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abstract

Within the last couple of years a new weight loss strategy emerged with the findings that fat cells can be driven to burn fat instead of storing fat. This newly discovered type of fat cell is called brown fat cell and the process of turning fat storing cells into fat burning machines is called browning. We found that an ethanol extract of mustard sprouts induces browning of the skin fat tissue and thus is an ideal candidate to help in burning fat. To efficiently reduce cellulite appearance as well, the mustard sprout extract was combined with natural capsaicin to locally activate the microcirculation in the skin. This oil-soluble mixture activates two important mechanisms in the skin that help to visibly reduce cellulite and to shape the body.

Introduction

Adipocyte Browning – A Novel Mechanism to Burn Fat

The worldwide obesity problem is steadily increasing [1], which necessitates the search for new targets to combat the accumulation of fat tissue, also called adipose tissue. A highly interesting target for slimming and weight loss is a process called “adipocyte browning”. This recently unraveled mechanism stimulates fat-storing adipocytes to burn fat through thermogenesis, by generating heat. It was long thought that in humans, only newborns possess the ability to burn fat into heat as a protection from cold since they cannot shiver. Interestingly, it was recently discovered that apart from normal white adipose tissue (WAT), which is responsible for storing fat, adult humans possess a pool of brown adipose

tissue (BAT) [2-6]. These two types of fat cells differ in their composition, function, as well as lipid and mitochondria content (Fig. 1). Mitochondria are cellular organelles which are especially numerous in brown adipocytes. They are known as the powerhouse of the cell as they generate ATP, the universal energy carrier in our cells. They achieve this by using the electron transport chain to generate a proton (H^+) gradient at the inner membrane, which is then used to generate ATP (Fig. 2). When the ATP pool is filled up, the electron transport chain stops. In brown adipocytes however, a high expression of the protein UCP1 uncouples the electron transport chain from ATP by forming another channel through which protons leak. As a consequence, saturation of ATP will never be established, thus the electron transport chain will constant-

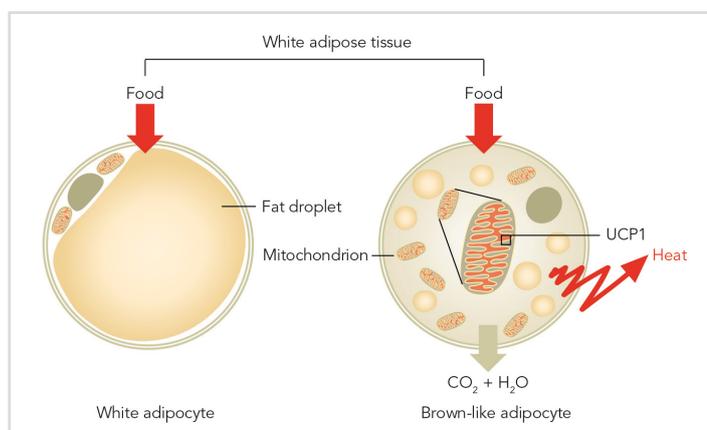


Fig. 1 Schematic representation of different characteristics of white and brown-like adipocytes. White adipocytes contain a large lipid droplet and few mitochondria whereas brown-like adipocytes contain a few smaller lipid droplets and a higher mitochondrial density. In brown-like adipocytes, the protein UCP1 is an important factor that mediates the transition from fat storing to burning fat into heat

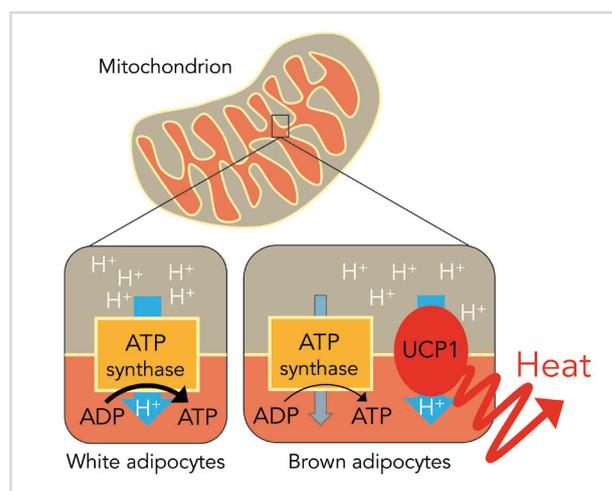


Fig. 2 Schematic representation of the differences in mitochondrial activity in white and brown adipocytes. In brown adipocytes, the proton gradient is short circuited by the protein UCP1 which leads to the generation of heat

ly continue, which will finally result in heat production [7] (Fig. 2). The use of glucose and fatty acids [8, 9] to fuel this process leads to an increase in basal energy expenditure and therefore promotes weight loss [10]. Therefore, adipocyte browning, which means stimulating the production of UCP1 that leads to the conversion of normal white fat cells into brown-like adipocytes, is a highly promising target for eliminating fat deposits.

The best known triggers for the induction of adipocyte browning are cold exposure [11] and activation of the beta3-adrenergic receptor that is present in fat cells [12]. Interestingly, it was shown that the beta3-adrenergic receptor is activated in mice by an ethanolic extract of *Brassica campestris* roots, a plant from the mustard family (*Brassicaceae*) [13]. This had an anti-obesity effect on these mice even when they were fed with a high fat diet. Therefore, plants from the mustard family are intriguing candidates to stimulate adipocyte browning.

What causes Cellulite and how Can it be Reduced?

Cellulite is characterized by an uneven skin profile, mostly on the upper thighs, abdomen and buttocks and affects around 90% of women [14]. The dimply appearance is caused by subcutaneous fat tissue that protrudes into the dermis. Additionally, decreased blood flow in this region of the body makes it difficult for lipids to be released from the adipose tissue. At the onset of cellulite development, the capillary network in the dermis and adipose tissue start to break down. This leads to the accumulation of fluids and suboptimal supply of oxygen. The metabolism of fibroblast cells in the dermis is disturbed resulting in dermal thinning which facilitates the protrusion of adipose tissue. A cosmetic active that increases local blood flow and induces adipocyte browning to burn fat would be an ideal candidate to reduce cellulite.

Mustard and Chili – Two Spicy Ingredients that Possess the Activity to Shape the Body

Here we investigate the effect on these two processes through treatment with a novel cosmetic active, ShapePerfection, an oil-based mixture of *Brassica alba* (Mustard) sprout extract and capsaicin, the spicy component of chili peppers (INCI: Brassica Alba Sprout Extract, Capsaicin, Caprylic/Capric Triglyceride; from here on named shaping active). Both components are known as vasodilators which can stimulate local blood flow. Capsaicin activates the release of the calcitonin gene-related peptide messenger, which is a potent vasodilator. The mustard sprout extract contains the glucosinolate sinalbin, which is known to induce a feeling of warmth after topical application. And mustard sprouts as members of the mustard family have a beta3-adrenergic

receptor activation potential and are therefore adipocyte browning inducing candidates.

In addition to the ability to stimulate microcirculation in the skin and adipocyte browning, we tested the effect of the active on body girth as well as cellulite appearance.

Materials and Methods

Induction of Adipocyte Browning

Human preadipocytes derived from abdominal plastic surgery were cultured in differentiation medium (DMEM supplemented with 2mM L-glutamine, 50 U/ml Penicillin, 50 µg/ml Streptomycin, 10% FCS, 20 µg/ml Insulin, 0.4 mM Indomethacin, 2 µM Dexamethasone, 1 mM IBMX) in the presence or absence (control) of 0.33% *Brassica alba* sprout extract for 7 days. Differentiation of adipocytes was controlled by analyzing the expression of differentiation markers by RT-qPCR (LightCycler System, Roche, Switzerland). Browning of adipocytes was investigated by measuring the expression of the brown adipose tissue markers UCP1 and ZIC1 by RT-qPCR.

Subcutaneous Microcirculation Measurement

A double-blind, placebo-controlled clinical trial was performed with 21 women (mean age 37.7 years). A small amount (max. 1 ml) of cream containing 2% shaping active and a corresponding placebo cream was applied on each of the volunteer's frontal part of the thighs with a cotton swab by a laboratory technician. Subcutaneous blood flow was immediately measured after application using a Laser Doppler DRT4 instrument (Moor Instruments, UK) for 75 minutes in 15 minute time intervals.

Clinical Study with Dermis-Hypodermis Junction Distance and Girth Measurements

A double-blind, placebo-controlled clinical trial was performed with 18 women (mean age 42.3 years) that presented cellulite on thighs (Curri's grades 2 & 3). Volunteers applied a cream containing 2% shaping active on the abdomen and one of their thighs and arms and a corresponding placebo cream on the other thigh and arm twice daily for eight weeks. The dermis-hypodermis junction distance was measured in triplicates using ultrasonography (DermaScan C, Cortex Technology, Denmark) and mean values were calculated out of two close replicas. Girth measurements on arms and thighs were performed in three areas in triplicates, measurements on waist and abdomen were performed in triplicates as well (Fig. 3).

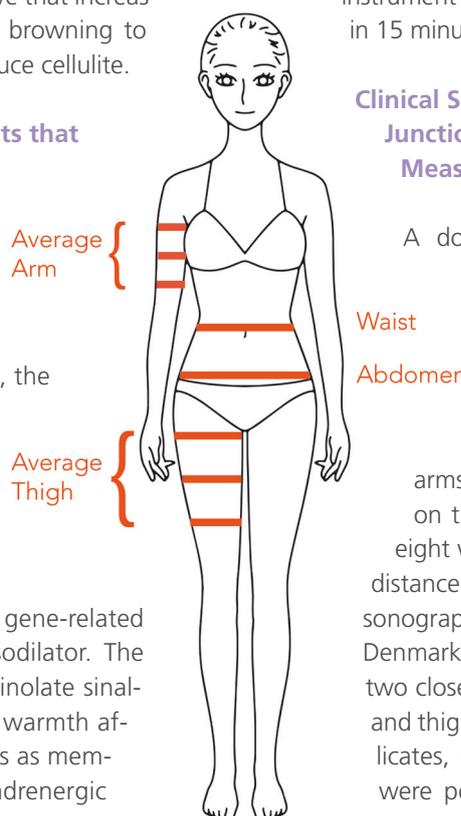


Fig. 3 Schematic representation of girth measurement zones

Additionally, photographs were taken with a Canon EOS 450D camera to document visible changes.

Results and Discussion

Brassica Alba Sprout Extract Induces the Expression of Brown Adipocyte Tissue Markers

In order to investigate whether components of *Brassica alba* are able to induce browning of adipocytes, preadipocytes were grown in a medium that induces adipocyte differentiation and treated or not with an ethanol extract of *Brassica alba* sprouts. Following adipocyte differentiation, expression of UCP1 [7] and another classical marker for brown adipocytes, ZIC1 [15], were measured in treated and untreated adipocytes. Differentiated adipocytes treated with 0.33% *Brassica alba* sprout extract expressed 125% more UCP1 and 86% more ZIC1 than control cells (Fig. 4), indicating that the treatment induced adipocyte browning.

Shaping Active Leads to Increased Subcutaneous Blood Flow

A single application of an emulsion containing 2% shaping active on the thigh of the volunteers had an instant effect on the increase of subcutaneous blood flow (Fig. 5) whereas the placebo emulsion had no significant effect on the microcir-

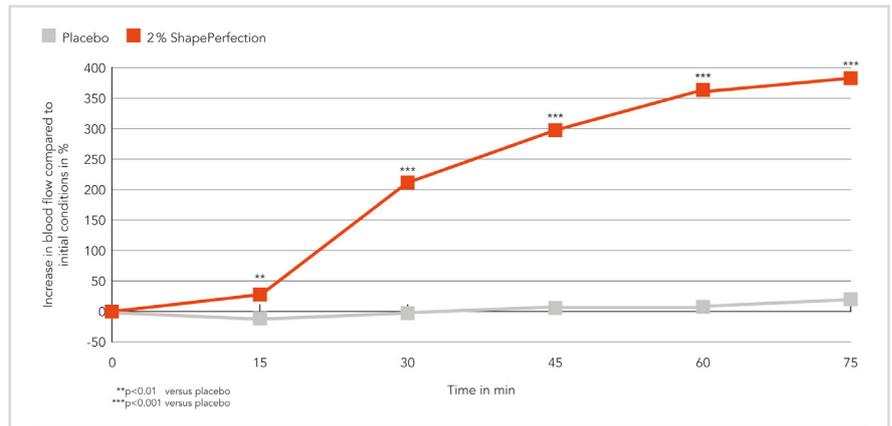


Fig. 5 Increase in subcutaneous blood flow immediately following a single application on the thigh

ulation. Although blood flow was increased by the shaping active, no redness or irritation was observed on the treated area in all volunteers.

A Slimming and Anti-Cellulite Effect of Shaping Active

As the *Brassica alba* sprouts extract induces adipocyte browning in vitro and a formulation containing 2% shaping active leads to higher microcirculation in the skin, one would expect that continuous application could lead to the reduction of the appearance of cellulite as well as a slimming effect. To test this, a placebo-controlled clinical study was performed where the dermis-hypodermis junction distance (DHJD) was measured as a readout for the severity of cellulite. The length of the junction between the dermis and hypodermis is increased if the junction is irregularly shaped, for example

when fat deposits protrude into the dermis. Therefore, a decrease in DHJD would correspond to a reduction in cellulite. After treatment with an emulsion containing 2% shaping active for 8 weeks, the dermis-hypodermis junction distance was reduced by more than 18% (Fig. 6). Additionally, circumferences of waist, abdomen, thighs and upper arms were measured before and after

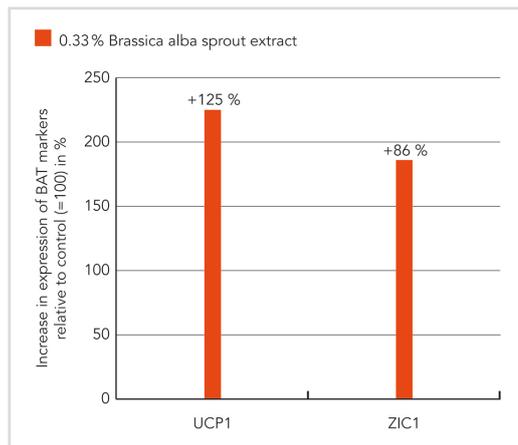


Fig. 4 Changes in gene expression of UCP1 and ZIC1 in adipocytes treated with *Brassica alba* sprout extract compared to control cells

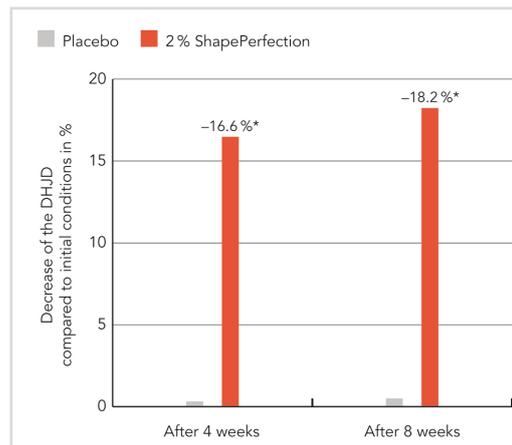


Fig. 6 Decrease of the dermis-hypodermis junction distance (DHJD) after treatment with 2% shaping active or the corresponding placebo cream

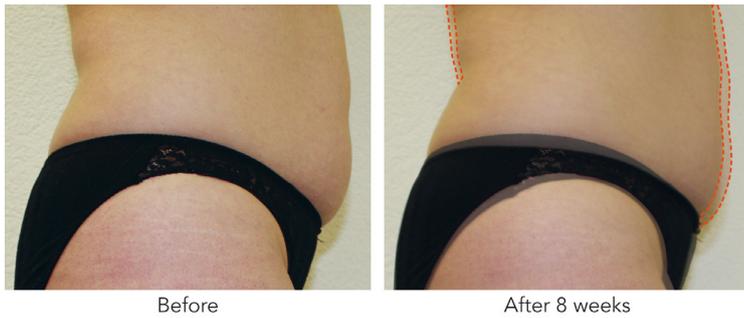


Fig. 7 Pictures taken before (left side) and after 8 weeks of treatment (overlay with the before picture, differences are indicated in red; right side) with 2% of the shaping active

8 weeks of treatment with 2% shaping active. A significant reduction in all measured mean circumferences was observed after 8 weeks of treatment: -3.4 cm in waist girth, -4.1 cm in abdomen girth, -0.9 cm in upper arm girth and -2.2 cm in thigh girth. This reduction was also visible in before and after pictures (**Fig. 7**).

Conclusion

Altogether, this shows that ShapePerfection is a novel cosmetic active that affects intracellular processes as well as vascular function, which together lead to a shaping effect and a visible reduction of cellulite.

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