Healthy aging

When exceptional longevity inspires cosmetic ingredients industry

Figure 1. Getto leaves, Okinawa Island. The plant *A. zerumbet* (Pers.) B.L. Burtt & R.M. Sm, syn. *Alpinia speciosa*.

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The latest global report issued by the World Health Organization[1] highlights the importance of promoting "Healthy Aging" and proposes a public health framework with the initial key measures along these lines[2].

From this perspective, the study of centenarians living in regions with higher than average life expectancy such as Okinawa Island constitute a valuable research material to understand healthy aging. As an illustration, the Okinawa Centenarian Study (OCS) conducted on more than 900 centenarians since 1975, suggested that genes, lifestyle and psychosocial factors are key to explain this phenomenon[3].

Inspired by these unique characteristics, Seqens Cosmetics went to Okinawa to meet local pharmacopoeia experts as well as the principal OCS investigators in order to take a closer look at the nutritional and psychosocial factors contributing to this exceptional longevity.

OUR EXPERT

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Healthy aging and nutritional factors

Beyond the intuitive influence of nutrition on longevity, the US study conducted in 1990-2010 has confirmed the major role of dietary factors in the risk of early death and in reducing healthy life expectancy (DALY)[4]. Conversely, the mortality rate due to coronary heart disease and cancer is 80% and 40% lower, respectively, among the elderly population in Okinawa, compared with the American population[5]. The "Traditional Okinawa Diet" is often mentioned in order to explain the healthy longevity of the Okinawa population, together with caloric restriction, which involves reducing calorie intake without causing malnutrition or deficiencies[6]. In this context, the Okinawa generations born before the Second World War and their "*hara hachi bu*" philosophy, consisting in eating until 80% satiety, represents one of the best human examples of a naturally calorie restricted population. In terms of mechanisms, one consensus currently favours the hypothesis according to which this low nutrient intake induces a hormesis or low level stress phenomenon, which involves positive regulation of the biological pathways for resistance to other forms of stress (FOXO3, mTOR)[7].

Alongside this phenomenon, caloric restriction mimetics (CRM) liable to stimulate autophagy were also identified in the "Okinawa Diet"[8]. This diet is thus thought to represent a rich source of CRM, with specific herbs and condiments, which are the foundations of traditional medicine. Owing

to its local popularity and the significant data on life expectancy in certain animal models[9], the plant known locally in Japan as *getto* (Figure 1) is still receiving particularly close attention, as its consumption is thought to contribute to longevity[10].

Healthy aging and psychosocial factors

In addition to their dietary habits, centenarians stay active by walking or gardening daily and remain physically independent until a very advanced age in comparison with certain Western populations[11]. According to tradition, they don't eat on raised tables and chairs, but rather by sitting on tatami mats on the floor: sitting down and standing up several times during the day is therefore a vital part of daily physical exercise among the elderly, which improves physical balance and prevents the risk of falls which often result in detrimental bone fractures. The results of a large-scale population study in Japan, conducted by the *Japan Public Health Centre* (JPHC), establish a clear correlation between daily physical exercise in Japan and a significant reduction in the risk of all-cause mortality among both genders[12].

Although harder to quantify, longevity in Okinawa is also facilitated by the existence of genuine reassuring social networks, notably with the local tradition of *moai*, or social support groups. This preserves a very ancient tradition which developed among the farming communities in Okinawa, and which promoted sharing and daily support, notably in the context of mutual arrangements for performing manual tasks[13].

The existence of this social support offers members essential emotional security; research thus suggests that real connections and social trust through traditional local events help preserve good mental health[14].

Aware of the important role of these social connections in longevity and "healthy aging" in this geographical area, Seqens aimed to study whether parallels could be drawn at skin level. In other words, this involved determining whether strengthening cutaneous connections could improve its appearance, similar to how emotional connections promote good general health.

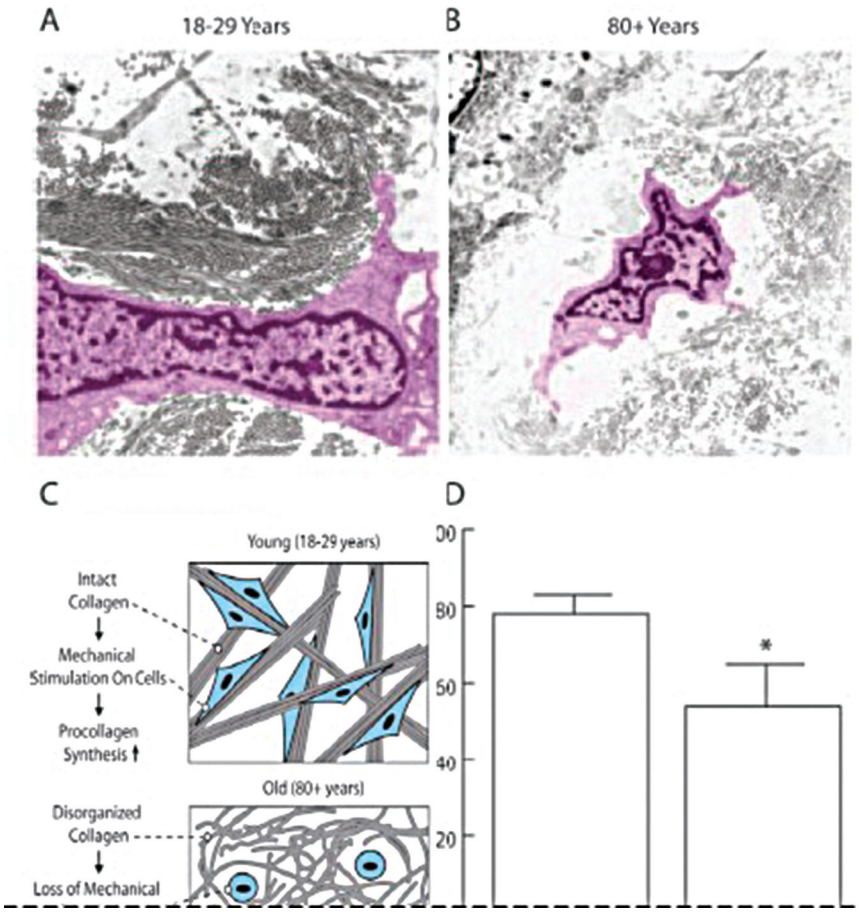

Figure 2. **Ultrastructural appearance of dermal fibroblasts in healthy sunprotected hip skin from young and old individuals[18].** A and B: The cell from the section of young skin (A) is flattened and well spread, in contact with collagen fibers over a high percentage of its surface. The cell in the old skin sample (B) is round and is in contact with collagen over a smaller portion of its surface. C: Modelization of fibroblast interaction, Young versus Old. D: Quantification of contact between cells and collagen fibers. Values represent the percentage of the cell boundary in contact with collagen fibers ± SEM (P=0.01; two-tailed Student's t-test).

By studying the consequences of aging at tissue and cellular level, the research teams thus endeavoured to identify biological pathways liable to promote "healthy skin aging".

Healthy skin aging

From the age of 50, dermal quality starts to deteriorate with a decrease of dermis thickness and undulations of the dermo-epidermal junction (DEJ). Age-related deterioration of the papillary region disrupts the organisation and structure of the matrix[15], also affecting the reticular dermis. These tissue changes notably cause slackening and the gradual development of wrinkles.

At cellular level, changes in the quality of fibroblast anchorage to the extracellular matrix increase the open spaces surrounding the cells and reduce the amount of contact between these cells and collagen fibers[16] with a negative impact on traction forces and dermal cohesion. This decreased mechanical tension on fibroblasts reduces the production of matrix constituents and stimulates the synthesis of enzymes which cause deterioration of the matrix[17]. Cell-cell interaction is also affected by the aging process, with consequences on fibroblast productivity: an aged cell isolated from its

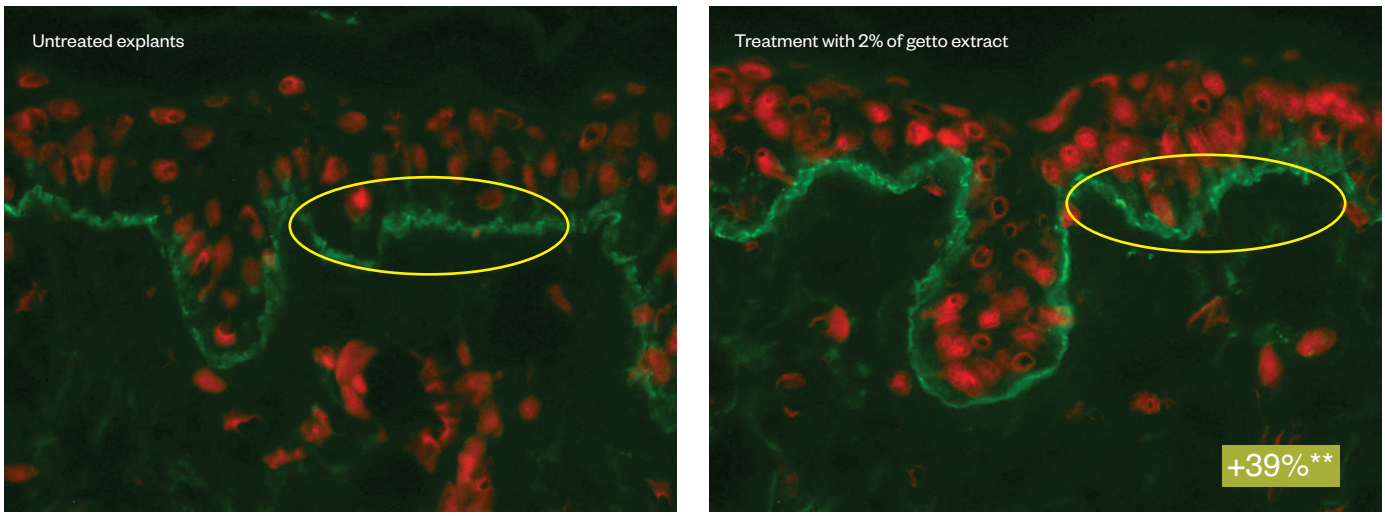

Figure 3. ***Ex vivo* results: Skin explants treatment with getto leaves extract at 2% *versus* untreated explants.** After treatment of skin explant: Dermal-epidermal junction (DEJ) morphology and undulation are enhanced. The immunostaining (green) highlighted a significant enhancement of 39% ($p<0.01$) of laminin 5.

Figure 4. **Clinical Results.** After 28 and 56 days of use, formulation with 2% of getto leaves extract on the top 20 responders improves skin texture and complexion (skin rosy *versus* yellowish aspect).

fibroblast cluster, for instance, synthesizes less type I procollagen than a young fibroblast exposed to the same conditions[18]. Two-dimensional skin sections also show that fibroblasts obtained from elderly populations have a smaller surface area in contact with intact collagen fibrils compared to cells obtained from young skin sections (Figure 2)[18].

In addition to the reduction in the number of fibroblasts during the aging process, their secretory profile also changes. Among the 998 secreted proteins identified, 77 displayed an age-dependent secretion pattern; these are known as "skin aging-associated secreted proteins" (SAASPs)[19].

The identification of substances liable to boost extracellular matrix synthesis and organisation, fibroblast interaction with

the surrounding environment, together with cohesion between the dermis and epidermis through dermo-epidermal junction thus represents an interesting strategy for preserving healthy skin and improving its general appearance.

From inspiration to active ingredient

The research strategy for developing a natural healthy aging ingredient at Seqens was thus guided by this question: can we help achieve visibly healthy skin by promoting compartmental and cell-matrix connections at skin level?

These biological avenues were therefore investigated with the development of a *getto* leaf extract (*Alpinia zerumbet; Alpinia speciosa)*; plant known to contribute to longevity in Okinawa. This *getto* extract was tested at transcriptomic, proteomic and clinical scale. These studies were able to demonstrate a benefit regarding the expression of genes associated with SAASPs on an "aged" fibroblast model (Hayflick replicative senescence model). Treatment with 2% of *getto* extract stimulates the expression of the majority of genes involved in extracellular matrix synthesis and organization, and in cell-matrix interactions, such as collagens, elastin, biglycan, dermatopontin, tenascin C, or integrin alpha-11. Effects on the inhibition of the expression of genes involved in the deterioration of the extracellular matrix, inflammation, or in the response to oxidative stress were also observed.

At *ex vivo* scale, after treating skin explants with 2% of *getto* extract, an improvement (*versus* untreated controls) in DEJ morphology and undulation was observed. Immunostaining also evidenced a significant increase, for the treated explants (*versus* untreated controls), in the level of markers such as collagen I and laminin 5, known to be key for skin cells anchorage (Figure 3).

In terms of clinical evaluation, VISIA-CR evidenced an improvement in skin texture after treatment with 2% of *getto* extract formula *versus* placebo at 28 days and 56 days. This treatment also contributes to a "healthy" appearance, by promoting a rosy glow instead of a yellowish complexion, one of the visible signs of skin aging (Figure 4).

Conclusion

Experts in exceptional longevity suggested that aging is not limited to genetic considerations, but also involves aspects such as nutritional and biopsychosocial factors. Seqens Cosmetics thus studied the properties of *getto* extract, known to contribute to the particularly high life expectancy in Okinawa. These studies therefore showed that this plant, in addition to its nutritional effect, also had a beneficial cutaneous effect by promoting tissue and cellular connections, while giving the skin a healthy appearance. This extract thus represents a botanical active cosmetic ingredient which falls within the scope of "healthy aging" skincare product segment. Hence, these products no longer try, in vain, to make time stand still, but rather embrace the passing of time by promoting healthy aging ●

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