Zone 2 is the extrusion of the hypodermis into the dermis. Zones 3–5 are the upper, middle and lower parts of the hypodermis. From Mirrashed *et al.* [9].

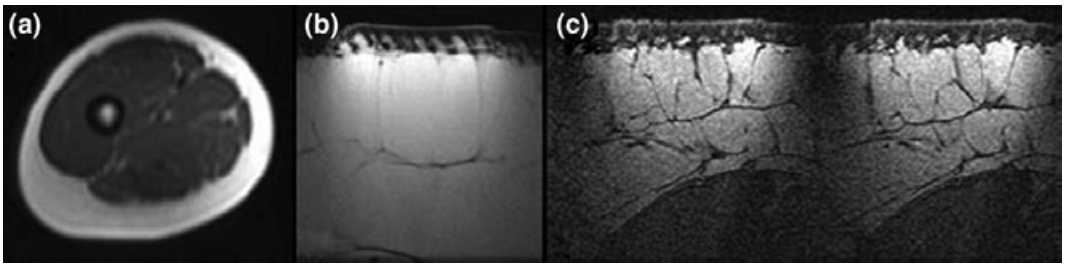

Figure 4 Magnetic resonance images of adipose tissue. (a) Hypodermis of the whole thigh. Hypodermis appears hyperintense. The dermis is not visible at this spatial resolution; (b) high spatial resolution 2D image, 3 mm thick, of hypodermis on the dorsal side of the thigh of a woman with cellulite. With a resolution of 70 μm in the depth of the skin, Camper's fascia separates the adipose tissue in two layers. Deep adipose indentations into the dermis are clearly visualized. Fibrous septae appear as hypointense thin structures. (c) Two contiguous thin images from a series of 64 images. A slice thickness of 0.5 mm offers an optimal contrast between fat lobules and fibrous septae allowing the 3D reconstruction of the fibrous network architecture. From Querleux *et al.* [8].

also induce collagen synthesis. Increased capillary pressure, a decrease in plasma osmotic pressure and an increase in interstitial osmotic pressure (or a decrease in lymphatic flux) lead to intercellular oedema. The increased osmotic forces will also influence the cellular phenotype of the fibroblasts.

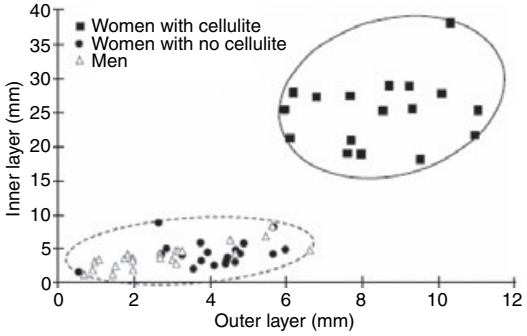

Figure 5 New characteristic marker of cellulite. Magnetic resonance imaging shows that women with cellulite have a much greater increase in the thickness of the deep inner adipose layer compared with normal women or men. From Querleux *et al.* [8].

Equally, as discussed by Pierard in this series of articles, however, the progressive vertically oriented stretch in the subcutis from the hypertrophic adipocytes also occurs in cellulite and the fibroblasts will accommodate to this by remodelling the extracellular matrix.

The anatomy of the subcutaneous fat includes two layers separated by a superficial fascia. The layer closest to the dermis is called the areolar layer and is formed by globular large adipocytes arranged vertically. The blood vessels in this region are numerous and fragile. In the deeper lamellar layer the cells are smaller and arranged horizontally whereas the blood vessels are larger. When a person gains weight it is this layer that enlarges. Women (and children) have a thicker areloar layer. This layer is predominantly under the control of oestrogen and in the femoral region the adipocytes are more resistant to lipolysis. Several hormones stimulate lipogenesis (insulin, oestrogen, prolactin) but it is decreased by others; catecholamines stimulate lipolysis through the activation of adenyl cyclase. However, contrary to popular belief, it is insufficient to just induce adipocytes lipolysis to remove the excess triglycerides in these cells. The released fat would just be transferred into the circulatory system and processed by the liver which then increase the levels of very low-density lipoproteins in the blood which on return to the subcuta-

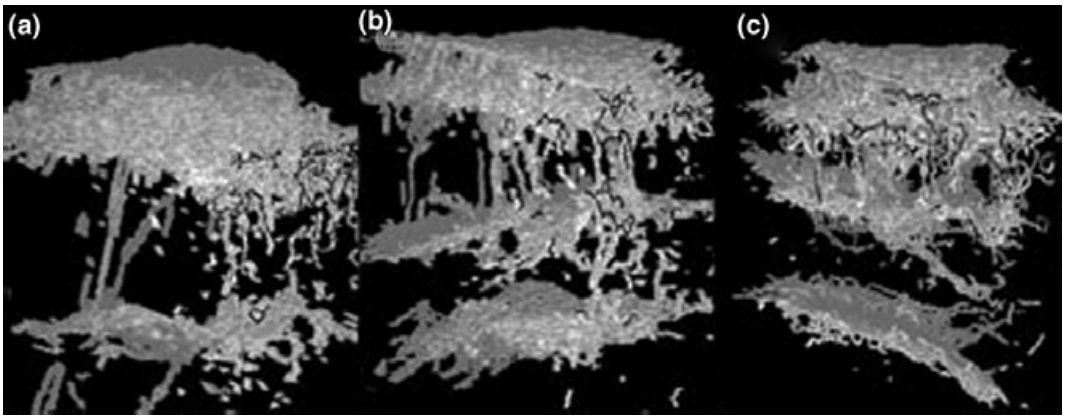

Figure 6 Visualization of the 3D architecture of fibrous septae in subcutaneous adipose tissue. (a) Woman with cellulite; (b) woman without cellulite; (c) man. From: Querleux *et al.* [8].

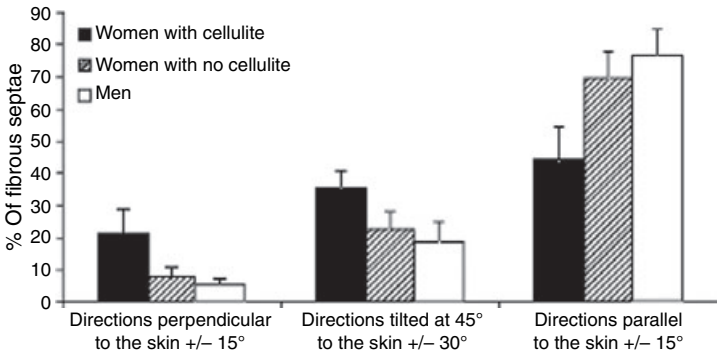

Figure 7 Structural patterns of the fibrous septae network according to sex and presence of cellulite. These quantitative findings give more evidence about the heterogeneity of the septae, and suggest modelling the 3D architecture of fibrous septae as a perpendicular pattern in women, whereas it is tilted at 45° in men. From Querleux *et al.* [8].

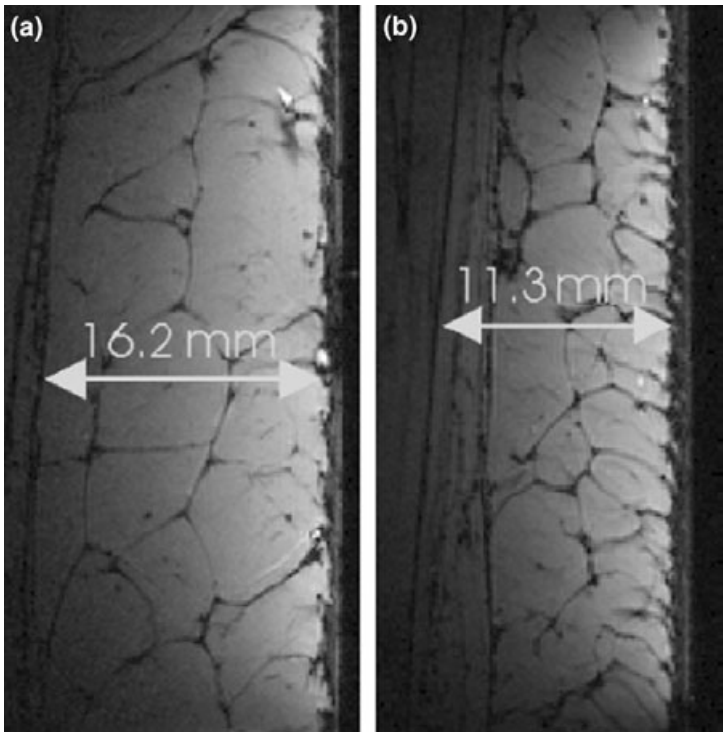

Figure 8 Skin of two females both from low body mass index group: (a) cellulite grade = 2.5, hypodermis 16.2 mm; (b) cellulite grade = 0, hypodermis 11.3 mm. From Mirrashed *et al.* [9].

neous fat layer will be utilized again and after the action of lipoprotein lipase to make more adipocyte triglyceride. Although this is an energetically expensive and inefficient way of redirecting triglyceride transport around the body some calories are lost in this futile cycle. However, the most efficient route to adipocyte fat removal would be to increase the levels of mitochondrial uncoupling proteins and 'burn' the fat locally (thermogenesis). Several agents are reported to enhance this process.

As many of the nuclear hormone receptor ligands [e.g. the retinoid receptors and the peroxisomal proliferator-activated receptor (PPAR)] influence the skin cells involved in forming and aggravating the cellulitic condition it is appropriate to give a summary of their general mechanism of action and some of their effects in other conditions than cellulite.

Gene expression is regulated through the interplay of specific DNA-binding transcription factors. On binding ligands co-repressors dissociate from the transcriptional machinery complex and coactivators bind to initiate gene transcription. Nuclear hormone receptors are transcription factors that regulate many cellular functions. This superfamily of receptors has been segregated into four major subgroups. The class II subfamily consists of nuclear receptors that form heterodimers with the retinoid X receptor (RXR) [11] which for example include the retinoic acid receptor (RAR) and the PPAR [12]. Stimulation of these receptors, in particular, regulates keratinocyte proliferation and differentiation, influences melanogenesis and stimulates dermal matrix reconstruction.

Retinoid receptors

Vitamin A is a recognized and well-established anti-ageing active. Originally used as an anti-acne treatment, retinoic acid is now used to treat the signs of ageing. Retinoic acid mediates its effect via binding to its nuclear transcription factors. The RAR binds all trans-retinoic acid (RA) and its stereoisomer 9-cis RA; and the RXR binds 9-cis RA. A common feature of these receptors is that they bind to certain regions of DNA known as hormone response elements and thereby initiating ligand-dependent gene transcription. The retinoid transcription factors bind to a retinoic acid response element in the promoter of genes composed of a 6-bp sequence (AGGTCA) (Fig. 9). Similar base pair sequences are shared by other members of this superfamily which differ only by the insertion of additional base pairs. RARs and RXRs are known to contain at least three different subtypes: alpha, beta and gamma each of which

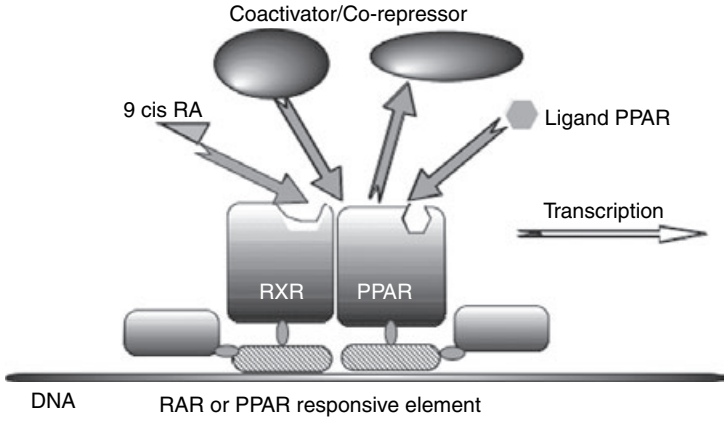

Figure 9 Mechanism of binding and action of ligands to the retinoid and peroxisomal proliferator-activated receptors. From Wiechers *et al.* [23].

have several isoforms. The RXRs predominate in human skin especially RXRalpha. Of the RARs 87% are RARgamma and 13% RARalpha. Only small amounts of RARbeta are found in dermal cells and melanocyes. Retinoic acid treatment results in major epidermal changes only weeks after treatment but in the longer term dermal effects are observed (angiogenesis, synthesis of new connective tissue components and increases in the numbers of more active fibroblasts). Varani *et al.* [13] has also reported that 0.5% retinol (ROH) is as effective as 0.05% RA. However, this level of ROH cannot be used in cosmetic products and even if it was allowed the irritation levels are comparable between the two agents. Nevertheless, topical application of retinol can reverse the skin changes associated with ageing by increasing fibroblast proliferation, increasing skin collagen levels and decreasing Matrix metalloprotease (MMP) levels [13].

Peroxisome proliferator-activated receptors

Peroxisome proliferator-activated receptors (PPAR) are a recently discovered family of nuclear transcription factors [14, 15] and three PPAR receptor types, PPARalpha, PPARbeta or delta, PPARgamma have been characterized. PPARs bind to the peroxisome proliferator response element within the promoter region of the DNA in the target gene in the form of heterodimers with the RXR (Fig. 9).

Peroxisome proliferator-activated receptors are activated by the fibrate hypolipidaemic drugs, fatty acids, eicosanoids and prostanoids but of these chemical types the fatty acids are of the most interest for skin applications. The ability of saturated, monounsaturated and polyunsaturated long chain fatty acids to bind and activate all three PPAR subtypes has been well documented. However, saturated fatty acids have very low activity as PPAR ligands, whilst monounsaturated fatty acids are substantially more active and polyunsaturated fatty acids are generally the most potent with the optimum chain length required for activation being between C18 and C22. In terms of receptor subtype selectivity, the saturated and polyunsaturated fatty acids do not differentiate between PPARs, whereas, in contrast, the monounsaturated fatty acids appear to have a high affinity for PPARalpha. Gamma-linoleic acid, myristic and palmitic acids also show a greater affinity for PPARalpha and PPARdelta compared with PPARgamma but their IC_{50} values are still in the micromolar range [16].

Peroxisome proliferator-activated receptors were first identified in the epidermis in 1992. However, it was not until recently that the importance of PPARs in epidermal homeostasis has become apparent with the discovery that activation of PPARalpha, with either lipids or the hypolipidaemic drug clofibrate, can accelerate epidermal barrier formation and induce epidermal differentiation. Rivier *et al.* [17] at Galderma first reported that PPARalpha ligands influence lipid biosynthesis in living skin equivalents. Keratinocyte serine palmitoyl transferase and glucocerebrosidase activities were increased in these studies and there was a particular increase in ceramide biosynthesis particularly for ceramides 1, 2 and 3 (CER EOS, CER NS and CER NP).

Peroxisome proliferator-activated receptor delta was recently observed to be the predominant PPAR subtype in human keratinocytes, whereas PPARalpha and gamma were only induced during

epidermal differentiation suggesting different receptors are used during differentiation [18]. PPARdelta ligands were found to be the most potent in inducing epidermal differentiation (tetrathioacetic acid) by increasing involucrin and transglutaminase while decreasing proliferation. This is consistent with PPARdelta-deficient mice exhibiting an exacerbated epidermal hyperplastic response to TPO in contrast to the minor abnormalities seen in PPARalpha-deficient mice.

Studies from scientists within my previous research group at Unilever has highlighted the benefits particularly of petroselinic acid [19] and conjugated linoleic acid (CLA; Unilever patents: US6423325, US6403064, US6287553, US6042841, WO0108650, WO0108652, WO0108649) as potent PPARalpha activators improving epidermal differentiation, reducing inflammation, increasing extracellular matrix components and eliciting skin lightening. *In vitro*, increases in levels of transglutaminase, involucrin, filaggrin and corneocyte envelope formation were observed in keratinocytes whereas increased levels of pro-collagen 1 and decorin were observed for fibroblasts. These effects were confirmed *in vivo* by short-term patch testing studies over a 3-week period and increases in the levels of involucrin and filaggrin were also observed. These biochemical changes translated into improvements in the signs of photodamage and skin tone in a 12-week clinical study on forearm skin [20]. There is further evidence that PPAR ligands can also mitigate the pigmentation process and induce skin lightening [21, 22]. Wiechers *et al.* [23] reported that octadenedioic acid is a pan PPAR agonist and reduces tyrosinase transcription. All PPARs are found in adipocytes.

Some of the approaches taken to reduce the appearance of cellulite will be reviewed and where possible with examples of the effect of agents from both a topical and oral perspective.

Treatment of cellulite

Massage

Vigorous massage is used to encourage removal of interstitial fluid and improve lymphatic drainage in individuals with decreased venous return. Initially the skin improvements are short term and just related to the removal of excess fluid [1]. However, more prolonged treatments may improve the underlying condition. LPG Endermologie (LPG Endermologie USA, Fort Lauderdale, FL, USA) is a machine-assisted massage system that allows positive pressure rolling in conjunction with applied negative pressure to the skin which improves body contour and skin texture. Chang *et al.* [24] reported up to 1.83 cm reduction in body circumference when using this equipment. However, Collins *et al.* [25] reported that 28.5% of subjects using this approach over a 12-week period noticed improvements in their cellulite condition. Obviously, use of topical creams involves a massaging action and the direct physical stimulus of rubbing a cream which may contribute to an improvement in the condition with time. The effects may not be fantasy as research on the mechanobiology of skin has increased [26]. Although Yucatan minipigs do not suffer from cellulite Adcock *et al.* [27] showed that deep mechanical massage enhances the presence of longitudinal collagen bands whereas distortion and disruption of adipocytes was noted. Fibroblasts are known to respond to tensional forces in the extracellular matrix and produce collagen. Increases in keratinocyte proliferation also occur when stretched possibly leading to a thicker epidermis. Conversely, mechanical stretching of adipocytes inhibits their differentiation and is related to a reduction in PPARgamma levels via activation of extracellular signal-regulated protein kinase pathway [28]. Collectively, these findings provide a molecular basis for the physiological significance of the local application of mechanical stimuli, massage in this case, to the skin and the possible relief from the signs of cellulite.

Topical treatments

As with many skin conditions, cellulite is a complex condition and as a result combinations of different ingredients to influence the different aspects of the pathophysiology of the condition is recommended. It goes without saying that the concentration of the ingredient has to reach the site of action and at the right concentration for its effects to be realized as has been outlined by Wiechers *et al.* [29]. Equally, however, cellulite is a condition that develops over years and will take several months before any effect may come apparent to the clinician and well as the subject. However, in most cases the individual is more likely to perceive an improvement in the condition before changes in the clinical grade occurs. Using the photonumerical scale outlined in Fig. 2, Perin *et al.* [6] showed the improvement in cellulite

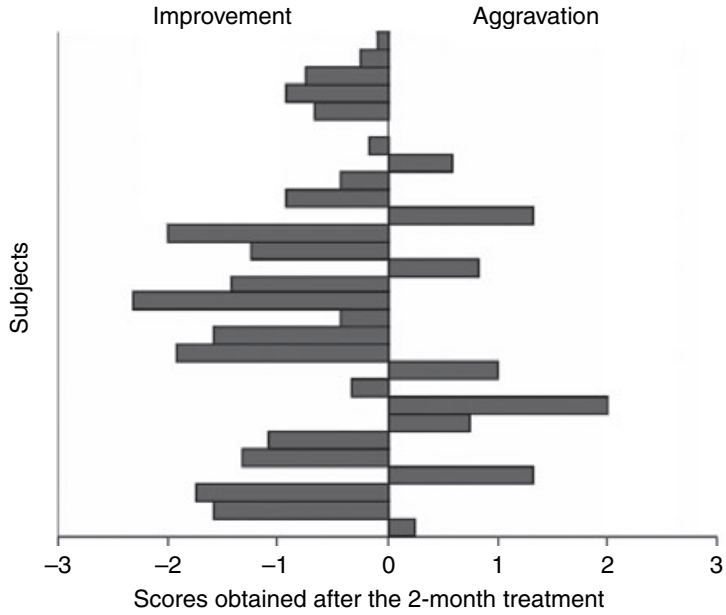

Figure 10 Variation of cellulite index after 2 months of treatment. A significant effect of the slimming product was observed with improvement of the cellulite index in 21 subjects. From Perin *et al.* [6].

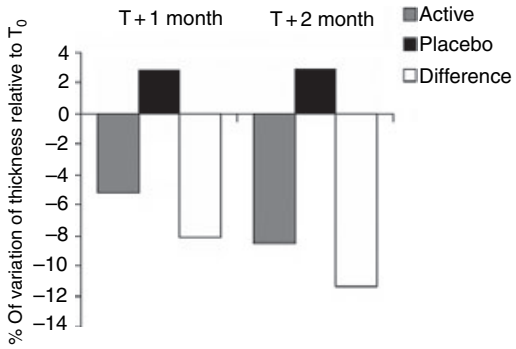

Figure 11 Variation of the thickness of thigh subcutaneous adipose tissue determined by ultrasound imaging after 2 months treatment with either the active slimming preparation or placebo. A −11.4% significant differential slimming effect was observed (active-placebo; $P < 0.0001$). From Perin *et al.* [6].

with a commercial cream from Christian Dior compared with its placebo. The variation and improvement in treatment effect can see in Fig. 10 and average scores decreased from 3.64 to 2.81 ($P < 0.05$). A significant decline in the thickness of the thigh subcutaneous adipose tissue was also determined by ultrasound imaging (Fig. 11) and the self-perception data are given in Table I.

Xanthines

Methylxanthines are common ingredients used in cellulite products, e.g. caffeine, aminophylline, theophylline, etc. and are used because of their proposed effect on adipocyte lipolysis via inhibition of phosphodiesterase, and increasing cyclic adenosine monophosphate (AMP) levels. Nevertheless, on its own aminophylline was reported not to improve the condition over a 12-week period. Equally, Collins *et al.* [25] also reported that only 10% of the subjects observed an improvement in their condition.

Greenway and Bray [30] demonstrated a significant reduction in thigh thickness when aminophylline was used together with isoproterenol (a beta-adrenergic receptor agonist and yohimbine, an alpha-agonist). However, in these studies the phosphodiesterase inhibitor was also reported to be effective on its own.

Uncoupling proteins (UCP) are present in the mitochondria of all cells and they have the capability of dissipating the mitochondrial proton gradient generated by the respiratory chain. It is through this process that we keep warm in the cold, i.e. non-shivering thermogenesis. UCP-1 is expressed in brown adipose tissue of which humans have little while UCP-2 is expressed in white adipose tissue. In transgenic animals that over express these proteins have a reduced adipose tissue mass and, thus, their expression in humans adipose tissue may help with the expression of cellulite. More work is needed in this area but caffeine increases UCP-3 levels in subcutaneous white adipose tissue adipocytes and was synergistic in the presence of noradrenaline [31]. Ligands for the retinoid and PPAR receptors are also

Table I Main results of self-perception in cellulite study

	Cellulite		Smoothing of the skin		Firming		Silhouette	
	Active	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**	**Active**	**Placebo**
Effect (%)	86.7	43.3	90.0	60.0	56.7	53.3	80.0	40.0
No effect (%)	13.3	56.7	10.0	40.0	43.3	46.7	20.0	60.0
Significance	<0.001	NS	<0.0001	NS	NS	NS	<0.01	NS

From Perin *et al.* [6].

capable of inducing these effects (see later in oral supplement section).

Herbal treatments

Many herbal extracts are used in slimming products such as verbena, green tea, lemon, kola nut, fennel, algae, ivy, barley, strawberry, marjoram and sweet clover [32]. Some are reported to improve the peripheral microcirculation and facilitate lymphatic drainage. One of the few studies that have been reported scientifically is that of Buscaglia and Conte [33] who examined the effect of caffeine, horsechestnut, ivy, algae, bladderwrack, plankton, butcherbroom and soy protein applied for 30 days. A 2.8 mm decrease in subcutaneous fat thickness was reported which reappeared in the regression phase of the study. Rao *et al.* [34] evaluated a cream containing black pepper, sweet orange peel, ginger root extract, cinnamon bark extract, capsaicin, green tea and caffeine which was applied under occlusion with neoprene shorts. Of the 34 subjects who completed the study, 63% (21/34) noticed an improvement in their cellulite and 62% (13/21) reported a greater effect for the treatment. Dermatologists found the thighs that were treated with the active product showed a greater improvement than the placebo (Fig. 12). Thigh circumference reduction was 1.9 cm for the active product and 1.3 cm for the placebo. The results of Perin *et al.* in Figs 10 and 11 were obtained from using a hydroglycolic gel containing extracts of *Terminalia seracea*, *Visnaga vera*, *Plectreinthus barbatus* and *Cola lipa* together with cyclic AMP (courtesy of F. Bonte).

Fragrances

Inhalation of essential oils such as pepper, estragon, fennel or grapefruit oils increase sympathetic neural activity by up to 2.5-fold. Activation of the sympathetic nervous system this way in combina-

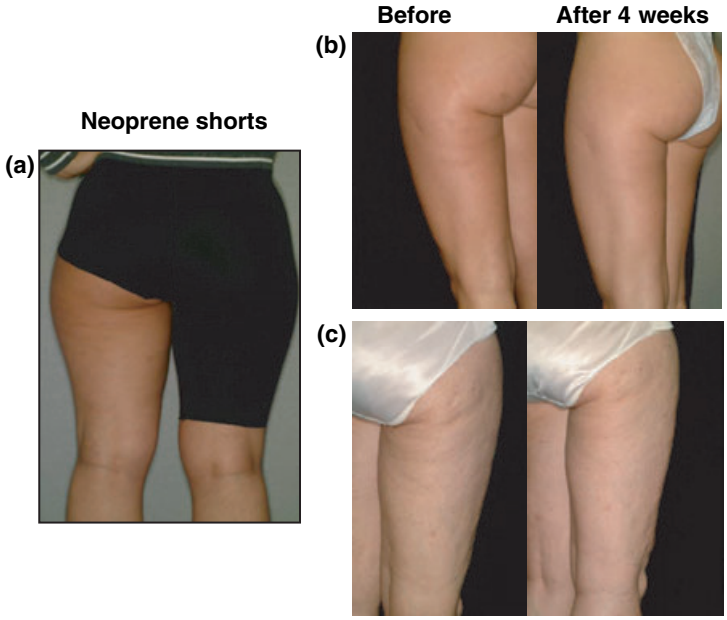

Figure 12 (a) The modified bioceramic-coated neoprene shorts with one leg removed, to provide occlusion on one thigh only. (b, c) Photographs taken immediately before and after 4 weeks of Spa MD Anti-Cellulite Cream™ with occlusion by a Bioceramic-Coated Neoprene Garment for two subjects. Courtesy of La Jolla Spa MD and from Rao *et al.* [34].

tion with a topical caffeine-containing cream has been reported to have a slimming effect. Hariya *et al.* [31] proposed the UCP theory in which inhalation of an appropriate odorant stimulates the secretion of noradrenaline which acts in synergy with percutaneously absorbed caffeine to both simulate lipogenesis and thermogenesis to 'burn' the locally produced fat (Fig. 13). Although cellulite was not graded in these studies, the average weight loss was 1.1 kg and 25% of subjects lost 2 kg with decreases of 1.5 and 1.3 cm at the waist and hips.

Retinoids

Kligman *et al.* [35] used retinol (0.3%) over a 6-month period and demonstrated an improvement in cellulite; 12 of 19 subjects showed an improvement in the condition. These effects may be due to the known effects of retinoids increasing the dermal content and architecture of collagen and dermoepidermal proteins together with anchoring and elastic fibrils. However, Pierard-Franchimont *et al.* [36] could not find any change in the orange peel condition but did observe an increase in skin elasticity and a decrease in its viscosity. Increased factor XIIIa+ dendrocytes were observed indicating an improvement in skin condition. Later Bertin *et al.* [37] tested the effects of retinol combined with caffeine and ruscogenine decreased the orange peel effect and improved cutaneous microcirculation. However Garcia *et al.* [38] and Machinal-Quelin *et al.* [39] proposed that retinol itself is also anti-adipogenic by inhibiting the differentiation of human adipocyte precursor cells by reducing the expression of the *ob* gene. Nevertheless, on its likely conversion to retinoic acid *in vivo*, it is also capable of increasing mitochondrial coupling proteins, thereby contributing to the reduced subcutaneous fat levels through cellular heat dissipation [40].

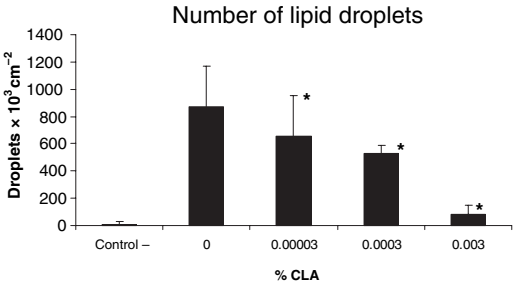

Figure 14 Histogram showing reduced triglyceride accumulation in adipocytes following conjugated linoleic acid treatment. Courtesy of D. Imfeld, Pentapharm.

PPAR agonists

Agonists of PPAR are known to improve epidermal differentiation, increase collagen levels, suppress sebogenesis, are anti-inflammatory and skin-lightening agents [12]. They also increase UCP levels. Thus, like retinoids they deliver pleotropic benefits. The use, however, requires a pan-agonist activity as stimulation of PPARgamma alone increases adipogenicity. It is therefore not too surprising that these have been evaluated as anti-adipogenic compounds and as anti-cellulite treatments. CLA has been shown at Pentapharm to prevent lipid accumulation in adipocytes *in vitro* (Fig. 14) and in

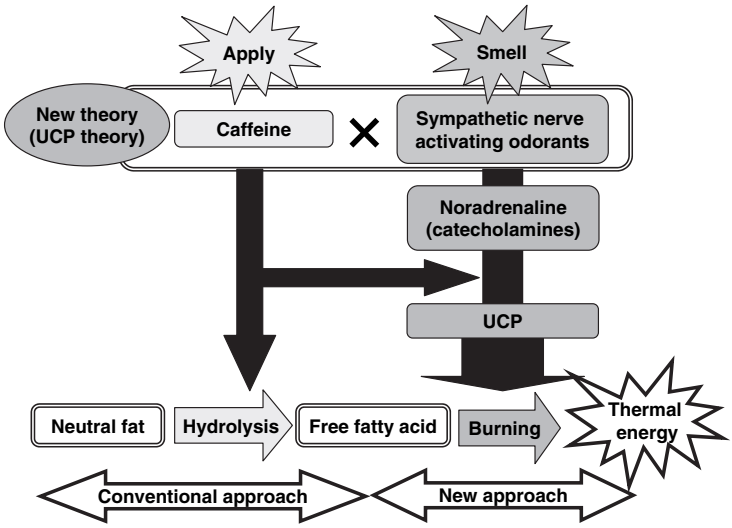

Figure 13 Novel slimming theory (uncoupling proteins theory, UCP). Activation of the sympathetic nervous system by inhalation of an appropriate odorant prompts secretion of noradrenaline. The increase of noradrenaline acts synergistically with percutaneously absorbed caffeine to promote gene expression of the UCP, that burns up free fatty acids in adipose tissue. From Hatiya *et al.* [31].

in vivo studies CLA reduced adipose invagination into the dermis as judged by ultrasound and improved the appearance of cellulite (Fig. 15) (D. Imfeld, personal communiation, Pentapharm).

Alphahydroxyacids

Alphahydroxyacids (AHAs) and particularly lactic acid have been proposed in the treatment of cellulite [41]. However, there are no reported studies. Nevertheless, as these agents have an anti-ageing effect (increased collagen levels) and improve the signs of photodamaged skin [42] as well as improving epidermal differentiation and barrier function as reported by Rawlings *et al.* [43] and Berardesca *et al.* [44] it is likely that this class of ingredients will improve the skin surface orange peel appearance in cellulite.

Oral treatments

Many of the above-mentioned agents are also used in oral supplements for the treatment of cellulite and like the topical treatments there are very few scientifically reported studies examining their effects on improving the condition. As a result, examples will be given from the recent literature on agents that also help with weight control as these may also influence the appearance of cellulite.

PPAR agonists

Oral supplementation of PPAR agonists has also been considered by the supplement industry. In fact, an oral intervention study on mice for 4 weeks CLA and docosahexanenoic acid compared with linoleic acid decreased subcutaneous fat thickness which was related to reduced size of adipocytes. Increased collagen levels were also observed [45]. In humans Birnbaum [46] compared the effects of an undisclosed herbal anti-cellulite pill with increasing concentrations of CLA over 60 days [group 1, herbal pill (HP) alone; group 2, HP plus 400 mg CLA; group 3, HP plus 800 mg CLA and each group consisted of 20 women]. These treatments had a beneficial effect in 75% of the women who took the pills and the thigh circumference was reduced by an average of 0.88 inch. Figure 16 shows the improvements in thigh cellulite appearance and thigh circumference measurements on completion of the study. Improvements in the microcirculatory patterns were also observed. Although no more studies have been conducted on cellulite, CLA has repeatedly been shown to reduce body fat mass in obese individuals with a corresponding increase in lean body mass, i.e. muscle [47].

Centella asiatica

Hachem and Borgoin [48] reported on the effects of *Asiatic centella* extract given orally one a day (60 mg) for 90 days. In these studies there was a significant reduction in the diameter of adipocytes especially in the gluteo-femoral region and a decrease in interadipocyte fibrosis. In addition to antioxidants such as quercetin, these extracts will contain ursolic acid lactone, ursolic acid, pomolic acid, 2-alpha,3-alpha-dihydroxyurs-12-en-28-oic acid, 3-epimaslinic acid, asiatic acid, corosolic acid and rosmarinic acid. The ursane- and oleanane-type triterpene oligoglycosides such as centellasaponins B, C and D are also present and although mechanisms were not discussed at the time it is highly likely that these agents are PPAR agonists.

Figure 15 Decrease in cellulite grade following 84 months topical treatment with conjugated linoleic acid. Courtesy of D. Imfeld, Pentapharm.

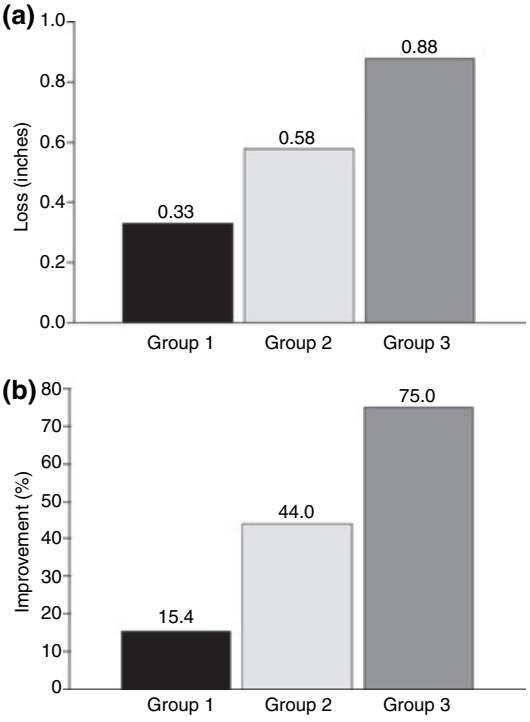

Figure 16 (a) Standardized thigh circumference measurements at and of oral conjugated linoleic acid (CLA) treatment. Group 1: Herbal anti-cellulite pill. Group 2: Herbal pill plus 400 mg CLA. Group 3: Herbal pill plus 800 mg CLA. (b) Percentage of women showing improvement in thigh cellulite at end of study. Group 1: Herbal anti-cellulite pill. Group 2: Herbal pill plus 400 mg CLA. Group 3: Herbal pill plus 800 mg CLA. From Birnbaum *et al.* [46].

Hydroxycitrate

Hydroxycitrate from *Garcinia cambogia*, also known as *Malabar tamarind*, is a lipogenesis inhibitor and it has been used on its own or together with niacin-bound chromium or *Gymnema sylvestre* (gymnemic acid) to help with weight control and reduce body weight [49]. It is highly likely that these will improve the appearance of cellulite. Of note this is a hydroxyacid and may improve collagen synthesis just like other AHAs. Exploitation of these types of agents has exploded in the beverage markets.

Green tea and polyphenols

Although not tested for their effects on cellulite, green tea extracts have become a topic of interest for the treatment of obesity. Chantre and Lairon [50] have shown that after 3 months of intervention an 80% ethanolic dry extract standardized at 25% catechins decreased body weight by 4.6% and waist circumference by 4.48%. This was proposed to be acting by inhibiting gastric lipases and increasing thermogenesis. More recently Wolfram *et al.* [51] and Klaus *et al.* [52] reported that epigallocatechin gallate (EGCG) prevented obesity in rodents. Fatty acid synthase and acetyl-CoA carboxylase mRNA levels were reduced and EGCG inhibited adipocytes differentiation *in vitro*. It is interesting in this respect that green tea leaf extracts increased PPARalpha and gamma protein expression [53]. Black tea extracts also appear to have moderate PPAR activity, albeit lower, than green tea extracts.

Cellasene

Cellasene is a herbal supplement sold for improving the appearance of cellulite by Medestea (Torino, Italy). It contains *Ginko biloba*, sweet clover, sea weed, grape seed oil and evening primrose oil. Lis-Balchin [54] failed to observe any improvement in the cellulite condition over 2 months but no bioinstrumental methods were used in this study. However, Leibaschoff *et al.* [55] testing a slighty different formula with fish oil and borage oil in place of the evening primrose oil (two capsules per day) found improvements in the lipoedema and skin muscular fascia diameter. About 71% of subjects had some symptom improvements. Obviously, this product is effective through a variety of mechanisms but especially on adipocyte lipolysis, cutaneous microcirculation and collagen synthesis. However, as the authors explain the grape seed extract is a powerful antioxidant and will act on the microvascular system, *Ginko biloba* also effects the vascular system, *Asiatic centella* triterpenoids favour lymphatic drainage and stimulates synthesis of the extracellular matrix, *Mellilotus officinalis* also improves capillary resistance whereas *Fucus vesiculosus* influences the metabolic activity in subcutaneous fat and in fact 30% of subjects receiving the Cellasene-containing focus extract experienced an improvement in their body contour profiles. Further testing on a newer formulation is ongoing which contains *Vitis vinifera*, *Ginko biloba*, *Centella asiatica*, *Melilotus officinalis*, *Fucus vesiculosus*, fish oil and borage oil (see Distante *et al.*, Int. J. Cosmet. Sci. **28**, 191–206 (2006)).

Conclusions

Cellulite is a cosmetic problem and is of increasing concern for women with its 'orange-peel' or 'cottage cheese' appearance affecting at least 85% of women. It is not specific for overweight women

although increased adipogenicity will exacerbate the condition. It is a complex problem involving the microcirculatory system and lymphatics, the extracellular matrix and the presence of excess subcutaneous fat that bulges into the dermis. Differences in the septae architecture have recently been reported. Weight loss has been reported to improve the cellulite severity by surface topography measures although on obese subject's skin dimpling does not seem to change appreciably [56]. However, histological examination suggests that fat globules retract out of the dermis with weight loss.

Cellulite has been treated by massage and topical or oral treatments. Massage will reduce oedema but there is also some evidence for increased collagen synthesis after such treatments albeit in animal studies. Equally, its benefits could be via its likely effects on stimulating fibroblast (and keratinocyte) activity while decreasing adipocytes activity. Nevertheless a variety of agents are usually used in these topical creams but with few studies reported. Xanthines, botanicals, fragrances and ligands for the retinoid and PPAR receptors appear to be giving some benefit. Reducing adipogenesis and increasing thermogenesis appears to be primary routes while also improving the microcirculation and collagen synthesis.

Orally, many agents are being investigated for weight management (hydroxycitrate, EGCG, CLA, etc.) and some of these agents seem to be beneficial for the treatment of cellulite. In fact, CLA was shown to ameliorate the signs of cellulite. One product, Cellasene from Medestea, containing a variety of botanicals and polyunsaturated fatty acids also appears to provide some relief from these symptoms.

Regular exercise and an appropriate diet can help control weight and thereby the appearance of cellulite. Like the supplement industry, the food industry has extensive research programmes investigating the effects of CLA, diglycerides, medium chain triglycerides, green tea, caffeine, capsaicin and calcium on weight control. These approaches may also be useful for the treatment of cellulite. It is quite possible, however, that synergies between both oral and topical routes may be the best intervention to ameliorate the signs and symptoms of cellulite.

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