CELLULITE AND ITS TREATMENT

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MASTER OF COSMETIC SCIENCE

IN COSMETIC SCIENCE

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AN INDEPENDENT STUDY SUBMITTED TO

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ABSTRACT

Cellulite or lipodystrophy described a dimpled, orange peel like skin, found frequently in areas around buttocks and thighs. It occurs more in women than in men because of differences in hormone levels as well as structure of skin fat layer. As the amount of fat gets accumulated, cellulite appearance becomes more visible. There are four stages in cellulite development, in which the most severe level causes pain as well as the blood and lymphatic microcirculation disturbance. Therefore, cellulite is both aesthetic and health related skin problems. Instrumental, oral, and topical treatments are basically three main approaches for cellulite treatment. This report provides scientific backgrounds the origin of cellulite, its mechanism, as well as treatment methods, with primarily focuses on topical and oral approaches. There is not yet a product with hundred percent guaranteed on its efficacy. Many active ingredients have been tested on its efficacy and safety issues. However, longer conducted study in larger populations is needed to assess other aspects, especially on long-term usages. It is essentially important for oral supplements, since it deals directly to metabolic function in the body. In short, there are many factors contributed to cellulite formation. Therefore, a combination of treatments is recommended. Monitoring diets and exercise regularly is recommended for good health and sustained results.

Keyword: Cellulite / Lipodystrophy

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CHAPTER I

INTRODUCTION

1.1 Background of the study

The demand for cosmetic products and aesthetic treatments increase dramatically. The figures from Thai customs department show that imported cosmetic products from the United States have an increase almost 10%. On the other hand, the exported figures to the world show a stronger increase of about 15%. [appendix 1].

The frequently seen topical cosmetic products over the counter and supermarket are those for faces. These products come in many forms and different indications, from basic application such as cleansing to more sophisticated propose such as prevention of DNA cell damage. Face products probably are more available than those for body. The reasons maybe that body imperfection can be corrected by suitable clothes, which can cover the bad and show more of the good. Nevertheless, good balanced body is desirable, not only because it looks good but it also implies healthy diets.

Currently, world's population faces both overweight and obesity problems, which lead to many health issues such as heart disease, diabetes, and high blood pressure [1,2]. Moreover, the current trend leans towards health, youth and beauty. The media creates the perfect image of female figure to be attained. As a result, weight loss and slimming products gain more popularity over the years.

Cellulite is a term described a dimpled, orange peel like skin, found frequently in areas around buttocks and thighs. It occurs more in women than in men because of differences in hormone levels as well as structure of fat layer. Some literature reviews that cellulite comes from distortion of adipocyte's cell wall from overloaded fat storage. As the amount of fat gets

accumulated, cellulite appearance becomes more visible. The degree of severity increases more rapidly if blood circulation and skin elasticity are decreased. [3-5]

Treatment products for cellulite then follow. Commercial available products include both topical and oral forms, which use many active ingredients, as well as technological equipments. Looking closely to those products, only little facts or even none are explained to consumers for choosing proper treatments and setting expectations. Simply, the information flow from the experts often get skipped, and ignored. Instead, concentrating on the cost and advertisement. As a result, problems may occur in terms of safety, and expectations patients set.

Therefore, understanding scientific backgrounds lead to choosing proper treatments and setting expectations, preventing complications or problems that maybe followed.

1.2 Objectives of the study

1.2.1 To study origin of cellulite mechanisms,

1.2.2 To study cellulite treatment methods and how they are related to its roots,

1.2.3 To study efficacy and safety issues of active ingredients that are widely accepted and used in anti-cellulite treatments.

1.3 Scope of the study

This independent study is intended to explain scientific points the origin of cellulite as well as mechanisms for cellulite treatments, both in topical and oral applications. It also includes efficacy measurements and safety issues of many different active ingredients based on scientific case studies.

1.4 Benefits of the study

This study reviews scientific documents from early researches to the more recent ones to give a better picture of cellulite mechanism. Knowing basic background leads to better understandings of commercially available treatments, and setting expectations. Besides, efficacy and safety guidelines of active ingredients are discussed. An important document not only for consumers, but also manufacturers for developing products, including any interested parties for using these insights for future studies.

CHAPTER II

LITERATURE REVIEWS

2.1 Scientific perspective of Cellulite

The term cellulite was originally a French imposture [6]. It is a dimpled, spongy appearance of the skin around buttocks and thighs, and it is also commonly known as the 'orange peel' effect. Dermatological term is usually called "lipodystrophy".

Figure 2.1 Thigh, one of cellulite's preferred areas [7]

Evidently, cellulite is often occurred commonly more in women than men. This fact is supported by many biological factors. First, men relatively have more lean muscle mass than females. The fat tissue volume in women represents 20-30% of the body weight compared to 15-20% in men. In women, fat in the bottom half of the body is often stored because of the female hormones, which is to provide energy needed for reproduction. Secondly, the connective tissue in women is more stretchable than in men. Consequently, the adipocytes move more easily between fibers, thus distorting the connective tissue and giving the skin a padded aspect. Thirdly, in women, the activity of lipoprotein lipase, the key enzyme for lipid storage in adipocytes, is higher in gluteal than in abdominal fat [4]. Last, the spatial configurations of the fatty lobules in women is perpendicular to cutaneous surface, and are separated by arched dividing walls of connective

tissue, the corium. As female body aged, the corium become thinner, allowing fat cells to easily protrude into the derm. In obese individuals, it is more apparent because of heavier pressure. While in men, the lobules are smaller and are slanted in relation to the cutaneous surface, more like a criss-cross connective tissue walls. More recent study evidently supported this fact by using MRI (Magnetic Resonance Imaging) for evaluation as seen in figure 2.2. [8-10].

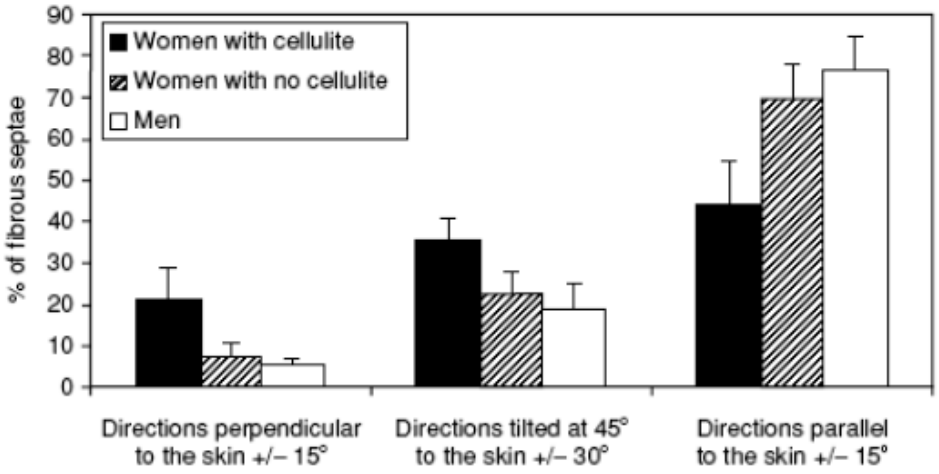
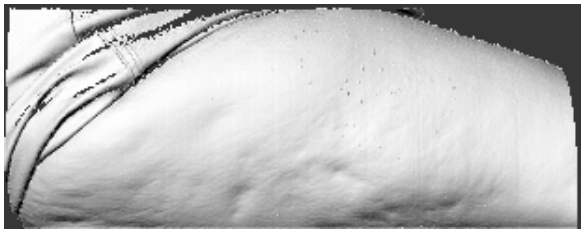


Figure 2.2 Structured patterns of fibrous septa network [11]

Although the cause of cellulite is the most controversial topic, there are evidences concluded by many dermatologists supported on the origin of cellulite.

Appearance of cellulite is often misunderstood and is believed to relate to obesity. However, cellulite can appear in individuals of all ages, races and body weight. Because adipocyte is where fat stored, both size and number of adipocytes presented are then related to the degree of severity of cellulite appearance. Thus, weight gain can worsen the appearance of cellulite. In a study, there is a significant improvement of cellulite appearance after weight loss from 200 lbs. to 152 lbs. in 24 week- period as seen in figure 2.3 [8, 10, 12]



200 lbs: 0 week (Base Line)

Figure 2.3 Correlation between cellulite appearance and weight loss

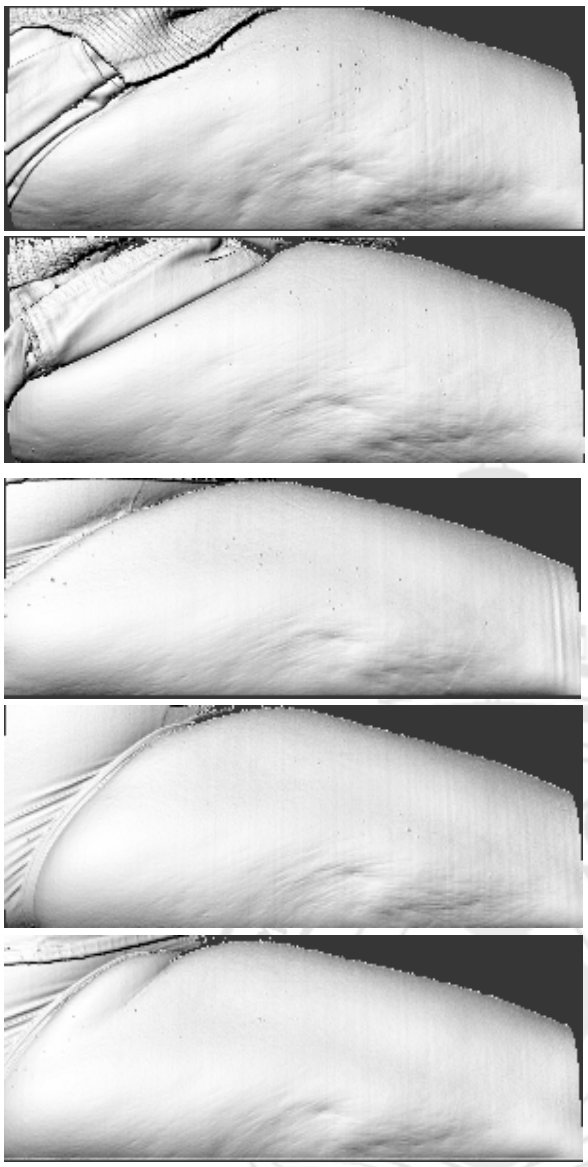


Figure 2.3 Correlation between cellulite appearance and weight loss (continued)

The amount of stored fat is in the form of triglyceride. Meaning that to reduce the amount of fat stored, lipolysis must be promoted.

Lipolytic process [figure 2.3]is controlled by nervous system and plasma insulin level. Signal molecules that control this nervous system are catecholamines, such as adrenaline. Adrenaline composed of epinephrine and norepinephrine, which adrenergic receptors interact with these compounds. Catecholamines can stimulate lipolysis via G_s proteins on β-adrenergic

receptor, or inhibit lipolysis via G_i proteins on α_2-adrenergic receptors [4, 6, 8, 13]. Cellulite is more often found in specific anatomical sites (thighs and buttocks) because of the presence of adrenergic receptors in these sites [14]

Activation of lipolysis is mediated by an increment of cAMP concentration. An increased cAMP level can be stabilized by inhibiting phosphodiesterase, leading to activation of protein kinase A (PKA), and hormone-sensitive lipase (HSL) respectively. HSL hydrolyses triglycerides to free fatty acid(FFA) and monoacrylglycerols. In a last step of hydrolysis monoacrylglycerols are decomposed into glycerol and FFA [figure 2.4].

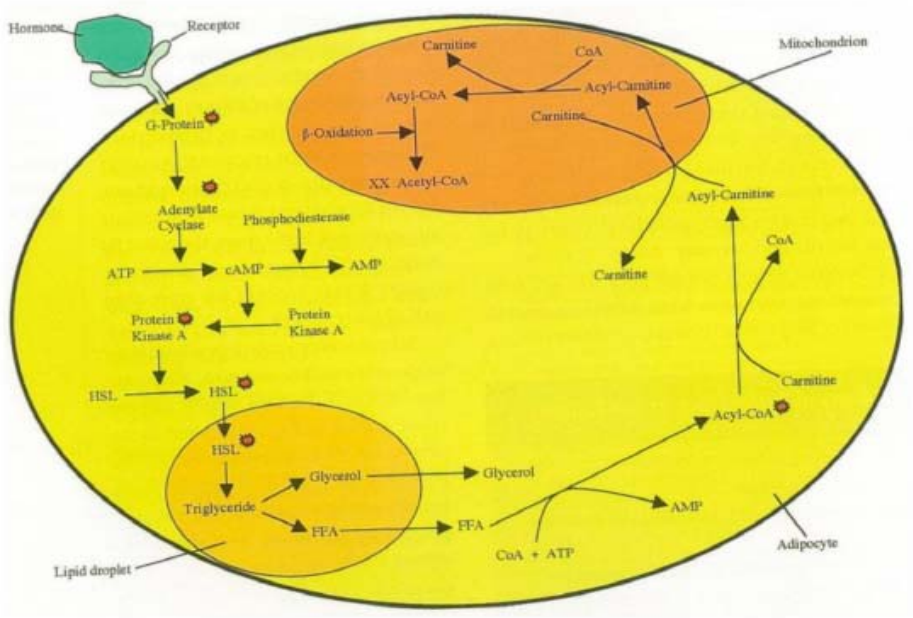


Figure 2.4 Lipolysis process [4]

FFA is a source of fuel for the generation of ATP. Oxidation of FFA involves the formation of fatty acyl-coenzyme A (acyl-CoA), and translocates across mitochondrial membrane, which subsequently undergoes β-oxidation in mitochondrion. Each turn of cycle acetyl CoA and a fatty acryl-CoA with two fewer carbon atoms are produced. [4,13]

In short, lipolysis can be stimulated by β-adrenergic receptor agonists, α_2-adrenergic receptor antagonists, phosphodiesterase inhibitors, and beta-oxidation stimulators. [4]

2.2 Development of cellulite stages [12]

The skin is composed of the epidermis and the dermis. Beneath the dermis is the hypodermis or subcutaneous fat layer (figure 2.5). The subcutaneous fat layer can be thought of as being composed of 2 sub-layers. One is the deeper localized fat deposits and the other is more superficial layer of fat.

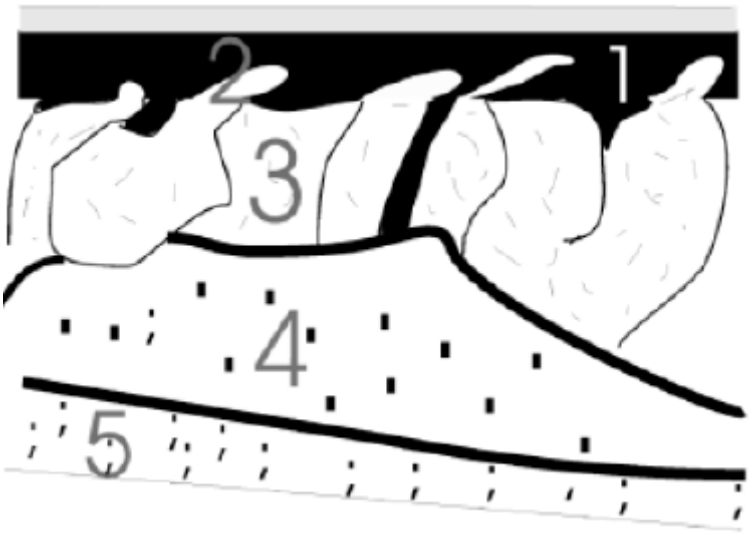


Figure 2.5 Schematic diagram of skin structure, showing (1) dermis,
(2) extrusion of the hypodermis into the dermis,
(3)-(5) upper, middle and lower parts of hypodermis. [15]

Cellulite appears to originate in the fat layer where structural compartmentalization of fat tissue is predominant. The compartment of fat tissue are encircled and separated by bands of connective tissue called ‘septa’. When the fat cells in these compartments become bigger and/or fluid accumulates, the compartments begin to bulge, pressing against septa, contributing to the appearance of dimples and bumps on the surface of the skin—cellulite. With age and sun damage, the septa becomes weakened and thickened, resulting in shrinkage and contributes to the indentations seen on the surface of the skin.

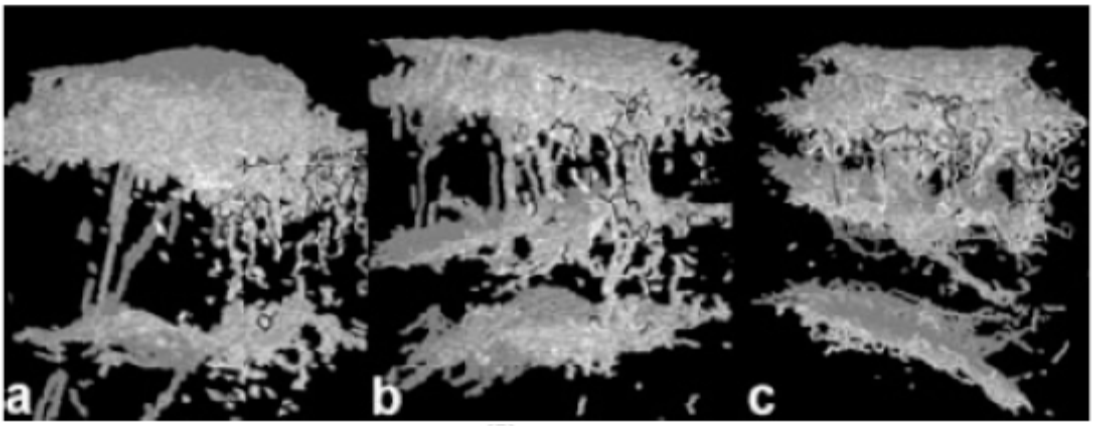


Figure 2.6 Visualization of fibrous septae in subcutaneous adipose tissue
(a) woman with cellulite; (b) normal woman; (c) normal man. [11]

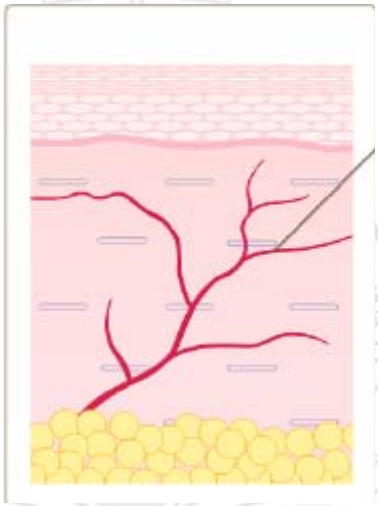


Figure 2.7 Healthy skin

Cellulite has levels of severity, looking at pathological view point, the appearance of dimpled effect can be distinguished into 4 stages [5].

Stage 1: Blood vessels deteriorate from dehydration and deprivation of cell-building nutrients, which allows wasted water to accumulate outside the cells. These excess moisture causes collagen and elastin to begin breaking down. Due to the looser connective tissue, the upper fat cell in hypodermis fat starts clumping together. At this stage, there is almost none or only minimal appearance of cellulite.

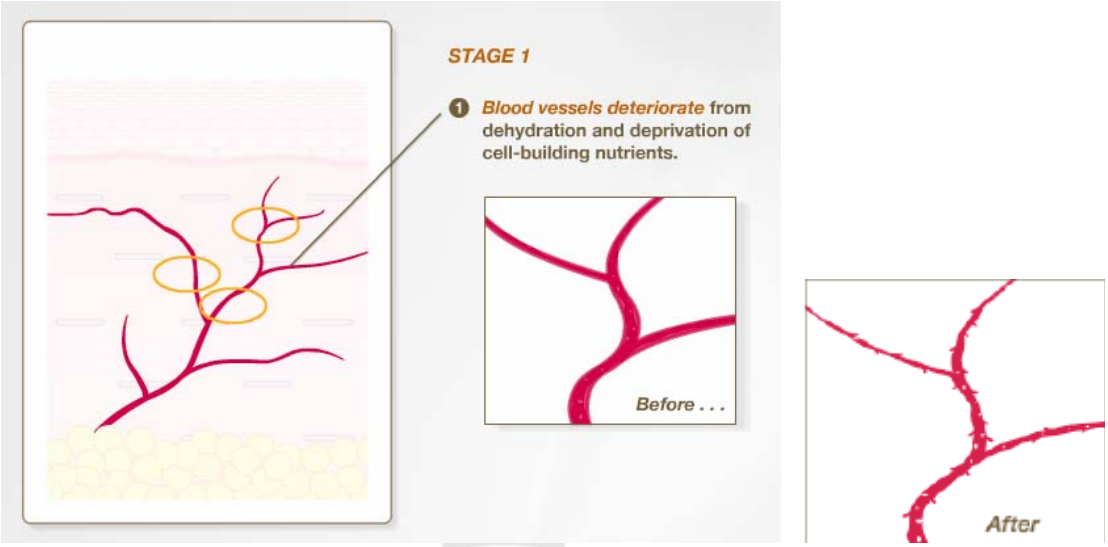


Figure 2.8 Development of cellulite in stage 1

Stage 2: The excess moisture continues to break down collagen and elastin in the dermis. This weakening dermis allows subdermal fat cell to move up into the dermis. Consequently, orange peel texture becomes visible.

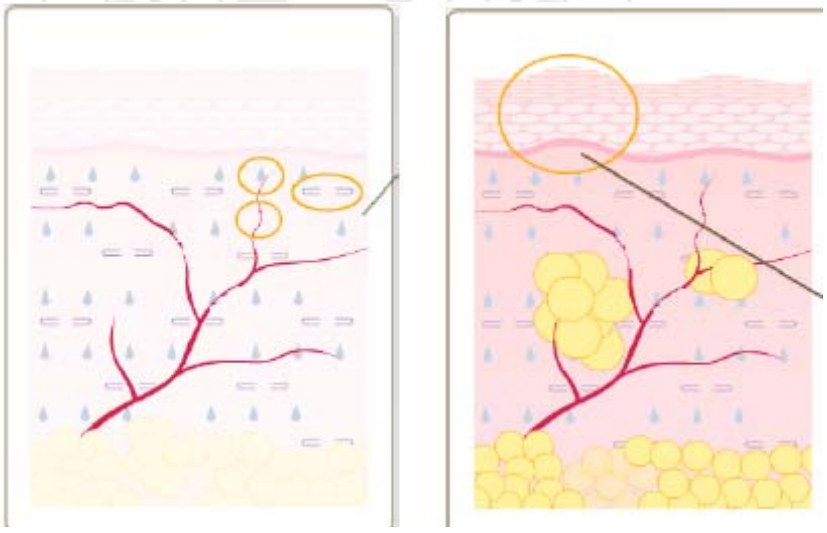


Figure 2.9 Development of cellulite in stage 2

Stage 3: Synthesis of new collagen and elastin slows down, causing accumulation of more fluid. The fat cells swell and become surrounded by fibrous connective bands, called Septa. At this stage, significant orange peel texture becomes visible when pinch.

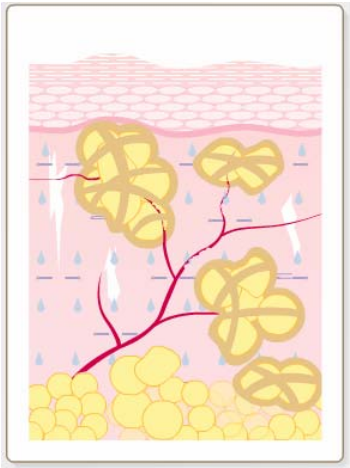


Figure 2.10 Development of cellulite in stage 3

Stage 4: The connective tissue continuously breaks down, and Septa becomes harden and thickens. Hard nodules can be felt. Changes to skin texture always visible, accompanied with pain and tenderness.

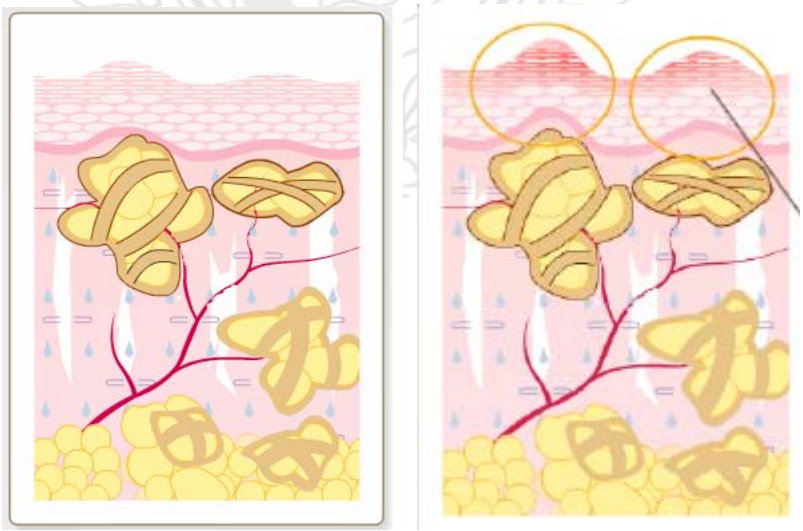


Figure 2.11 Development of cellulite in stage 4

The assessment of severity degree of cellulite appearance is important in order to go for treatment properly as well as to evaluate effectiveness of such treatments. One method uses photograding technique (Figure 2.11). Some studies assigned visual cellulite grading scale for skin appearance assessment (Figure 2.12), which are aligned with the development of cellulite at different stages.

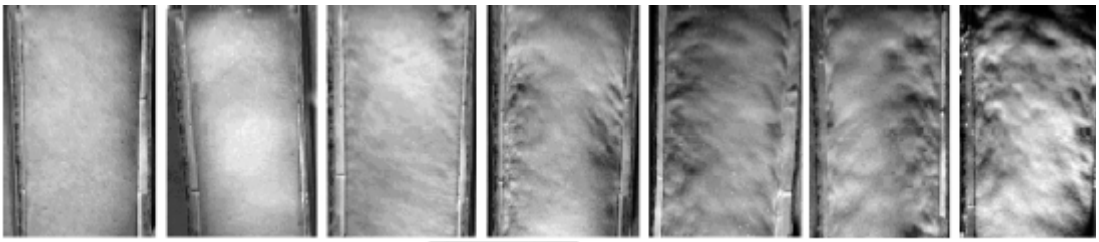


Figure 2.12 Photonumerial scale representative of the different grade of cellulite: from no cellulite (left) to very severe sign (right) [16]

Cellulite grading scale	Skin appearance
0	No dimpling – smooth skin
1	Few number of small, shallow, visible dimples, sparsely located on the thighs
2	Moderate number of visible dimples (some large) on the thighs
3	Large number of visible dimples (many large) over most of the thighs
4	Cottage cheese appearance of skin

Figure 2.13 Descriptive visual grading scale for cellulite assessment [15]

Various treatment methods currently become available. If cellulite appearance is minimal, usually, topical method possibly is sufficient at optimal cost and duration. However, if the degree is more severe, treatment cocktail and longer treatment duration are necessary.

Cellulite treatments can be easily categorized into three groups; instrumental, topical and oral methods. Looking closely at instrumental method, various equipments are available for consumers to choose. These equipments theoretically target in reducing both the size and amount of adipocytes either by using mechanics or bypassing SC and dermis to deliver active agents at specific fat tissue. The differences are delivery system techniques, in which some use electric current and some use thermodynamics. From literature reviews [17], the following are equipments commercially obtainable in the market.

1. *Iontophoresis*: the interstitial fluid, and blood, contain electrolytes. This allows it to act as an electrical conductor. The stratum corneum, on the other hand, acts as a non-conducting barrier. By applying a galvanic current on the skin surface, it allows drug to pass through SC into the dermis. However, it is also important to study the polarity, the structure and the molecular size of the drug that is used.

2. *Ultrasound*: High frequency vibrations, which have both thermic and vasodilator effects, help in the penetration of active drugs.

3. *Thermotherapy*: this technique uses heat or cold to obtain vasodilation. However, its effectiveness is questionable, and the use of high temperature may lead to protein denaturation.

4. *Electrolipophoresis:* this method consists of application of several pairs of thin(0.3 mm) long (5-15 cm) needles which are connected to a low frequency current generator. An electromagnetic field is created which modifies the interstitial tissue, aiding circulatory drainage and promoting metabolic changes and lipolysis.

5. *Mesotherapy:* this is a therapeutic approach in which the drug is administered directly into the dermis using needles. It involves the infusion of a small amount of the active drug directly to the affected site using needles, by passing the resistance of the epidermal barrier. The ideal drug used must be hydrosoluble, isotonic, have an adequate pH, be physically, and chemically stable, be well tolerated after dermal administration, and have low allergenic potential. As for the treatment of cellulite, a combination of active ingredients used are phosphatidylcholine and deoxycholate. They are believed to act as an emulsifier to dissolve fat and remove small amount of adipose tissue [12].

6. *Endermologie ®:* A rather old method initially developed in late 1970s. This is non invasive, suction-assisted massage technique. This mechanical device consists of two moving rollers that travel across the skin with a suction-generated vacuum between the rollers [figure 2.13]. It is claimed to stimulate lymphatic flow as well as increase skin tone and elasticity [18].

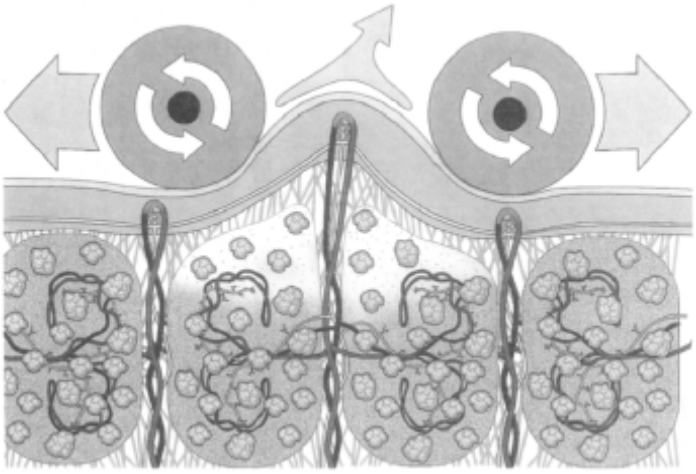


Figure 2.14 Illustration of the effect of the mechanical rollers and suction on the skin

The mechanism is similar to pressotherapy, which utilizes a pneumatic massager to perform sequential compression. Instead Endermologie ® is a device. The effects maybe temporary and require multiple visits. [21]

7. Carboxy Therapy(carbon dioxide therpy): this is an invasive method, referring to transcutaneous administration of carbon dioxide into the fat layer. Carbon dioxide mechanically kills fat cells and it also has strong vasodilatory effect on the capillaries in the area, reducing fluid built up between the cells. The pain is often felt at the site of injection, but usually short lasting.

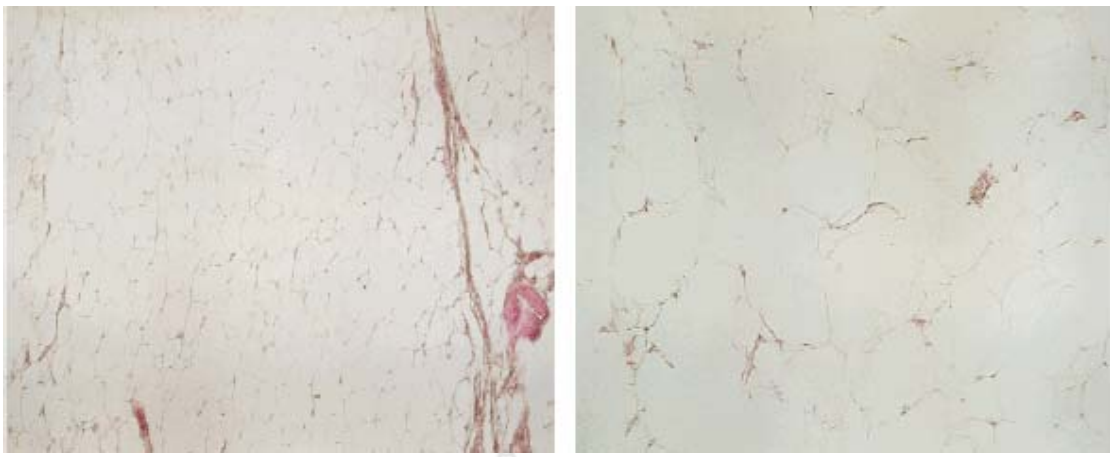


Figure 2.15 Histological features of subcutaneous layers before (left) and and after(right) CO_2 treatment [19]

8. *Velasmooth*®: device based on a combination of two different ranges of electromagnetic energy: infrared and radio frequency, combined with mechanical method.

9. *TriActive*® laser: a device intended to reduce the appearance of cellulite through the combination of low-energy diode laser, contact cooling, suction and massage.

The last two methods were relatively newer than other methods mentioned above. In a comparison study to determine efficacy on improvement of cellulite between both systems, the average mean percent change calculated was roughly the same for both treatments [25].

CHAPTER III

RESEARCH METHODOLOGY

This independent study is based on literature review, in which the focus is on the scientific backgrounds on the origin of cellulite as well as treatment methods available in the market. Oral and topical methods will be more emphasized to conclude efficacy and safety aspects of various active ingredients.

The information obtained are from various sources; journals, websites, books, magazines, and interviews. Scientific journals, books and magazines are mostly related to cosmetic science, nutrition, food and health. All of the information reviewed is from year 1998 up to year 2007.

Moreover, information acquired through interviews of five people from medical, beauty, and spa business. Phitrphiboon Siribencha, MD., and Chonchanok Ruamrak, MD. have experiences with carboxy therapy and mesotherapy approximately three years, whereas Naris Wadepinyo, MD. LT. has experience with carboxy therapy for five years. The other two were from owners of clinic and beauty & spa. Mrs. Damrongwattanapokin is owner of Romrawin clinic who provides knowledge about new instrumental technology of slimming products. Romrawin clinic offers wide range of advanced instruments for cellulite treatment. In addition, Mrs. Khemataechit has long been in spa business and is the owner of Princess beauty and spa. Her area of expertise focuses more on massages for lymphatic drainage using herbal extracts. The interview questions can be found in appendix E.

CHAPTER IV

RESULTS AND DISCUSSIONS

4.1 Treatment methods

In summary, combating cellulite problem can be done pathogenically in different ways.

4.1.1 Decrease of adipocyte contents (promoting lipolysis, and preventing lipogenesis)

4.1.2 Protection and enhancement of fundamental substances,

4.1.3 Improvement of microcirculation.

The methods for cellulite improvement, either instrumental method or topical and oral methods, mechanisms still are aligned with three mechanism as suggested.

As mentioned in Chapter 2 regarding instruments used for cellulite treatment, it is seen that newly developed equipments such as Velasmooth® and TriActive® adapt and combine different ranges of electromagnetic waves, rather than using a single frequency like older methods [Figure 4.1].

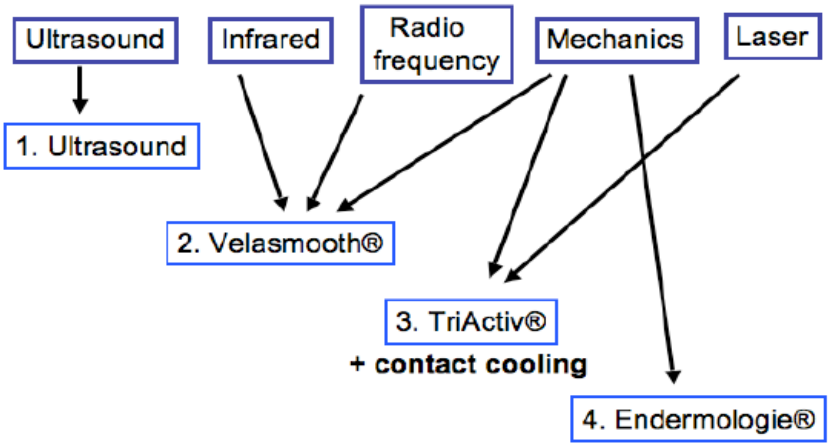


Figure 4.1 Instruments using combination of different approaches

From the interviews with the doctors and owners of beauty clinics [20-24], carboxy therapy and mesotherapy are probably the most commercial available. These two methods are US FDA approved and are allowed to practice only under physicians' supervision, which mean they are not allowed at beauty and spa. These methods bypass stratum corneum (SC) and dermis to deliver agents in reducing size of fat cells, rupturing fat cell membrane. Thus, lymphatic drainage by other mechanisms, such as using Endermologie®, Velasmooth®, and massages are usually recommended to patients in addition to using instruments for best results. Massage course usually involves body wrapping to reduce water retention, followed by combination of dry sauna and using topical cream/gel containing actives such as caffeine, kiwi, and horsetail. One course is consisted of 10 massage sessions. Using massage technique takes longer time for improvement of cellulite appearance, whereas using carboxy therapy or mesotherapy, result may become apparent within 1-2 sessions. However, these two methods have some drawbacks and some precautions.

Carboxy therapy requires professional experiences for injection of carbon dioxide. It may cause death if carbon dioxide gets into the blood vessels. Likewise, mesotherapy cannot be practiced with patients who have metabolic diseases such as heart disease, high blood pressure, and thyroid. In targeting fat cells, phosphatidylcholine is often used. However, this agent may not well dispersed or scattered evenly, causing nodules and fibrous tissue. These two methods are recommended differently in treating cellulite. At cellulite stage 0-1, carboxy therapy gives good result. However, if cellulite is more severe, stage level greater than 2, mesotherapy is often preferred. [24]

Endermologie® uses vacuum for smoothing effect, but this method involves pain. Also, this method requires regular visits, because cellulite becomes re-visible if treatment is stopped. On the other hand, Velasmooth® uses tri-actions of vacuum, infrared (heat), and radio frequency, for cellulite treatment, and is claimed to have lifting effect from collagen synthesized by stimulation of radio frequency. However, the equipment is more expensive (two millions baht) comparing to Endermologie® (200,000 baht). Therefore, this method is not widely available to consumers. Table 4.1 summarized widely used commercial instrumental methods for cellulite treatments.

Table 4.1 Comparison of widely used commercial instrumental methods for cellulite treatments

	CARBOXY THERAPY	MESO THERAPY	ENDERMOLOGIE®	VELASMOOTH®
MECHANISM	agent-carbon dioxide	agent-active cocktails	mechanical	mechanical
SESSION	5-10	5-10	10	5-10
RISK	high	high	no risk	no risk
AVERAGE PRICE	1,000-2,000 baht/session/area	3,000-5,000 baht/session/area	1,000-2,000 baht/session	20,000-30,000 baht/course
PAIN INVOLVED	yes	yes	yes	no

As discussed, instrumental methods have both benefits and some drawbacks. Although using instrument may seem to target cellulite at specific sites, and treatment results possibly become visible after single visit, most methods requires professional practitioners, and some methods involve relatively high risk, complications, and pain. Some methods are probably available at specific places, and might not be convenient for consumer; especially ones that require regular doctor visit. Besides, instrumental method is usually more costly comparing to oral and topical methods.

Topical method and oral treatment are more accessible to the consumers, and do not need skilled consultants. Topical and oral treatments use several active ingredients through various mechanisms; usually to promote lipolysis and prevent lipogenesis. Because of its ease of use and acceptable effectiveness, there are wide ranges of products for consumers in the market.

As said, topical and oral methods are alternatives that require less money, skilled consultants, and time for patients who want to see improvement of cellulite appearance. Many active ingredients are discussed as follows,

4.2 Active ingredients used for cellulite treatment

Active ingredients can be delivered in targeting fat cells and enhance fundamental substances through both oral and topical.

4.2.1 Topical: [3, 17, 26-32]

Table 4.2 Example of plants and their active components used for treatment of cellulite

PLANT	ACTIVE COMPONENT
Rosemary (*Rosmarinus officinalis* L.)	Carnosic acid, carnosol, rosmarinic acid, ursolic acid
Wild Marjoram (*Origanum vulgare* L.*)*	Rosmarinic acid
Bitter orange (*Citrus aurantium L. var. amara*)	Naringin, hesperidin, neohesperidin
Lady's thistle (*Silybum marianum* GAERTN)	Flavanolignans
Cypress (*Cupressus sempervirens* L.*)*	Cetechin derivatives
Blackcurrent (*Ribes higram* L.*)*	Flavonoids
Lady's Mantle (*Alchemilla vulgaris* L.)	Tannins
Horsetail (*Equisetum arvensis*)	Silicon
Grape vine (*Vitis vinifera*)	Leucocyanidines (bioflavanoids)
Centella (*Centella asiatica*)	Pentacyclictriterpenes (Asiatic acid, Madecassic acid, Asiacoside and Madecasspsode)
Gingko (*Gingko biloba*)	Ginkgo-flavonoid glucosids, terpenoids
Algae (*Fucus vesiculosus*)	Polysaccharides, bromine and iodine
Ivy (*Hedera helix*)	Falcarinol
Horsechestnut (*Aesculus hippocastanum*)	Aescin, Escin(seeds)

Table 4.2 Example of plants and their active components used for treatment of cellulite (continued)

PLANT	ACTIVE COMPONENT
Butcher's broom (*Ruscus aculeatus*)	Ruscogenin, neoruscogenin (bioflavanoids)
Coffee (*Coffea spp*.)	Caffeine
Lotus (*Nelumbo nucifera*)	Bioflavanoids
Green tea (*Thea sinensis*)	Flavanoids, methylxanthines
Algae or Bladderwrack (*Fucus vesiculosus*)	Iodine
Witch hazel (*Hamamelis virginiana*)	Tannins
Cola (*Cola nitida*)	Polyphenolic compounds (Tannic acid, Catechin, Epicatechin)
Barley (*Hordeum vulgare*)	Catechin, tocopherol, and lutein
Bearberry (*Uva ursi*)	Glycoside arbutin (mild diuretic)
Hawthorne berry *(Crataegus spp*.)	Bioflavanoids
Cayenne (*Capsicum annuum* L.)	Capsaicin
Ginseng (*Zingiber officinali*)	Ginsenosides
Ginger *(Zingiber officinalis* Rosc.)	Gingerols, shogaols
Chilli *(Capsicum frutescens* L.)	Capsaicin, cryptoxanthin, capsorubin, carotenoid
Garcinia *(Garcinia atroviridis* Griff)	(-)- Hydroxycitric acid, tartaric acid, malic acid, ascorbic acid
Wheat germ (*Triticum vulgare* Vill.)	Peptides

Table 4.3 Example of chemicals substances used for cellulite treatment

CHEMICAL SUBSTANCES	MECHANISMS
Coenzyme A	Induce active transport through mitochondria
L-carnitine	Induce active transport through mitochondria
Vitamin A	Stimulate turnover of skin
Retinoic acid	Stimulate turnover of skin
Xanthines and xanthine derivatives	Phosphodiesterase inhibitor
Co-enzyme Q10	Antioxidant
Vitamin C	Antioxidant
Vitamin E	Antioxidant

From table 4.2, and 4.3 above, these plants contain chemicals compounds beneficial for cellulite treatment. They minimize cellulite appearance through many mechanisms as suggested below.

1. Decrease of adipocyte contents

In order to stimulate lipolysis process, one of which is to use β-adrenergic agonist and α_2-adrenergic inhibitor. Xanthines and xanthine derivatives are a class of pharmacological actives. They are beta-adrenergic agonists, and work by inhibiting phosphodiesterase, which finally leads to conversion of triglycerides into free fatty acids and glycerol [figure 4.2]. Caffeine is the most popularly used ingredient in anti-cellulite product, and is one of xanthines classification. Other examples include theobromine, theophylline and aminophylline. α_2- adrenergic inhibitors that work in similar process are yohimbine, α-yohimbine, piperoxine, phetolamine and dihydroergotamine [8,34].

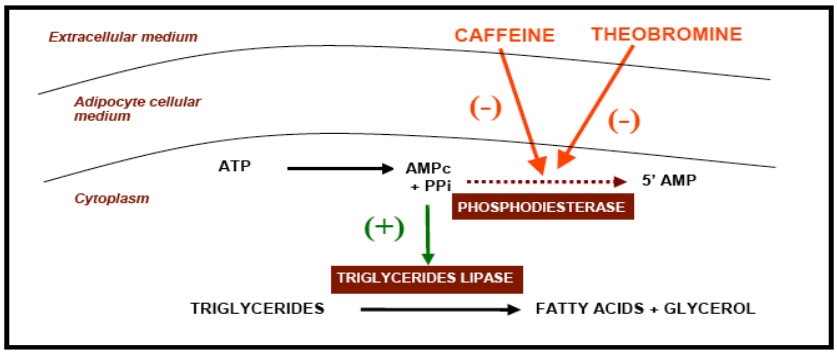


Figure 4.2 Action of caffeine and theobromine on lipolysis regulation [35]

From the study of 4 weeks period in 40 volunteers to determine the efficacy of theophylline 1.5% gel, it suggested that theophylline gel can reduce thigh circumferences above knee at 15 cm and 25 cm by 1.23 $\pm$ 1.19 cm and 1.69 $\pm$ 1.43 cm respectively. [36]

Coenzyme A and *L*-Carnitine are described of having ability to stimulate mobilization and destruction of free fatty acids as well as induce active transport through the mitochondria membrane. This is important because FFA may saturate the system, leading to negative feedback of lipolysis. Moreover, this process releases ATP, which increases lipase activity, enhancing hydrolysis of triglycerides [17].

Other herbal extracts that are claimed to promote lipolysis include cayenne extract, and ginger extract claiming to have thermogenic effects [17]. A study of body shaping cream containing capsicum, ginger, and garcinia extracts at 1% w/w in 20 volunteers for a period of 28 days illustrated a significant decrease of average perimeter of the waistline (-6.55 $\pm$ 0.52 cm) in all volunteers. However, there is non-significant decrease of the body weight (-0.43 $\pm$ 0.28 kg) in 77% of the volunteers. [32]

(a) (b) (c)

Figure 4.3 Illustration of various plants from left to right:
(a) Bitter orange, (b) Horsetail, and (c) Butcher's broom [33]

2. Protection and enhancement of fundamental substances

Both vasculature and the septa in the hypodermis play vital role in the development of cellulite. All connective tissue, including collagen, elastin, fibronectin and various glycosaminoglycans (GAGs), can be adversely affected by matrix metalloproteinases (MMPs). MMPs are often released by cells in the response to inflammation, for example, collagenases and elastases. Therefore, a goal of slimming formulation is to target inflammation and MMP deactivation, as well as directly strengthen the connective tissue. To summarize, the factors contributed to loss of skin elasticity are:

1) Free radicals

2) Skin Enzymes (mainly elastase)

3) Slow turnover of the skin

The reduction of free radicals can be achieved by using antioxidants, which helps improve inflammation, and resultant release of MMPs that target the destruction of connective tissues. Antioxidant scavengers can also be found in various foods and plant extracts. For example, grape seed extract, green and white tea extracts, vitamin C, vitamin E, coenzyme Q10 (co-Q10), genistein, lycopene, carotenoids such as beta-carotene and lutein, pomegranate

extract, alpha lipoic acid, reservatrol and pine bark extract. Other sources include spices such as garlic, onion, turmeric, sage, thyme and oregano. [12]

Another mechanism helps to stimulate turnover of skin to produce healthy collagen or elastin can be achieved by using retinoic acid, retinols, vitamin A, vitamin C. In a study using 0.3% retinol over 6 month period showed an improvement in cellulite in 12 out of 19 subjects. However, another study could not find any change in the cellulite appearance but observe an increase in skin elasticity and a decrease in its viscosity. [37]

A study using plant complex, lady's thistle, alchemilla or yarrow, horsetail and germinated seeds, which contain corresponding actives, silybin, tannins, silicon, and peptides respectively exhibit inhibition of elastase enzymes. Besides, positive results in increased skin elasticity as well as decreased wrinkle by 36.7% was observed. [27]

Other herbal sources include *Asiatic centella* extract, which consists chemically asiaticosideo (40%), madecassic acid (30%) and Asiatic acid (30%). From *in vitro* study, it acts on fibroblasts, stimulating collagen and mucopolysaccharide systhesis [17].

3. Improvement of microcirculation [38,9]

Another hypothesis regarding appearance of cellulite is a decreased microcirculation, which is the direct result of deterioration of dermal vasculature [38]. The mechanisms to achieve are to strengthen walls of veins, improve blood flow, and reduce water retention.

Rutin is a citrus flavanoid glycoside found in buckwheat, the leaves and petioles of the *Rheum* species, and the fruit of the Brazilian Fava D'Anta tree. It acts as capillary-strengthener as well as slow down lipogenesis. Citrus bioflavonoids from lemons, grapefruits and oranges as well as fruit bioflavanoids such as hesperidin, eriocitrin and flavonones from grapes, plums, apricots and cherries, also strengthen capillaries and regulate their permeability. Besides, butcher's broom extract and horsetail extract are known to strengthen walls of arteries and veins.

Uva ursi: an herb derived from bearberry, juniper berries, couch grass, buchu have been associated with the loss of excess fluids in tissues, leading to reduce water retention. Xanthine derivatives such as goto kola has also property of diuretic effects.

Other plant extracts that assist blood circulation include bilberry extract, ginkgo biloba, hawthorne berry, ivy, and ginseng.

A clinical study on 27 female subjects with cellulite at the thighs involving a daily massage with a commercial preparation containing caffeine, ivy, butcher's boom showed after 1 month a significant diminution of the thickness of subcutaneous fat tissues using instrument as well as visual examination. However, the result was opposite to another study done in the same manner on 15 female subjects [3].

As for topical treatments, numbers of studies have been reported on the efficacy of the actives, which are summarized in table 4.4. It is noticed that the experiments done on different measurement approaches, so as the period and numbers of subjects. However, there are no reports on adverse effects using topical approach.

Table 4.4 Summary of case studies using topical approach for cellulite treatment

ACTIVE INGREDIENTS	METHOD	PERIOD	# SUBJECTS	RESULTS
Theophylline 1.5% gel	Thigh circumference above knee 25 cm	4 wks	40	-1.69 $\pm$ 1.43 cm
Aminophylline 10%	Thigh circumference	49 days	28	-1.25 inches
Ginger, capsicum, garcinia extracts 1% w/w	Waistline circumference	4 wks	20	-6.55 $\pm$ 0.52 cm
Caffeine, *L*-carnitine, coenzyme A	Thigh circumference above knee 20 cm	4 wks	3	-1.26 cm
Caffeine, ivy, butcher's broom	Tactile examination and Ultrasonic echography on thigh	1 month	27	Decrease thickness of subcutaneous fat

Table 4.4 Summary of case studies using topical approach for cellulite treatment (continued)

ACTIVE INGREDIENTS	METHOD	PERIOD	# SUBJECTS	RESULTS
Retinol 0.3%	Laser Doppler velocimetry on thigh	6 months	19	12 positive results, 7 no improvement
Herbal extracts 5%	Image analysis	45 days	6	-36.7% decrease in wrinkle

In summary, chemicals substances found in natural extracts can be generally grouped according to their activities through three mechanisms:

1. Decrease adipocyte contents:
   1) β-adrenergic agonist: xanthines and xanthine derivatives
   2) Thermogenesis effect: capsaicin, gingerols
2. Protecting and enhancing fundamental substances:
   1) Free radical scavengers: flavanolignans, as well as polyphenolic compounds.
   2) Anti-elastase activity: tannins, catechin derivatives, aescin, in which the studies found in lady's mantle, cypress, and horse chestnut respectively.
   3) Regulation of dermal structure: silicon, iodine, pentacyclictriterpenes.
   4) Stimulate synthesis of fundamental elements: peptides, retinoic acid, vitamin A
3. Improvement microcirculation:
   1) Strengthen walls of capillaries: fruit bioflavanoids, citrus bioflavanoids.
   2) Loss excess fluid: glycoside arbutin

4.2.2 Oral:

Although theoretically speaking, cellulite does not necessarily appear in obese people, obese individuals have more adipose tissue mass than thin people do. Therefore, chances are obese people often face cellulite problem. There is an evidence showing the correlation between decreased body weight and improvement of cellulite [39]. For that reason, weight loss products are related to cellulite treatments by reducing size and number of adipose tissue mass.

As for oral treatments, ingredients that have an effect on reduction of body weight, and potentially on the improvement of cellulite, can be achieved through food daily intakes, supplements, or even as a prescribed drug. Some chemicals compounds are everyday found in various foods that also promote other health benefits.

Conjugated Linoleic Acid (CLA):

CLA has been a subject of interest in many studies since a discover of its anti-cancer property. [40] CLA is a term for a group of geometric and positional isomers of linoleic acid. It is a type of trans fatty acid, occur naturally in food, especially in daily products such as meat, cheese, and milk [41]. One of the most interesting aspects of CLA is its ability to reduce body fat while enhancing lean body mass. Therefore, some literatures suggested that there were positive effect of using CLA in treating cellulite [37, 42]. Conjugated linoleic acid is a mixture of geometric and positional isomers, with double bond at [9,11], [10,12], [8,10], [7,9], and [11,13]. *Cis*-9, *trans*-11 is the most abundant form found in natural food products (>80%). The commercial CLA available is a mixture of *cis*-9, *trans*-11 and *trans*-10, *cis*-12. Currently, most reports focus on the activities of these two isomers [figure 4.4]. This is not because other isomers have no effect, but rather that their activities are unknown. The known biological effect of the minor isomers is that the *trans*-19, *trans*-11 CLA isomer inhibits platelet aggregration and antiproliferative effect [42, 43, 40].

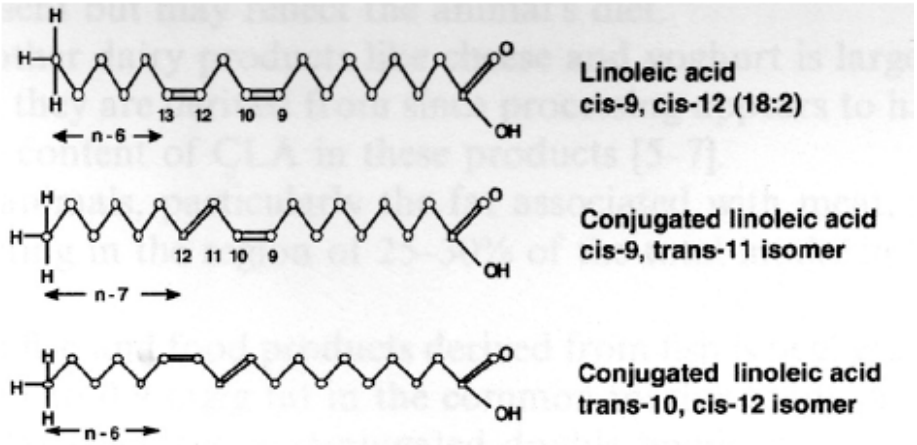


Figure 4.4 Structure of fatty acid linoleic acid and its two main conjugated derivatives [40]

Although present naturally in negligible amount, the *trans*-10, *cis*-12 CLA isomer is active isomer affecting lipid metabolism and body fat reduction, while *cis*-9, *trans*-11 isomer improves growth performance in young rodent [37, 42,43,44]. A study supported on the isomeric form of *trans*-10, *cis*-12 that it is highly specific in preventing lipid accumulation in adipocytes. A small structural changes in the molecule totally abolish this effect. [45]

Studies in mice found out that they are most responsive to CLAs (mixed isomers) with levels of 0.5% of diet, decreasing ca. 40%-80% in body fat. However, studies in rats show a less decreased magnitude than those observed in mice. Reduction on body fat is dependent on strain and on the specific anatomical site of the adipose tissue.

Norway was the first that conducted studies of the effect of CLA supplementation on body composition in humans. Active men and women (10 per group) took either 1.8 g/d of a CLA mix or an olive oil control supplement for 12 weeks. No changes in body weight were observed but the CLA group showed 4% decrease in body fat compared to the placebo group. It was seen that greatest effects on body fat reduction were found with trained athletes and the suggestion was that CLAs prevented the uptake of fat into the adipocyte. This evidence would make CLAs ideal for prevention of weight gain common after a weight-reducing course [40, 46]. Others studies from 1999 to 2006 [appendix B] to determine CLA effectiveness showed that the results of giving CLA at least 3.4 g/d gave a reduction of body fat in both short

term (8 wk) and long term (2 yrs). However, these findings were conducted differently and the results were less clear.

The main areas of concern regarding safety in humans are focused on glucose/insulin metabolism and liver function because of adverse changes in some animal studies. Mice develop increasing does of CLA, particularly the *trans*-10*, cis*-12 isomer. Mice also develop triglyceride accumulation and liver enzyme elevations on CLA, and the effects are dose related. In humans, insulin resistance was reported with ingestion of a supplement enriched with *trans*-10*,cis*-12 isomer, but not with a mixed isomers of mainly *cis*-9*, trans*-11 and *trans*-10*, cis*-12 isomers. However, in a 18 week doubled-blind placebo controlled study, enriched *trans*-10*, cis*-12 CLA isomer were given to 81 healthy men and women at 3g/day. It is shown that there were neither effect on insulin resistance nor liver function abnormalities. In one- year study, consisting of three phases, in which subjects were given 6g/day of CLA or placebo. Phase 1 was a low calorie diet (13 kcal/kg desirable weight) for 12 weeks or until 10-20% of initial body weight was lost. In phase 2, from weeks 12-28, subjects were fed a diet providing 25-30 kcal/kg of desirable body weight. Phase 3 was open label, with subjects from both groups taking CLA from weeks 28-52. At biweekly visits, subjects completed a questionnaire evaluating side effects and adverse events. Blood was taken for assay of liver function, glucose, insulin, serum lipids, blood counts, and general chemistry. Laboratory tests showed no adverse effects on CLA [appendix C] Adverse events and side effects where less in the CLA group compared to placebo. Therefore, it could be concluded at CLA is safe. [44]

(-) -Hydroxycitrate (HCA):

HCA is a chemical compound found in the peel of the fruit of *Garcinia cambogia*, also known as Malabar tamarind[26, 32, 47]. HCA is a competitive inhibitor of ATP-citrate lyase, and therefore fatty acid systhesis. This has led to suggestions that HCA administration could inhibit lipogenesis. Studies with rats and mice indicate that HCA decreases weight gain. The most likely mechanism for the decreased weight gain seems to be a decrease in appetite (animals consuming HCA do eat less), but the mechanism by which HCA produces such an effect is unclear. One suggestion is that HCA divert calories toward the synthesis of liver glycogen, in which animal studies support increased gluconeogenesis and glycogen systhesis in response to HCA. The resulting increase glycogen, or possibly glucose itself, might be involved

in the satiety signal. However, this is only one possible mechanism, since the synthesis and breakdown of glycogen involve highly regulated processes [48].

A study in overweight humans, volunteers consumed three times daily for 2 week 100 ml tomato juice (placebo), separated by 2-week wash-out period, 100 ml tomato juice with 300 mg HCA. After two weeks, twenty-four-hour energy intake was decreased by 15-30% with HCA treatment compared to placebo, while satiety was sustained. However, reduction of body weight was not clear [47]. These findings are aligned with the studies done in mice and rats. However, longer study period is needed for conclusive results. It has been used on its own or together with niacin-bound chromium (NBC) or Gymnema sylvestre extract (gymnemic acid) to help with weight control, while promote healthy blood lipids level. [26, 49]

Green tea and oolong tea [37]:

Green tea extracts have become a topic of interest for the treatment of obesity, although it is not tested on the effect of cellulite [26]. Green tea and oolong tea are made from leaves *Camellia sinensis* L. Green and oolong tea are the non- and partially fermented/oxidized products respectively. Chemicals constituents presented in high quantities are catechin polyphenols such as epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate, and caffeine.

A number of studies indicated that consumption of green tea has benefits for body weight or fat mass/distribution. In a nonplacebo controlled trial observed that 12-week ingestion of green tea (caffeine:150 mg/day; catechins: 375 mg/day) led to decreases in body weight and waist circumference (4.6% and 4.5% respectively) in moderately obese subjects. A Japanese study has shown decreased body weight, waist circumference and body fat over 12 week ingestion of high does of tea catechins (caffeine:75 mg/day; catechins: 483 mg/day).

Green tea in the doses used in weight control trials has been shown to be free of side effects. The most common adverse effects from consuming large amounts (many cups per day) of green tea would be insomnia, anxiety and other symptoms caused primarily by caffeine.

Besides the benefits of green tea on body weight reduction, there are evidences indicated other health beneficial effects such as lowering cholesterol levels, reducing platelet aggregation, lowering blood pressure, as well as other positive properties such as antioxidant and anticancer effects.

Cellasene:

It is a herbal supplement sold for improving the appearance of cellulite. It contains *ginkgo biloba*, sweet clover, seaweed, grape seed oil, *fucus vesiculosus* extract, fish oil and evening primrose oil. Clearly, looking from the ingredients, this product is effective through various mechanisms [26]. *Ginkgo biloba* extract is known for its benefits to promote blood circulation and stimulate the metabolism of fat. Sweet clover extract is claimed to increase blood circulation and assist in the removal of fluid build-up. The grape seed is believed to be powerful antioxidants that protect cells and blood vessels from damage. Dried *focus vesiculosus* is known to stimulate metabolism, and help reduce localized fats. Finally, evening primrose oil and fish oil, rich in polyunsaturated fatty acids, are source of energy that may increase metabolism and help reduce saturated fatty acids. The efficacy of the product is unclear. A 8-week study was carried out at a hospital in Italy, which indicated that Cellasene decreased hip and thigh circumference in more than 90% of patients and improved appearance of cellulite in more than 80%. However, there were only 25 women participated and 15 of them received placebo [50]. However, the efficacy of the product was tested by a parallel placebo-controlled clinical study done in 11 women over a period of 2 month, and has found no significant changes in body weight, fat content, thigh circumference, hips. Rather, seven of 11 women gained weight. Only 3 of women of Cellasene group thought that their cellulite had slightly improved [51]. The information regards to Cellasene effectiveness, as well as safety issues is very limited, and left to be further investigated.

Caffeine /Ephedrine mixture [52-54]

As mentioned, caffeine is β-adrenergic agonists, inhibiting phosphodiesterase, which leads to lipolysis process, and ephedrine is a central nervous system stimulant. In the 20-week study performed to investigate efficacy and safety of a caffeine/ephedrine (CE) mixture in obese children, two groups were either given CE mixture or placebo as well as were put on restricted diets. Those weighing less than 80 kg took one tablet three times (100 mg ephedrine/10 mg caffeine), whereas those weighing more than 80 kg took two tablets three times per day. The decrease in relative body weight, body mass index (BMI), and body fat was significantly greater in the CE group than in the placebo group. Relative body weight decreased by more than 5% in 81% of the CE group, but only in 31% in the placebo group. As for safety concerns, adverse

effects were negligible and did not differ between the two groups. In other experiments of period of 6 month and 12 week randomized, double-blind placebo controlled trial, given 90/192 mg/day ephedrine/caffeine), and herbal supplements containing ephedrine, caffeine, other herbal ingredients, respectively, produced similar results of body weight and body fat reduction without significant adverse events.

Although the results of given mixture of ephedrine/caffeine are quite positive, the longer period study at different conditions are still needed.

Capsaicin and other pungent spices

The pungent spices in foods have potential effects on thermogenesis and fat oxidation. The chemicals contribute to their pungency are the capsaicinoids (capsaicin and dihydrocapsaicin) and capsaicinoid-homologues (gingerols and shogorals), which are found in red pepper, Tabasco sauce, mustard and ginger. Capsaicin has been reported to act by stimulating catecholamines secretion from sympathetic activation of the central nervous system. There is a study showing that chilli and mustard have thermogenic effects. A 25% greater increase in metabolic rate over 150 min was observed with a meal containing 3 g of chilli sauce and 3 g of mustard sauce compared to nonspiced control meal. Another study showed the addition of red pepper (10 g; capsaicin: 30 mg) to a meal increased energy expenditure by 23% after the meal [37].

Orlistat

It is a prescription medication to help people lose weight. It is approved by US.FDA for treating overweight and obese people. Orlistat has a unique molecular structure, which allows it to bind to the active site of GI lipase and block that enzyme's activity. The enzyme is thus unable to break triglycerides down into their component parts. A significant proportion of dietary fat therefore remains undigested and unabsorbed, passing through the GI tract unchanged. However, 70% of ingested fat is digested in the normal fashion, ensuring sufficient absorption of fat-soluble vitamins [55]. On average, Orlistat results in obese people losing an additional 3-4% of their initial body weight over diet alone during a 2 year period. However, there was no strong evidence that this short-term weight loss would have a longer-term impact on morbidity and mortality [56]. A very large group study in 11,131 women, and 4,418 men with average body mass index (BMI) 34.7 kg/m2 and mean duration of obesity 13.7 years,

patients were advised to take orlistat 120 mg three times daily. After 7.1 months, 87% of women and men lost weight >5% weight and 51% lost >10% weight. Compared with baseline, 65% of the patients agreed that their general state of health has improved. For more than 90% of the patients, physicians described the success of the treatment as satisfactory, and 62% of patients were willing to continue with the treatment [57]. Orlistat in the treatment of obesity. Further research is needed, not only to clarify the longer-term impact of Orlistat treatment, as well as other related safety issues.

It is seen that there are numbers of studies both in topical and oral products in determining their efficacies, as well as the numbers of products available in the market [appendix D]. Although most of case studies of active ingredients, both natural and synthetic, proved positive effects on the improvement of cellulite appearance, or body fat reduction, there are still some questions left regarding safety issues. Most of the studies conducted were all in short periods and usually last for only a couple of weeks or a few months. Long- term assessment in a big group is still necessary, especially for oral treatments, in which safety issue is so crucial. As mentioned, degree of cellulite appearance becomes worse in overweight, obese people, since cellulite is directly related to fat tissues. Overweight/obese people often face other health problems, such as heart disease, and diabetes. Thus, they are on prescriptions, and issues still remain on how these supplements interact with those prescribed drugs. Another interesting point, to the extent of information gathered, is that there is no plants or active compounds that are claimed to have an effect on female hormone level, and there is no studies conducted among menopause women.

As described, many plants offer benefits through various mechanisms differently in targeting cellulite. Therefore, there are no doubts why conducted studies used combination of herbal sources for efficacy assessment. From literature reviews, although various studies have been performed, comparison studies for each plant's activity still remains unknown.

In summary, studies done on efficacy of various active ingredients can be found in the following table 4.5

Table 4.5 Summary of case studies of weight loss products

ACTIVE INGREDIENTS	PERIOD	RESULTS
CLA mixed 1.8 g/d	12 weeks	Body fat ↓ 4%
HCA 600 mg/d	2 weeks	24-hour energy intake ↓, body weight ↓
Green tea (Caffeine 150 mg/d, catechins 375 mg/d)	12 weeks	Body weight ↓ 4.6%, waist circumference ↓ 4.5%
Green tea (Caffeine 75 mg/d, catechins 483 mg/d)	12 weeks	Body weight ↓, waist circumference ↓
Cellasene	2 months	No change in body weight, fat content, thigh circumference
Caffeine/Ephedrine mixture (192/90 mg/d)	6 months	Body weight ↓, body fat ↓
Capsaicin 30 mg	After a meal	Energy expenditure 23% increase

Similar to the topical approach, the studies conducted were not applied the same protocols in specified criteria of volunteers, as well as the lack of long term studies to see efficacy of the active ingredients.

CHAPTER V

CONCLUSION AND SUGGESTION

Cellulite or orange peel-like skin increasingly becomes an aesthetic skin problem for women today. It is found commonly in the areas of buttocks and thighs, and evidently found more in women than in men, because of different in biological factors.

Although found commonly in overweight/obese individuals because of heavier pressure and more fat tissue, skinny people also face cellulite problem. If the degree of cellulite becomes severe, not only aesthetic problem individuals are facing, but also the pain is evolved.

The causes of cellulite are the most controversial topic among professionals, which led to many hypothesis and investigation of skin pathologies. Although noone has yet concluded the main roots, there are scientific evidences supported on how cellulite occurs, and the treatments of course counteract the causes. In short, cellulite can be treated via three mechanisms as follow;

1. Decreasing adipocyte contents (promote lipolysis, prevent lipogenesis),
2. Strengthening and protecting fundamental substances and connective tissues,
3. Improving microcirculation.

These three mechanisms can be achieved through various methods; instrumental, topical, and oral approaches. Instrumental approach is perhaps a rather invasive choice, consuming time, as well as requiring expert supervision. Other alternatives of using topical or oral treatments perhaps are more easily accessible, natural, and user friendly. Topical method is considered very safe, but the result might not soon become very visible, especially if the degree of cellulite is more than 2. It must therefore is needed in combination with massage to stimulate microcirculation and enhance percutaneous absorption. Delivery system is the key success for topical products, since fat tissue is located deep below the dermis. Besides, activities of plant extracts often are associated with anti-oxidants properties, thus, preserving activities of the herbal

ingredients from degradation is very important for successful improvement of cellulite appearance. Advanced technologies such as nanotechnology may help in developing new delivery systems to target at preferable sites, while preserving essential elements.

As for oral treatment, which can be acquired through food, supplements, and prescribed drug, is another option. Some food such as green tea, offer several advantages besides body mass reducer, but also having antioxidant benefits. However, since cellulite is related directly to fat, obese people usually face other health problems, and having high chances that they are on prescriptions. Lipolysis process is associated with metabolic function, dealing with role of insulin, which is closely related to disease such as diabetes. Therefore, a closer examination between drug and supplement interaction is needed for safety issues. In short, factors influencing selection and application of each method are;

1. Scientific support for efficacy both qualitatively and quantitatively of active ingredients.
2. Safety and toxicology
3. Ingredient sources
4. Dosage used
5. Delivery system
6. Availability to consumers

However, due to many factors contributed to cellulite development, other considerations besides what have mentioned above such as eating and exercising behaviors are also very important. Topical cream and supplement may temporarily improve cellulite appearance, but they do not give promises for sustained results. Diets and exercise contribute to the formation of cellulite. Thus, it is fundamental importance to monitor diet, as well as exercise regularly.

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APPENDIX A

Market data of import and export of beauty products

Import of Beauty products*

Billions of Thai Baht

Period: January-June

	2005	2006	2007	% Change
France	0.643	0.565	0.495	-12.43
The United States	0.729	0.587	0.709	20.82
Japan	0.464	0.494	0.459	-7.03

Export of Beauty products*

Billions of Thai Baht

Period: January-June

	2005	2006	2007	% Change
The World	2.299	2.829	3.255	15.05

* Beauty Products include face and skin care, make-up powder, eye make-up, lip make-up and nail preparations.

APPENDIX B

Summary of conjugated linoleic acid's effects on body mass in human studies

References	Dose (g/d)	Subjects (BMI, kg/m^2)	n	Duration	Results[a]
Atkinson (1999)	2.7	MF (28–30)	80	6 months	↓ BF, – BW, ↓ BFG
Blankson et al. (2000)	1.7, 3.4, 5.1, 6.8	MF (25–35)	47	12 wk	↓ BF, – BMI, ↑ FFM with 6.8 g
Berven et al. (2000)	3.4 (4.5 g 80%)	MF (27–39)	55	12 wk	↓ BW, ↓ BMI
Zambell et al., 2000	1.95	F	17	8 wk	– FFM, – BF, slight ↓ BW – energy expenditure
Riserus et al. (2001)	4.2	M (32)	24	4 wk	↓ SAD, – BMI, – BW
Smedman and Vessby (2001)	4.2	MF (25)	53	12 wk	↓ BF, – BW, – BMI, – SAD
Mougios et al. (2001)	0.7 and 1.4	MF (<30)	22	4wk each Total 8wk	↓ BF
Thom et al. (2001)	1.08	MF (<25)	10	12 wk	↓ BF, – BW, – BMI
Riserus, Arner, et al. (2002)	3.4, mix or 10,12	M (27–39)	57	12 wk	↓ BF, ↓ SAD, – BMI, – BW (↓ BW, ↓ BMI for *t*10,*c*12 only)
Kreider et al. (2002)	3.9	M [exercise]	23	4 wk	– BM, – FFM, – BF, – bone M, no benefit of exercise
Noone et al. (2002)	3 (50:50, 80:20)	MF (<25)	51	8 wk	– BW [exercise]
Kamphuis et al. (2003a)	1.8 or 3.6	MF (28)	54	13 wk	– BWG, favorable appetite effects
Kamphuis et al. (2003b)	1.8 or 3.6	MF (28)	54	13 wk	– BWG, ↑ FFM gain, ↓ BF ↑ resting metabolic rate
Belury et al. (2003)	6	MF [T2DM][b]	21	8 wk	↓ BW, ↓ BF with *t*10,*c*12
Gaullier et al. (2004)	3.4, TG, FFA	MF (25–30)	180	1 yr	↑ FFM, ↓ BW, ↓ BMI, ↓ BF ↓ Bon Mass
Malpuech-Brugere et al. (2004)	1.5 or 3 g of *c*9,*t*11 or *t*10,*c*12	MF (overweight)	81	18 wk	Slight ↓ BF (both isomers) – BW, slight ↓ BF
Riserus, Vessby, Arner, et al. (2004)	3.4, mix or 10,12	MF (30)	57	12 wk	Slight ↓ BMI
Riserus, Vessby, Arnlov, et al. (2004)	3 (83% mainly *c*9,*t*11)	MF (27–35)	25	12 wk	Slight ↓ BMI, ↓ BW, – BF
Eyjolfson et al. (2004)	3	MF	16	8 wk	– BW, – BMI, – BF
Whigham et al. (2004)	6	MF (27–35)	47	16 wk+ 24 wk	– BW, – BF
Gaullier et al. (2005)	3.4	MW	134	2 yrs	↓ BF, ↓ BW, ↓ BMI
Larsen et al. (2006)	3.4	MW (>28)	83	1 yr	– BWG, – BFG, – FFM (weight gai period)

[a] ↑ increased; ↓ decreased; –, no change; M, male; F, female; **TG**, triacylglyceride; FFA, free fatty acid; **BW**, body weight; BMI, body mass index; **B** body fat; FFM, fat free mass; BWG, body weight gain; **FMG**, fat mass gain; slight indicates non-significant change.
[b] Type 2 Diabetes mellitus.

Source: Ref. 8

APPENDIX C

Change in laboratory results in using conjugated linoleic acid

Change in laboratory results in phases 1, 2, and 3 (±SEM)

	Change from baseline to week 12			Change from weeks 12 to 28			Change from weeks 28 to 52		
	Placebo	CLA	*p*	Placebo	CLA	*p*	Placebo	CLA	*p*
Cholesterol (mg/dl)	−40.1 ± 5.1	−27.7 ± 4.8	NS	33.1 ± 5.3	19.2 ± 4.8	0.054	−2.7 ± 5.5	5.7 ± 4.8	NS
LDL (mg/dl)	−33.5 ± 4.9	−22.5 ± 4.5	NS	20.2 ± 5.0	12.1 ± 4.5	NS	5.1 ± 5.2	4.9 ± 4.5	NS
TG (mg/dl)	−37.0 ± 11.2	−32.2 ± 10.3	NS	12.6 ± 11.6	26.3 ± 10.3	NS	3.3 ± 11.9	−4.2 ± 10.3	NS
HDL (mg/dl)	0.3 ± 2.3	−0.3 ± 2.1	NS	10.3 ± 2.3	2.1 ± 2.1	0.01	−8.3 ± 2.4	1.5 ± 2.1	0.003
Hematocrit (%)	−1.0 ± 0.8	−0.8 ± 0.7	NS	0.1 ± 0.8	−0.7 ± 0.7	NS	−2.4 ± 0.9	−1.2 ± 0.8	NS
WBC (cells/m^3)	−1.03 ± 0.33	−0.97 ± 0.31	NS	0.90 ± 0.34	1.36 ± 0.31	NS	−0.52 ± 0.35	−1.06 ± 0.31	NS
Lymphocytes (%)	1.8 ± 2.8	0.3 ± 2.6	NS	5.9 ± 3.0	−0.3 ± 2.6	NS	0.5 ± 3.1	8.2 ± 2.7	NS
Neutrophils (%)	−1.2 ± 3.2	−2.3 ± 2.9	NS	−5.2 ± 3.3	2.5 ± 2.9	NS	−3.1 ± 3.4	−9.4 ± 3.0	NS
Monocytes (%)	−0.3 ± 1.8	−0.1 ± 1.6	NS	−1.9 ± 1.8	1.6 ± 1.6	NS	2.0 ± 1.9	−2.1 ± 1.6	NS

NS = not significant ($p > 0.05$).

Source: Ref. 13

APPENDIX D

Examples of topical anti-cellulite products in the market

Brand	Product Name	Active Ingredients	Dosage Forms
Biotherm	Celluli Intense Peel	Caffeine, Gingko, Salicylic Acid, Glycolic acid	Gel
L'Oreal	Sublime Slim(Day)	Caffeine, Par-Elastyl	Gel
Yves Rocher	Lipo Phenol Vegetal	Caffeine Extract	Cream
Dior	Plasticity Anti Cellulite Gel	Grape seed extract	Gel
Phytomer	AgeDeclic Firming Cream	Seaweed extract	Cream
Roc	Retinol Anti-Cellulite Expert Modelling	Retinol, Caffeine, Carnitine	Gel-cream
Espa	Detoxifying Body Oil	Essential oil(citrus, eucalyptus)	Massage oil
Shiseido	Body Creator Aromatic Sculpting Gel	Pepper, Taragon	Gel
Clarins	Total Body Lift	Caffeine, Mint oil	Gel
Payot	Triple Action Smoothing Gel	Retinol Complex	Gel-Cream
SK-II	Body Designer	Pitera body niacin complex	Gel
Chanel	Firming & Shaping Gel-Anti-Cellulite	Purple Bengle (from Indonesia)	Gel
Lancome	Body Sculptesse Gel	Pea Extract complex	Gel
L'Occitane	Almond Shaping Gel	Almond protein extract	Gel

source: Cellulite Buster, Elle magazine 2007; 150(4): 350-9.

APPENDIX E

Interview Questions

1. Do you have customers/patients with cellulite problems?

2. Who are they? (Race, gender, age, body weight)

3. What are the areas of cellulite often get treated?

4. What are the methods that are available at your place?

5. How do you make your recommendations?

6. What are the procedures?

7. What are some benefits and drawbacks for those methods?

8. Are there any complications, precautions, pain involved in those methods?

9. What about expenses for the methods recommended?

10. What are the new technological equipments available in the market?

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