
Botanical Extracts Used in the Treatment of Cellulite

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BACKGROUND. Cellulite is defined as skin relief alterations that give the skin an orange peel or mattress appearance. The lesions tend to be asymptomatic and may be considered the anatomic expressions of the structures in the affected area, such as the fat and subcutaneous septa.

OBJECTIVE. The present article reviews the most important botanical extracts used as active ingredients in the treatment of cellulite, as well as the steps to obtain these botanicals as raw material and their standardization and quality control, which are important to guarantee their therapeutic action.

METHODS. The current literature was reviewed, and we also obtained information from the manufacturers of the products that

contained botanicals because of the few publications about this subject.

CONCLUSIONS. The reduction in fat deposits through the continuous use of anticellulite products depends on the availability of the active ingredient at the action site, the concentration of the ingredient in the formulation, and the physiochemical characteristics particular to each active ingredient. The botanicals used in topical products must have standardized extracts, which would permit each phytomedicine to have the same effect anywhere in the world. New scientific research is necessary to verify the efficacy and ideal concentrations of such substances.

DORIS HEXSEL, MD, CECILIA ORLANDI, MD, AND DEBORA ZECHMEISTER DO PRADO, PHARM, HAVE INDICATED NO SIGNIFICANT INTEREST WITH COMMERCIAL SUPPORTERS.

THE TERM “cellulite” is used to characterize alterations to the skin surface that give the skin an orange peel or mattress appearance. It usually occurs in females, and the most affected areas are the thighs and buttocks. In recent years, people have been looking for more “natural” products, and an increasing number of botanical extracts are available to treat not only diseases but also cosmetic problems, such as cellulite.¹⁻⁴ The active botanical ingredients used in topical products for the treatment of cellulite should be capable of activating the circulation and aiding fat metabolism and lymphatic drainage. They can be administered orally or topically as creams, gels, or lotions or by mesotherapy, a method involving local injections that is used in some countries.

This article reviews the most important botanical extracts used as active ingredients in the treatment of cellulite, as well as the steps to obtain these botanicals as raw material and their standardization and quality control, which are important to guarantee their therapeutic action.

Cellulite

Cellulite is also called edematous sclerotic-fibrous-edematous paniculopathy atrophic panniculitis, cellulitic hypodermosis, panniculosis of the dermis, gynoid lipodystrophy, and multiple other names.⁵⁻⁷ It results from many complex events that involve the epidermis, dermis, and subcutaneous tissue.⁸ The most current theory is that of lymphatic drainage disruption, which states that the obstruction of both lymphatic and vascular flow leads to an increase in localized fat, leading to cellulite.¹

Cellulite affects the majority of postadolescent women and is usually related to the influence of estrogens. These hormones lead to the production and retention of fat, especially in the buttocks and thighs. The number of adipocytes in certain regions in women is five times larger than in other regions.⁹

The orientation and anchoring of fascial bands from the dermis to the deep fascia are vertical in women. These bands form fibrous septa, which constitute real “pockets” that store fat in a way similar to a mattress, and the fat is projected into the reticular and papillary dermis. An increase in dermal glycosaminoglycans has been found in these areas, and they produce greater water binding. When the process of cellulite progresses, the nerves and capillaries that run through the septa are compressed and may produce localized pain in the palpable nodules. They may also be strongly involved in the pathophysiology of this condition. The qualitative and quantitative modification

All pictures in this article were taken by one of the authors (D.H.) at the Botanical Gardens in Rio de Janeiro, Brazil.

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of fatty acids is produced by peroxidation by free radicals. All of these phenomena contribute to the worsening of microcirculation in lymphatic and venous systems and disrupt venous and lymphatic drainage.¹⁰

Most treatment methods work by stimulating lymphatic and vascular flow and drainage. Adipose cell fat comes from plasma-circulating lipoproteins. There is a dynamic process in which the stored fat is hydrolyzed and eliminated again to the plasma as free fatty acids and glycerol. Different enzymes, such as insulin and cyclic adenosine monophosphate (AMP), participate in this process.

On the surface of the adipocyte, there are receptors that promote the storing of fat and lipogenesis, such as $\alpha 2$ and neuropeptide Y. On the other hand, there are other receptors that promote the elimination of fat and lipolysis, such as β_1 and β_2 .¹¹

Triglyceride lipase is the most important enzyme that promotes lipolysis. This enzyme is activated by adenylyl cyclase stimulation by means of an antagonist effect. This inhibitory process causes triacylglycerol hydrolysis and releases free fatty acids and glycerol into the interstitial space and plasma.³

Cellulite Botanical Formulation Design

The clinical efficacy of botanical formulations depends not only on the pharmacologic properties of the active ingredient but also on its availability at the action site.¹²⁻¹⁴

The botanical extracts contained on topical products need to pass through the corneal stratum, which represents the main barrier, and reach the inner layers of the skin. However, the clinical efficacy of many active ingredients is limited owing to their inability to penetrate this barrier.^{13,14} For this reason, topical formulations include skin enhancers, which are substances capable of augmenting cutaneous penetration of the active ingredients. Skin enhancers are the solvents, vehicles, and surfactants that are selected on technical criteria, according to the physico-

chemical characteristics of each active ingredient. In recent years, advances in the pharmaceutical industry have led to new technologies, which facilitate the delivery of the active ingredients to the action site.

Formulations taken orally or via injection also have to reach the action site. Such formulations also include elements that facilitate the delivery of the active ingredients to the action site and are designed to have good absorption and a low incidence of secondary effects. The main concern with products taken orally is that their action mechanism is not debilitated during their passage through the liver. Although the design of injectables is more detailed, among other cautions, extreme care should be taken to ensure the sterility of the formulation.

Active Botanical Ingredients of the Products Employed in the Treatment of Cellulite

The aim of using active substances in topical treatments for cellulite is to reduce lipogenesis and activate lipolysis, helping to restore the normal structure of the subcutaneous tissue¹³ and acting as anti-free radicals. These active ingredients should be capable of stimulating the circulation and aiding fat metabolism and lymphatic drainage.¹⁵ Such products normally come in the form of creams, lotions, and gels.

Methylxanthines

Methylxanthines are classified as β -agonists and are the main category with documented action in the treatment of cellulite.^{3,8,16,17} The main methylxanthines obtained from botanical extracts are caffeine, theobromine, and theophylline.

The most useful and safest methylxanthine is caffeine, which is normally used at a concentration of 1 to 2%. It penetrates the skin very easily, which facilitates its absorption and action.¹⁸ Caffeine acts directly on adipose cells,

Table 1. Principal Methylxanthines and Respective Plants (Fonts) Used in Cellulite Treatment

Methylxanthine	Botanical Species
Caffeine	Coffee, <i>Coffea arabica</i> (Rubiaceae) originally from Ethiopia (Figure 1)
	Green tea, <i>Camellia sinensis</i> L (Theaceae), originally from China, Japan, and Indonesia
	Cacao, <i>Theobroma cacao</i> L (Sterculiaceae), originally from the Amazon rain forest
	Guarana, <i>Paullinea cupana</i> , <i>Paullinea sorbilis</i> (Spindaceae), originally from the Amazon rain forest
	Maté, <i>Ilex paraguariensis</i> (Aquifoliaceae), originally from South America
Theobromine	Cola or African colatier, cola nut, <i>Cola acuminata</i> , originally from Africa
	Green tea, <i>Camellia sinensis</i> L (Theaceae), originally from China, Japan, and Indonesia
	Cacao, <i>Theobroma cacao</i> L (Sterculiaceae), originally from the Amazon rain forest (Figure 2)
	Black tea, <i>Thea sinensis</i> R (Theaceae), originally from the Himalayas
Theophylline	Maté, <i>Ilex paraguariensis</i> (Aquifoliaceae), originally from South America
	Green tea, <i>Camellia sinensis</i> L (Theaceae), originally from China, Japan, and Indonesia
	Cacao, <i>Theobroma cacao</i> L (Sterculiaceae), originally from the Amazon rain forest (see Figure 2)
	Black tea, <i>Thea sinensis</i> R (Theaceae), originally from the Himalayas
	Maté, <i>Ilex paraguariensis</i> (Aquifoliaceae), originally from South America



Figure 1. (A and B) The *Coffea arabica* plant from which caffeine is extracted for use in the topical treatment of cellulite.

promoting lipolysis, inhibiting phosphodiesterase, and thus augmenting cyclic AMP.³ They activate the triglyceride lipase enzyme and transform triglycerides into free acids and glycerol. Caffeine also has a stimulating effect on the cutaneous microcirculation. A clinical study testing caffeine demonstrated the efficacy of this substance. The better reported results were with caffeine included in liposomes.¹⁹

The methylxanthines used in cellulite treatments are usually obtained from the leaves of the species listed below (Table 1).



Figure 2. Theophylline is obtained from the *Theobroma cacao* L. plant.

Clinical studies show increasing levels of free fatty acids in plasma after the topical application of these compounds, demonstrating a lipolytic effect.²⁰ Plasmatic concentration of caffeine, after 1 month of topical use of 1 g daily in a hydroalcoholic gel, is equivalent to 25% of the quantity we get after drinking one cup of coffee.²¹

There are reports of allergic reactions to topical products containing caffeine.²² There are also reports of cases of dermatitis in workers who handle the coffee grains, owing to the volatile oils present as constituents of the plant.²³

Bladderwrack (*Fucus vesiculosus* L.)

Bladderwrack is a brown marine algae that contains sulfated polysaccharides, iodine compounds, and alginic acid. It belongs to the family Fucaceae and is found on the shore of the north Pacific and north Atlantic oceans. The part used for the elaboration of the extract is the whole dried thallus.²⁴

Bladderwrack is reported to produce the contraction of the fibroblast-populated collagen gel through the increased expression of integrin molecules.^{25,26} The extract of this plant is usually used at a concentration of 1%.⁶ In cellulite, its action is related to the increased density of the connective tissue, and it has a stimulating effect on vascular flow.

Butcher's Broom (*Ruscus aculeatus*)

This phytomedicine is from the Liliaceae family, and its habitat and range are woods, bushy places, and dry hills in Europe.²⁴

This is a potent venous vasoconstrictor agent, and it has a diminishing edema effect. It acts as an agonist on α -adrenergic receptors of the smooth muscle of veins and reduces vascular permeability.²⁷ In the elaboration of the

extract of butcher's broom, the rhizome and flowering tops are used because they contain the main active ingredients, saponins, ruscogenin, and neoruscogenin.²⁸ The extract of this plant is usually used at a concentration of 1 to 3%.²⁹

Ginkgo (*Ginkgo biloba* L.)

Ginkgo biloba is a member of the Ginkgoaceae family. The leaf extracts contain substances such as flavonoids (eg, quercetin, campherol epicathecol derivatives), biflavons (ginkgetin), and terpenes (ginkgolide B), among others.²⁴ *Ginkgo biloba* is used in the treatment of cellulite owing to its numerous effects on peripheral circulation, such as reducing blood viscosity. The terpenes, especially ginkgolide B, inhibit the platelet-activating factor.²⁴ They increment red globule deformability, diminish vascular permeability, and improve vascular wall tonus. All of these actions produce improved microcirculation.

Ginkgo biloba also has flavonoids, which act as antioxidant and anti-inflammatory agents.²⁴ In topical formulations, the glycolic extract is used in a concentration of 5 to 10% and the dried extract in 0.2 to 2% concentration. The irritant chemical constituent is ginkgolic acid.²³ There are some reports in the literature of cases of hypersensitivity to *ginkgo* contained in anticellulite products.²² The recommended concentration is 1 to 3%.

Chofitol or Artichoke (*Cynara scolymus*)

This is a member of the Arteraceae family, and it is found in rich soils in the northern Mediterranean. The parts of the plant used to produce the extract are the leaves, flower heads, and roots.²⁴ Its principal active chemical constituents are numerous enzymes, cynarin, ascorbic acid, caffeoylquinic acid derivatives, and flavonoids.²⁴ It has an antiedema and diuretic effect, as well as a stimulating effect on the circulation.²⁴

Common Ivy (*Hedera helix*) and *Ground Ivy* (*Glechoma hederaceae* L.)

Common ivy is a phytomedicine that grows in places with rich soil, sun, or shade. It originally came from Europe and was later introduced into North America.

The parts of the plant used are dried leaves and stems. The leaves have flavonoids, such as rutosid and rutinoid, and saponins, such as hederin, hederacosid, and hederagenin.^{24,30}

The fruits have saponins, especially hederin, and the trunk has gomoresins and saponins. All saponins improve venous and lymphatic drainage and reduce edema. One of these compounds, hederin, also has an analgesic and anti-inflammatory effect. It has vasoconstrictor and antiexudative proprieties and can also reduce capillary permeability. It activates the circulation and so assists drainage of the

infiltrated tissue and reduces inflammation. On the other hand, there are reports of allergic reactions, more than 65 cases, in patients who used topical products containing ivy.²² The leaves of this plant are considered poisonous when ingested²³ because they contain arsenic oxide.

Ground ivy is from the Lamiaceae family and is also used in anticellulite treatment. The main constituents are flavonoids, triterpenoids, and phenolic acids. It grows in moist soil in Europe, especially the Caucasus, and in North America.²⁴

Both types are used in concentrations of 2%.

Indian or Horse Chestnut (*Aesculus hippocastanum*)

This plant belongs to the Hippocastanaceae family. The seeds and the shells are used in the elaboration of the standard extract.³¹ The active ingredients contained in the seeds are triterpenoid saponins, such as aescin and aesculin, and flavones, coumarins, and tannins,³¹ with anti-inflammatory and antiedema properties.³² Escin is the principal component of horse chestnut, and it has the capacity to reduce lysosomatic enzyme activity by up to 30%, probably by stabilizing the cholesterol content of the lysosome membranes, thus reducing enzyme release and capillary permeability.³³ Hypersensitivity has been reported in users of products containing this ingredient.³⁴ The recommended concentration is 1 to 3%.

Sweet Clover (*Melilotus officinalis*)

This is a plant from the Fabaceae family. The active ingredient is contained in the flowers and leaves. One of the components of this botanical extract is coumarin, which reduces lymphatic edema and diminishes capillary permeability.³⁵ It is usually recommended to patients with chronic venous insufficiency and lymphatic congestion, conditions that are believed to be associated with cellulite. The recommended concentration is 2 to 5%.³⁵

Centella Asiatica, *Asiatic Hydrocotyle*, *Gotu Kola* (*Hydrocotyle asiatica*)

Centella asiatica is a member of the Apiaceae family. The parts of the plant used are leaves and roots.²⁴ The principal active compounds are asiaticoside, madecassic acid, and Asiatic acid. Asiaticoside is a potent healing agent that is the most widely known property of this plant. Madecassic acid has an anti-inflammatory effect^{36,37} and is used at concentrations of 2 to 5%.

Centella asiatica is also used in oral therapy and mesotherapy.

Red Grapes (*Vitis vinifera*)

Red grapes are very rich in tannins, which are antioxidants that diminish lipid peroxidation. They have pro-

cianidins, which increase the permeability of lymphatic and microarterial vessels.³⁵ In topical products, the essential oil is used at a concentration of 2 to 7%.³⁵

There are some reports of dermatitis on the hands resulting from squeezing the fruit to obtain juice, which contains several acids, such as oxalic, malic, tartaric, and racemic.²³

Corynanth yohimbe, *Pausinystalia yohimbe*, and *Rauwolfia serpentina*

Yohimbe and alpha-yohimbine are alkaloid derivatives extracted from the leaves, shell, and roots of Rubiaceae and Apocynaceae.²⁴ They are sympatholytic drugs, adrenergic blockers capable of stimulating the burning of fat owing to the presence of alkaloids that act directly on the fat cells, stimulating their metabolism.^{24,38}

Papaya (*Carica papaya*) and *Pineapple* (*Ananas sativus*, *Ananas comosus*)

The fruits and leaves of these plants have anti-inflammatory and antiedema effects.^{33,39,40} They contain proteolytic enzymes, papain and bromelain, respectively. These plants are originally from tropical America and were introduced in southern Florida. The recommended concentration is 2 to 5%.

Dermatitis and eczema are rare conditions. They may be associated with the so-called "pineapple itch," which is due to a mite that infests pineapple plantations.²²

Quality from Botanical Raw Material

Plant Standardization

The inclusion of botanicals in the treatment of cellulite and other conditions requires parameters of standardiza-

tion. This represents a challenge because plants possess several and at times dozens of chemical substances mixed together. Such parameters principally involve criteria for the choice of the species used and the tracing of phytochemical variations during the process of the extraction of the active ingredients.

The initial process of standardization requires the collection of material from populations of plants of various origins, the registration and determination of the phytochemical profile, comparison with the desired standard, and evaluation of the plant's potential as a production source.⁴¹ When the phytochemical study of a plant is incomplete, as is the case with many plants from Brazil, there is a need to isolate and describe new molecules in order that the phytochemical profile of the species can be established and serve as a standard (Figure 3).

Quality Control

The quality control of botanicals can be described in the following steps^{24,41}:

- *Control of sources (original plants).* The botanical classification of the original plant is established, and a specialist provides a certificate. A phytochemical description based on the genetic load of the plant should be performed.
- *Control of planting.* At this stage, it is necessary to define the parameters for cultivation, such as climate, altitude, soil composition, and competition with other species (see Figure 1).
- *Control of botanical raw material.* The medicinal plant, once harvested, is called botanical raw material. The control of botanical raw material consists of some of the aspects listed in Table 2.

Table 2. Principal Aspects of the Control of Botanical Raw Material

Plant identification	Physical tests (organoleptic): comparison of the appearance, color, odor, taste of the botanical with a known reference standard, loss on drying, ash content, and microscopy Chemical tests include tests for solubility, thin-layer chromatography, etc.
Selection of the extraction method	Maceration, percolation, distillation, supercritical fluid extraction, countercurrent extraction, lipid extraction, etc.
Morphologic analysis	The proper method selection is essential to preserve the inherent property Carried out using a microscope or magnifying glass
Bacteriologic analysis	Identify the species and the foreign elements or contaminants present Inoculation in culture medium Identify contamination by bacteria with pathogenic potential in humans, such as <i>Salmonella</i> and <i>Shigella</i> , respecting internationally established limits for the quantity of contaminants in a batch
Chemical analysis	Gas chromatography, high-performance liquid chromatography, thin-layer chromatography, and spectrophotometric techniques, such as ultraviolet and infrared Verify organic and inorganic, molecular and elemental, qualitative and quantitative chemical botanical aspects of composition and verify the composition and presence of herbicides or chemical additives
Clinical and toxicologic controls	Same as those applied rigorously for other pharmaceutical products and that determine the validity and stability of the formulations



Figure 3. Area dedicated to the cultivation of medicinal plants in the Botanical Gardens in Rio de Janeiro.

Conclusion

The therapeutic value of medicinal plants is currently being researched and recognized in the scientific community, and their medical use is increasing. Despite the existence of a great number of anticellulite products, the reduction of fat deposits achieved through the continuous use of these products depends on a number of factors. Among them are the availability of the active ingredient at the action sites, the concentration of the ingredient in the formulation, and the physicochemical characteristics particular to each active ingredient. Moreover, the influence of other factors that affect cellulite, such as diet, physical exercise, and weight loss, hampers the evaluation of the response to treatment. Paradoxically, there is an indirect relationship between the range of products and active ingredients available and studies in the literature that verify their safety and efficiency in the battle against cellulite. New scientific research is necessary to verify the use of such substances.

The inclusion of botanical extracts in topical products has become necessary owing to present-day chemical knowledge, safety, and improvements. Although they may be recognized as medicine and produce expected results in the treatment of cellulite, it is necessary to be cautious with regard to the origin of these products and verify whether the raw materials are classified as standardized extracts. The standardized extracts are efficacious because they have a higher proportion of the active ingredients. Such standardization permits each phytomedicine to have the same effect anywhere in the world.

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Commentary

Cellulite is a condition that afflicts most postpubertal women in the United States. Any finding that is this common in a population certainly cannot be considered an abnormality or disease. Cellulite is simply part of being female. Yet this is not reassuring to patients. They want the cellulite gone!

It is truly amazing that something as ubiquitous as cellulite is so poorly understood. Several theories have been advanced to explain its presence. The theories fall under several categories: vascular, structural, and inflammatory.

Some investigators have postulated that cellulite is a degradation process initiated by deterioration of the dermal vasculature, particularly loss of the capillary networks. As a result, excess fluid is retained with the dermal and subcutaneous tissues. This loss of the capillary network is thought to be due to engorged fat cells clumping together and inhibiting venous return. After the capillary networks have been damaged, vascular changes begin to occur within the dermis, resulting in decreased protein synthesis and an inability to repair tissue damage. Clumps of protein are deposited around the fatty deposits beneath the skin, causing hard nodules composed of fat surrounded by hard reticular protein. Ultrasound imaging of skin affected by cellulite at this stage reveals thinning of the dermis with subcutaneous fat pushing upward, which translates into the rumpled skin known as cellulite.

Other investigators have observed that cellulite is more common in overweight and obese women. This is felt to be due to the presence of copious fat lobules within the subcutaneous tissue encased in fibrous septae with dermal attachments. These fibrous attachments surrounding abundant fat lead to the rumpled appearance of the skin characteristic of cellulite.

I happen to favor the inflammatory theory of cellulite. This theory maintains that cellulite is an inflammatory process resulting from breakdown of the collagen in the dermis, providing for the subcutaneous fat herniations seen on ultrasonography. The onset of cellulite with puberty and menstruation has caused some researchers to evaluate the hormonal changes necessary for sloughing of the endometrium. It appears that menstruation requires the secretion of metalloproteases (MMPs), such as collagenase (collagenase 1, MMP-1) and gelatinase (gelatinase A, MMP-2). The endometrial glandular and stromal cells secrete these enzymes to allow menstrual bleeding to occur. Collagenases cleave the triple helical domain of fibrillar collagens at a neutral pH and are secreted just prior to menstruation. However, the collagenase may break down the fibrillar collagens present not only in the endometrium but also in the dermis. With repeated cyclical collagenase production, more and more dermal collagen is destroyed, accounting for the worsening of cellulite seen with age. Eventually, enough collagen is destroyed to weaken the reticular and papillary dermis and allow subcutaneous fat to herniate between the structural fibrous septa found in female fat.

This article presented by Hexsel and coauthors describes some of the botanical agents in the cosmeceutical market to treat this condition known as cellulite. Botanicals can be safely used, but can they actually affect cellulite? Perhaps from a cosmetic aspect, they may provide improvement, but the elimination of cellulite at present remains a technical impossibility.

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