Sunny BioDiscovery™

SBD.4A – an *Angelica sinensis* Isolate with anti-Cellulite Bioactivity

Angelica sinensis is considered in China a “female ginseng" and its actions in general are geared towards female health. Specifically, the beneficial action of *Angelica* (often administered under the form of multicomponent soups) consists in “huo xue – hua yu” – “resolving nodules through moving blood”.

Cellulite, being defined as “nodularity” of subcutaneous fat, is an excellent target for *Angelica’s* bioactivity, however, the traditional oral way of this herb’s administration may not produce sufficient concentration of its active principles at the desired site of action (subcutis of the pelvic, abdominal and thigh regions). This has been corroborated in Japan, where *Angelica* (Ashitaba) is taken orally for cellulite relief, without scientifically-proven effect (Nagata et al., 2007). Therefore, we developed an isolate from this plant – arginine- and gallotannin-rich SBD.4A – for topical application, and we asked whether its bioactivity is consistent with resolving cellulite’s nodularities.

Figure 1. Angelica sinensis roots

1. Effect of SBD.4A on preserving blood vessels

Improving dermal microcirculation and lymphatic drainage are key prerogatives in resolving cellulite (Rawlings, 2006).
As illustrated on Fig. 2 SBD.4A was found to help preserving in vitro microvascular structures, which otherwise fall apart after a prolonged time of *in vitro* culture.

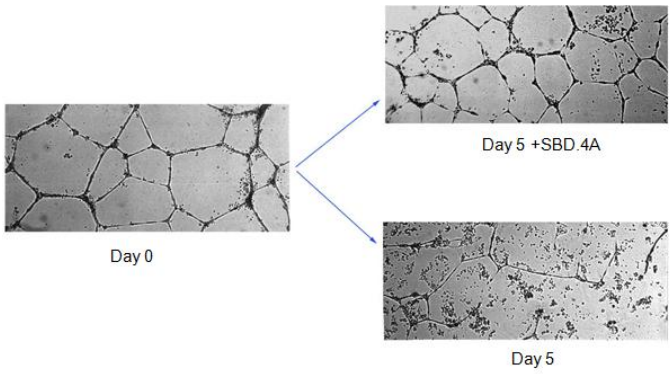

Figure 2. Microvascular structures incubated on Matrigel disintegrate after 5 days in the absence, but not in the presence of SBD.4A.

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2. Anti-senescence effect of SBD.4A

Enrichment of subcutaneous tissue with enlarged adipocytes gorged with fat is a common microscopic finding in cellulite. Cellular hypertrophy is also a hallmark of cellular senescence in general, as such terminally-differentiated cells cease to divide while secreting proinflammatory cytokines (Laberge et al., 2013). SBD.4A was found to have anti-aging effect at the cellular level, by decreasing the number of aged "fried egg"-like cells (see Fig. 3).

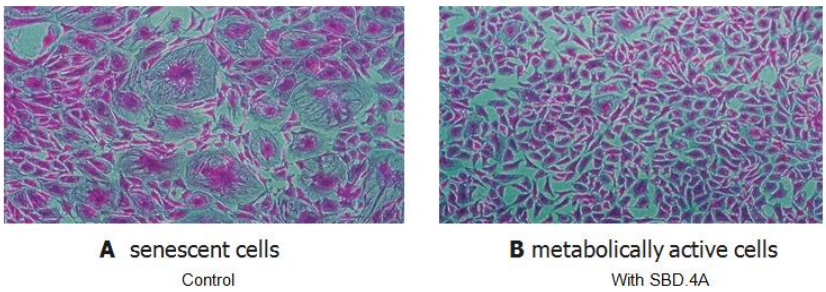

Figure 3. Prolonged incubation of cells in suboptimal conditions triggers terminal differentiation (senescence) in the absence (A), but not in the presence (B) of SBD.4A. Note large senescent cells in 9A) and their relative decrease in size and number in (B).

3. Modulation of gene expression by SBD.4A

In order to determine whether the observations above can be substantiated at the molecular level, engineered skin samples were incubated in the absence or presence of SBD.4A and whole genome expression analysis (DNA microarrays) was performed (Zhao et al., 2012 – see Fig. 4 for illustration). The results summarized in Table I indicate that SBD.4A not only has a positive effect on the reinforcement of the extracellular matrix (ECM) in the skin, but also, surprisingly, inhibits cAMP-specific phosphodiesterase (PDE4), thus clearing the way for lipolysis.

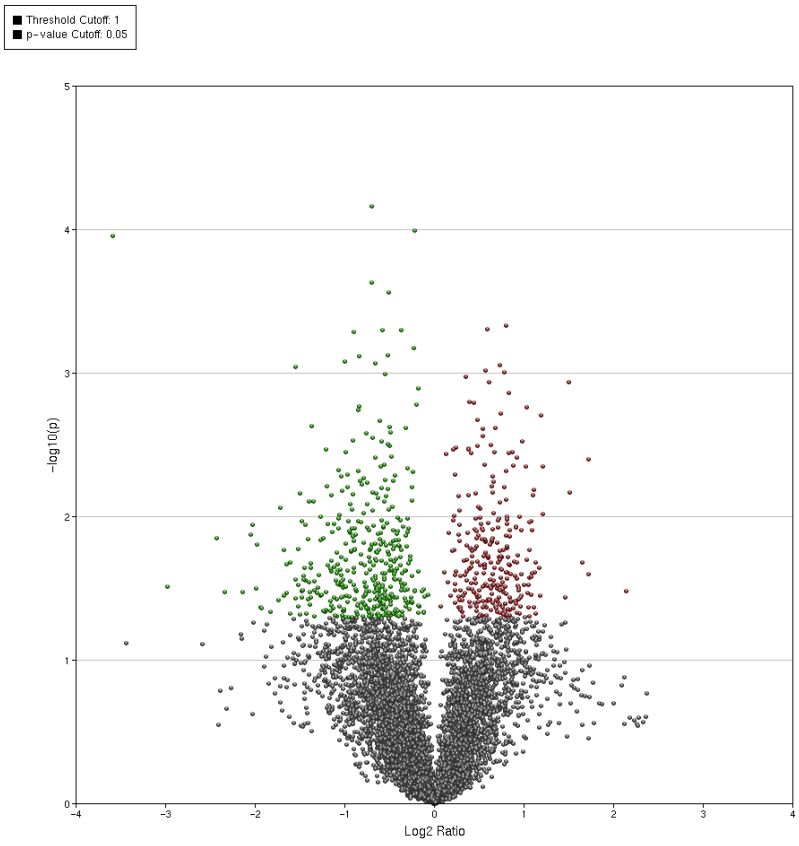

Figure 4. Bioactivity of SBD.4A. Incubation of full thickness EpiDerm tissues with SBD.4A results in the modulation of the expression of a subset of genes in the human genome (green – inhibition, red – stimulation vs. water-treated control).

Table I Genes modulated by SBD.4A relevant to Extracellular Matrix and lipolysis in the skin.

Gene Name	Protein Product	Modulation (up- down)	Protein Role
COL17A1	Collagen XVII	4.2 up	Major structural component of hemidesmosome, anchoring basal epithelial cells to the underlying basement membrane.
COL16A1	Collagen XVI	3.2 up	Fibril-associated collagen with interrupted triple helix important for tensile strength of the skin.
HAS3	Hyaluronan synthase 3	1.7 up	Synthesizes the most prominent non-proteinaceous component of the extracellular matrix in the skin.
LAMC2 LAMA3	Laminin ɣ-2 Laminin 5	3.9 up 2.6 up	Key component of the basement membrane (basal lamina), laminin 5 is involved in cell adhesion, signal transduction and differentiation of keratinocytes and laminin ɣ-2 interacts with laminin 5 to form anchoring filaments that connect epithelial cells to the underlying basement membrane. Laminin ɣ-2 is epithelium-specific.
SOD2	Superoxide dismutase 2	1.7 up	Mitochondrial Mn-dependant SOD-2 provides an important anti-oxidant activity, especially in tissues exposed to increased oxygen and free radical presence, such as in the wounds.
ADAM9	ADAM 9	1.7 down	Disintegrin metalloprotease interacting with type I collagen and implicated in delayed wound healing.
HBEGF	Heparin-binding EGF	1.6 up	Epidermal growth factor involved in wound healing and other regenerative processes in the skin.
CLDN1 CLDN4	Claudin 1 Claudin 4	2.0 up 2.0 up	Prominent components of the tight junctions, where they establish the paracellular barrier that controls the flow of molecules in the intercellular space between the cells of an epithelium.
PDE4c	cAMP-specific phosphodiesterase	-2.7	PDE4 isozyme-selective inhibitors trigger activation of brown adipose tissue, resulting in lipolysis

4. Conclusion

Angelica sinensis (Dangui) preparations have been known in China to “move blood” and “remove nodules” and have been used intraorally in Japan (Ashitaba) to treat cellulite. Here we present a proprietary *Angelica* isolate SBD.4A, with potent pleiotropic bioactivity against cellulite for topical use.

5. Literature

Laberge RM, Zhou L, Sarantos MR, Rodier F, Freund A, de Keizer PL, Liu S, Demaria M, Cong YS, Kapahi P, Desprez PY, Hughes RE, Campisi J. Glucocorticoids suppress selected components of the senescence-associated secretory phenotype. Aging Cell. 2012 Aug;11(4):569-78

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