A new discovery model of active molecules based on biomimicry

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Abstract

As a basic premise of zoopharmacognosy, animals utilize plant secondary compounds or other non-nutritional substances to medicate themselves. In order to select plants with dermatological effects, behavioral and health monitoring of Gorillas living in the Mamfe region of West Cameroon has been carried out. These observations highlighted the importance of *Aframomum melegueta* seeds and fruits: by its anti-inflammatory effect, this plant protect the myocardium of the gorillas from inflammation causing fibrocausal myocardiopathy.

In this context, SEQENS Cosmetics Innovation & Research Departments has set up a bio-inspired discovery platform for molecules with breakthrough efficiency at cutaneous level (Etho-phytology ™).

The study of *Aframomum melegueta* seeds extract highlighted anti-inflammatory properties at skin level:

- *Ex vivo*: genetic modulation of key mediators involved in inflammation resolution,
- Clinical study: improvement of the skin barrier function and reduction of skin redness.

Keywords: Biomimicry, zoopharmacognosy, bioinspiration, ethology, behavior, gorilla

Introduction

Daniel Janzen was the first scientist to publish and explain that certain vertebrates might just have acquired knowledge that enabled them to avoid certain toxic herbs and even

improve their own health through the they used[1]. The repeated observation of curative behaviors in animals has consequently given rise to a new field: zoopharmacognosy[2].

Members of the primate kingdom are known to consume a very wide range of plant-based substances for their therapeutic properties, including chewing on bitter stems or bark. Some cases of zoopharmacognosy in primates also involve them eating seeds. For instance, the western lowland gorilla is believed to eat the seeds of the grains of paradise plant (*Aframomum melegueta*) to protect its myocardium[3]. Monitoring the health and behaviors of gorillas living in the Mamfé region of Cameroon has helped to highlight the importance of *Aframomum melegueta* seeds in fighting certain inflammatory conditions responsible for cardiomyopathy. Furthermore, the lack of availability of *A. melegueta* to gorillas held in captivity has been found to have a detrimental effect on the animals' health[3]. The fact that the seeds contain molecules belonging to the gingerol family, such as 6-paradol, 6-shogaol and 6-gingerol, could explain the preventive effects it has been found to have on the gorilla's myocardium via the cyclooxygenase-2 (COX-2) pathway[4].

This study seeks to demonstrate that these anti-inflammatory properties are also found at the skin level.

Materials and Methods.

1. Ex vivo study

The goal of this study was to evaluate the potential pro-resolving effect of this *A. melegueta* seed extract on the genetic expression of key mediators involved in the inflammation such as IL-22, a pro-inflammatory cytokine, IL-10 and TGF-β, pro-resolving / anti-inflammatory cytokines and the FPR2 receptor, a receptor with a dual activity on inflammation.

Human skin explants were obtained from a 52 years-old Caucasian female donor undergoing abdominoplasty surgery, in triplicates. The inflamed state consisted in applying a cytokine cocktail to the biopsies to induce the inflammation. This cocktail contained the cytokines TNF-α, IL-4, IL-5, and IL-13.

Finally, after treatment, RNA extraction and PCR analysis were performed. The results were presented as ratios of gene expression for the non-stressed (basal) state batches and for the stressed (inflamed) state batches.

2. Clinical study

The objective of this double-blinded study was to assess objectively the clinical efficacy of *A. melegueta* extract at 3% *versus* placebo on healthy skin. For this clinical study, a panel of 22 subjects, 10 male and 12 female subjects with healthy skin, aged from 21 to 70 years old was selected. The study lasted 5 days and volunteers were asked to apply twice daily emulsions containing the active or the placebo on delimited irritated areas on the inner side of one randomized forearm.

As the aim of the study was to evaluate the improvement of the cutaneous barrier function, the skin needed to be irritated with an irritant agent. SDS (Sodium Dodecyl Sulfate) patches at 1% were used for this study and were applied for 24h and then removed before the beginning of the applications.

Several measurements were recorded on the volunteers at D0, at D+1 and at D+5, at the end of the study. Those measurements were:

- Skin transepidermal water loss (TEWL) analysis by evaporation meter SWL-5®,
- Skin vascularization analysis with high resolution photographs carried out with a high-resolution digital camera and dedicated software to identify the blood map (hemoglobin image).

Results

1. Ex vivo: key mediators involved in inflammation resolution are modulated

A. melegueta extract treatment decreases IL-22 expression (when overexpressed, acts as a pro-inflammatory cytokine) and therefore prevents a possible spreading of the inflammation. At the same time, *A. melegueta* extract increases IL-10 expression during the inflammation process and TGF-β expression after stress, both pro-resolving / anti-inflammatory cytokines, showing that the resolution phase is enhanced by the active.

2. Clinical results: skin barrier function is improved, skin redness is reduced

Improving skin barrier function

After only 1 day of use, *A. melegueta* extract at 3% significantly inhibited TEWL by 15% ($p < 0.05$ vs D0) compared to D0. The placebo induced a non-significant inhibition of TEWL after 1 day by 5%. A significant difference of TEWL was also observed between the two products after 1 day of use ($p < 0.05$ vs placebo).

Figure 1 summarizes the evolution of TEWL from day 0 to day +1 with the use of an emulsion containing *A. melegueta* extract at 3% or with an emulsion containing the placebo.

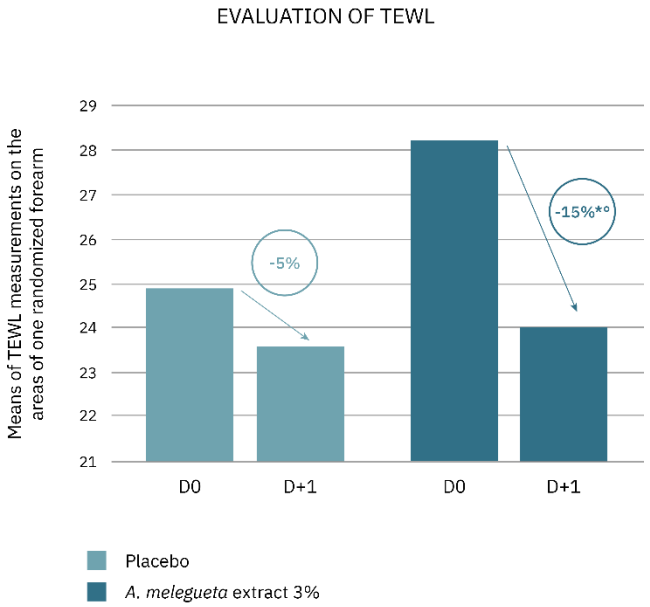

Figure 1: Evolution of TEWL from D0 to D+1 with placebo vs *A. melegueta* extract treatment at 3%, *$p < 0,05$ vs D0, °$p < 0,05$ vs placebo

Reducing skin redness

After 5 days of use, *A. melegueta* extract at 3% significantly reduced by 50% ($p < 0.05$ vs D0) skin vascularization and thus, skin redness, compared to D0. The placebo also induced a significant decrease of vascularization after 5 days by only 31% ($p < 0.05$ vs D0). A significant difference of vascularization was also observed between the two products after 5 days of use ($p < 0.05$ vs placebo). Figure 3 shows several pictures of 2 volunteers' forearms at D0 and at D+5 after 5 days of application of the emulsion containing *A. melegueta* extract at 3% or the placebo.

Figure 2 summarizes the evolution of vascularization from day 0 to day +5 with the use of an emulsion containing *A. melegueta* extract at 3% or with an emulsion containing the placebo.

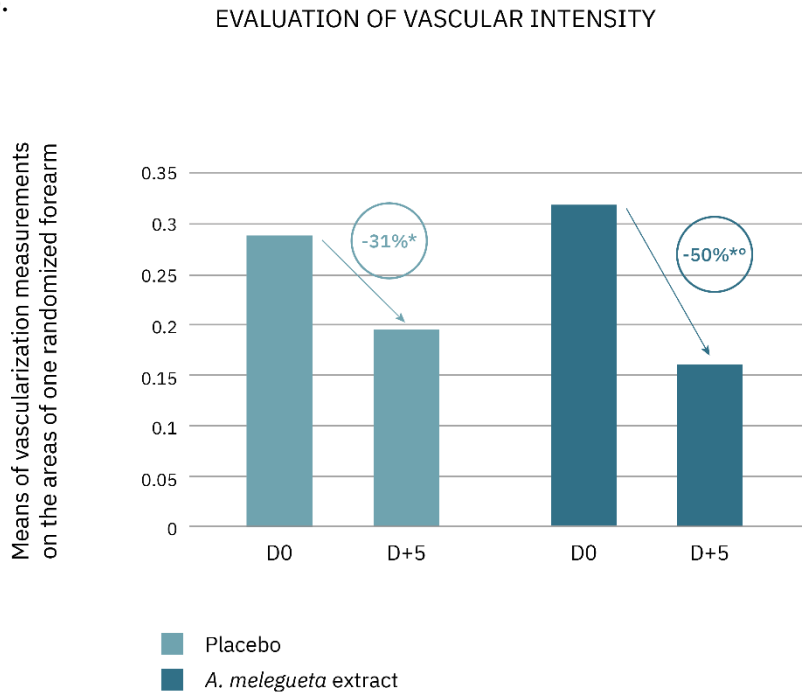

Figure 2: Evolution of vascularization from D0 to D+5 with placebo vs *A. melegueta* extract at 3%, *$p < 0,05$ vs D0, °$p < 0,05$ vs placebo

As shown on Figure 3, after 5 days of application of an emulsion containing *A. melegueta* extract at 3%, skin redness was visibly reduced thanks to the active ingredient.

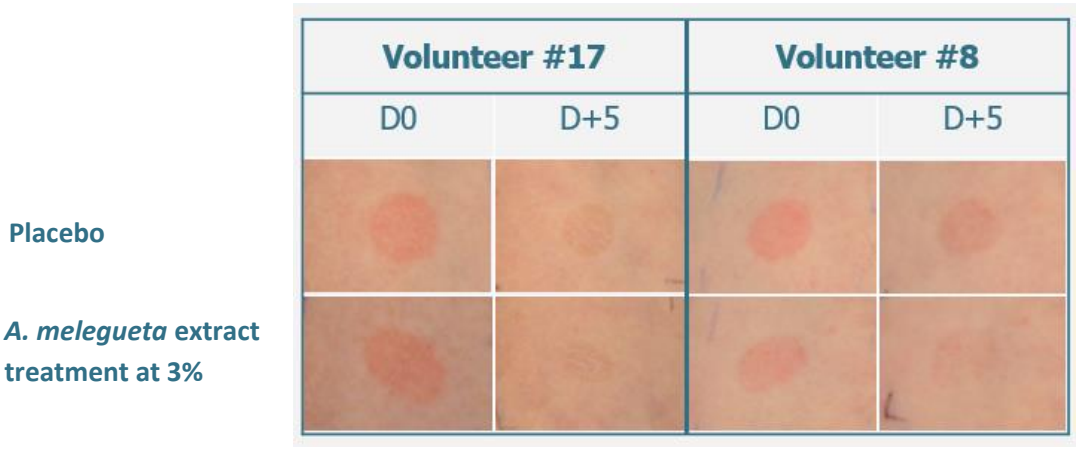

Figure 3: Pictures of the forearms of 2 volunteers at D0 and D+5 with placebo *vs A. melegueta* extract at 3%

Conclusion.

In a world increasingly aware that other species are affected by our behavior, there is an urgent need to realize that our progress also depends on them. Biomimicry thus encourages conservation for ecosystems and their inhabitants, because they hold the knowledge we need to thrive. Grains of paradise (*A. melegueta*) seeds, used by gorillas to heal themselves, inspired the development of a new cutaneous solution to limit chronic skin inflammation.
In its very definition, besides being a high-potential source of innovation, biomimicry invites us to understand nature rather than just take from it.

Grains of paradise extract treatment reduces TEWL and vascularization, thus improving skin barrier function and reducing skin redness. This is supported by the self-assessment questionnaire done on women with sensitive skin in which the volunteers thought that the product was making their skin less reactive, more protected, more uniform and with less apparent blood vessels.

This bioinspired approach allowed us to identify three plants to help the inflamed skin

Conflict of Interest Statement NONE.

References.

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