Neuregulin-4: a key BATokine serving as a central hub for slimming efficacy

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Introduction:

While adipose tissue (WAT) is the primary store of lipids of the body and is naturally innervated reacting to different stimuli by secreting important signaling molecules, Neuregulin-4 (NRG4) is a Brown Adipocytes Tissue Adipokine (BATokine) with robust effects on lipid metabolism [1-2]. NRG4 release in WAT is downregulated in obesity [3] and increases upon cold/exercise stimuli. As main functions, it stimulates brown adipocyte differentiation, modulates thermogenic markers positively increasing lipolysis, regulates glucose metabolism and promotes neurite outgrowth to improve adipose tissue innervation [4]. Obesity resulting from WAT excess is considered a prevalent health issue. The browning of WAT through the regulation of NRG4 levels, a central hub involved in the regulation of multiple biological processes, has been proposed as a promising therapeutic strategy in the treatment of obesity-associated metabolic disturbances.

After exhaustive research we have found a novel blend of botanical extracts, *Arctostaphylos uva-ursi* leaf extract and *Silybum marianum* extract (BL3BTE0030_0041) with impressive slimming efficacy. The blend exerts this activity via a unique mechanism of action, the increase in the release of NRG4, through which, a decrease in lipidic content, at both lipolysis and adipogenesis levels can be observed. Moreover, the novel blend is able to reduce the uptake of glucose, as well as, act as an inducer of thermogenic innervation of adipose tissue, needed to activate thermogenic functions.

Materials & Methods:

**MODULATION OF GENES BY qPCR**

Gene expression was determined by RT-qPCR in differentiated human subcutaneous adipocytes after treatment with the blend BL3BTE0030_0041 during differentiation (9 days, adipogenesis protocol) or once the preadipoocytes were terminal differentiated into mature adipocytes (the last 48 h, lipolysis protocol).

**MODULATION OF THE RELEASE OF NRG4**

The levels of NRG4 released by human subcutaneous adipocytes after treatment with BL3BTE0030_0041 was assessed by means on an ELISA test and by immunofluorescence.

**LIPID CONTENT QUANTIFICATION**

Using Adipored assay, lipid content was quantified in two different assays: for adipogenesis, treatment was performed during the differentiation of preadipoocytes into mature adipocytes for 9 days while for lipolysis, the blend was added during the last 48 h.

**GLUCOSE UPTAKE**

Glucose uptake was measured by luminiscence, in differentiated human subcutaneous adipocytes using a commercial kit (Glucose Uptake Glo™ assay (Promega)).

**NEURITE OUTGROWTH**

NRG4-rich conditioned medium from treated adipocytes was used to measure the induction of neurite outgrowth on SH-SY5Y cells by optical microscopy and Image J analysis.

**CLINICAL EFFICACY**

The efficacy of the blend was measured on the body of 30 healthy female volunteers (50% Caucasian and 50% Latin American). The study was conducted versus placebo: volunteers applied the active product, a cream containing the blend at a concentration of 2%, on one hemi-body (thigh and arm) and the placebo formulation on the other side, according to a previously defined randomization list; moreover, active product was also applied on all the subjects on the abdomen.

Product efficacy was evaluated after 14 (T14), 28 days (T28) and 56 (T56) days of daily use. Thigh arm and abdomen circumference of the volunteers was measured using a flexible millimeter ruler. Skin smoothness was assessed by means of Primos 3D (GFMesstechnik GmbH). In this study the Ra parameter was evaluated, which is a measurement of roughness of the skin (in this case, cellulite), therefore a decrease in Ra indicates an improvement in skin smoothness.

Conclusions:

The novel blend presented here, formed by *Arctostaphylos uva-ursi* leaf extract and *Silybum marianum* extract, through its action on NRG4, appears to exhibit a novel and highly innovative application of slimming and anti-cellulite, and consequently it is of high interest for the cosmetic industry.

References: