A new sandalwood extract developed with A.I.

Anne Clay, Jean-Marie Botto, Christophe Capallere – Ashland

Sandalwood extract (SW) is a natural biofunctional inspired by forest therapy to defy the skin olfactory signature of ageing. Obtained by supercritical CO2 extraction from Santalum album, this unique and patented biofunctional leverages the forest bathing trend for well ageing benefits. SW enhances skin olfactory receptors shown to decrease with age and air pollution. It reduces skin cell senescence and helps mitigate air pollution damage; It has clinically proven benefits on skin regeneration, firmness, wrinkles, and on the skin olfactory signature of aging. SW is the first biofunctional developed with Artificial Intelligence.

Leveraging the forest therapy trend
Forest Therapy, under the umbrella of nature or ecotherapy, has existed in Japan since the Forest Agency of Japan promoted Shinrin-yoku (forest bathing) as a practice for healthy living and part of a forest therapy program. The practice of shinrin-yoku is the art and science of how trees can promote health and happiness. Breathing in a forest is a possible mechanism that may induce the health benefits of forest bathing. Forests often deliver large amounts of odorant molecules, identified as "forest VOCs". These VOCs produced by trees are secondary metabolites with several functions including tree defence and communication. Inhaling some forest VOCs can result in antioxidant and anti-inflammatory effects, it may also be beneficial to improve cognitive performance by decreasing mental fatigue, increasing relaxation and mood. Forest bathing continues to grow in interest and stature and is now a new trend in the beauty industry.

Air quality is top of mind
We've seen clean eating and clean sleeping

have their moment, but big on the radar for 2021 is clean breathing. In 2018, 55 percent of the world's population lived in urban areas, and, by 2050, it will be 68 percent. Air pollution results from chemical reactions derived from various sources – mostly from vehicle exhaust and industrial gas emissions. Indoor air quality is important as it contains various pollutants with a significant influence on our own comfort and health. The low quality of indoor air is due to the emissions of volatile organic compounds (VOCs) from wooden elements of indoor furnishings. With a growing number of people living in urban environments and spending most of their time indoor, with no forest in their close surroundings, the joy and healing power of the trees is not readily available for most of them.

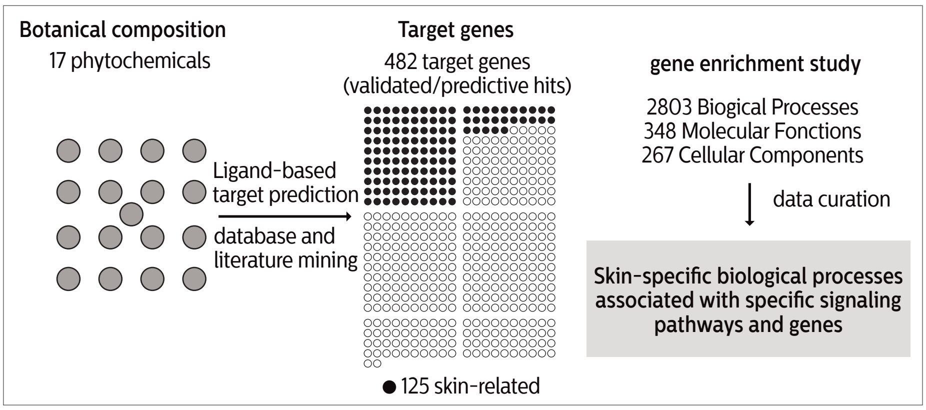

Figure 1: Network pharmacology approach for sandalwood extract.

4,000 years of spiritual rituals with sandalwood
Sandalwood has a 4,000-year-old history: the oil was used in religious rituals, and many deities, temples and sacred carvings were crafted from its soft wood. It was one of the most common incenses found burning in ancient Hindu and Buddhist temples around India and Tibet and is still used in temples today as it is believed to bring one closer to one's divine nature. Sandalwood is a highly prized for its oil that forms only with the right mix of genetics and environmental factors. The oil is the tree's defence mechanism against disease and stress which helps explain many of the medicinal properties for which it has been used over the centuries. In addition to its spiritual and medicinal properties, its intensely sweet, soft, woody, and slightly musky aroma made it a prized ingredient for luxury perfumes, incenses, and cosmetics from ancient India, to Egypt, to China, and to the rest of the world

Upcycling wood chips as part of a circular economy model
SW is obtained from *Santalum album* sustainably grown in Australia in a plantation using regenerative agriculture techniques, with rotational re-planting after harvest and water-efficient irrigation techniques. There is a full control over the entire supply chain from planting, growing, and harvesting the sandalwood to processing the essential oil by steam distillation without adding any chemical during the process. Wood chips depleted in oil are used for the extraction of SW by supercritical CO2 technology. The oil soluble extract is then solubilised in a bio-based solvent. SW is part of a circular economy model, creating value out of a by-product, with a minimal use of natural resources.

Using artificial intelligence and bioinformatics to develop a sandalwood extract
Over the past two decades, enormous amounts of data have been accumulated in the domain of human health, physiology and knowledge on the role of genes and biological mechanisms.

Due to its predictive potential, Artificial Intelligence (AI) can improve the success rate and speed up the process of active ingredient development. Indeed, AI can explore large datasets to detect concealed patterns and draw predictions that only the machine can discern. Bioinformatics can use AI approaches to explore structural chemistry and biology, genomics, proteomics, and pharmacologic data to predict potential interactions between phytocomponents and proteins and the possible modulation of gene expression and signaling pathways. This approach is identified as "network pharmacology", a term introduced in 2007 by Andrew L. Hopkins.

Systems pharmacology study of Sandalwood extract *in silico*

The analytical determination of SW has led to the identification of seventeen key phytocomponents with potential biological activity. Network pharmacology analysis was used to predict the potential skin biological activity (Fig 1).

First, a compound-target network was established via virtual screening based on similarity structure prediction combined with literature and database mining. Second, the curated compound-target network resulting in a total of 482 genes, served as a base to gene and pathway enrichment studies. This led to the identification of 2803 biological processes, 348 molecular functions and 267 cellular components, that were further refined to focus on a subset of 125 skin-related genes that served as a basis for skin biological activity prediction. The workflow of the study is presented in Figure 2.

Predicted skin biological activities (Figure 2) comprised: anti-ageing (including senolytic activity, telomere protection, extracellular matrix organisation), regulation of inflammation, response to various stresses, skin olfactory receptor modulation, skin barrier homeostasis (epidermal development and regeneration, cell-to-cell junctions), mitochondrial homeostasis, DNA repair, antioxidant defenses, sebum regulation, and hair growth and folliculogenesis. These predicted areas and the related genes constitute a pool of potential biological activities that can be further validated experimentally.

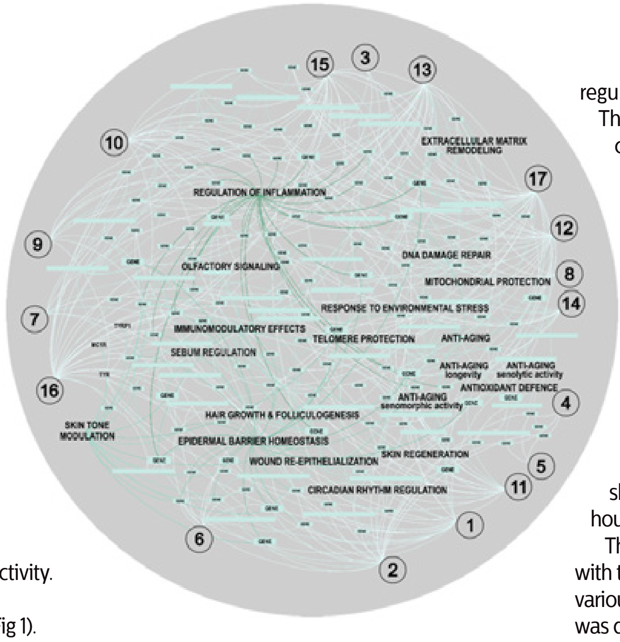

Figure 2: Skin-related network of predicted compound-target-skin biological activity relationships. The seventeen phytocompounds are numbered (1 to 17). Selected predicted biological activity is shown.

Experimental validation of the biological activity of Sandalwood extract *in vitro*

Part of the study of the biological activity of SW *in vitro* was undertaken on skin models to delineate the potential role of OR2AT4 in skin homeostasis.

The topical application of 1% and 2% SW extract on normal human skin biopsies showed an increase in OR2AT4 content after 48 hours (+17% and +21%, respectively).

The reconstruction of epidermal equivalents with the keratinocytes isolated from donors from various age suggested that OR2AT4 expression was decreased with age (Fig 3). This observation pointed out OR2AT4 as a sensory receptor that decreased with age and hence can be considered as a marker to evaluate the olfactory signature of ageing *in vitro*.

Next, experiments were conducted in order to determine if epidermal OR2AT4 could be modulated following the exposition to external stress such as the application of volatile organic compounds (VOCs) from car exhaust, in an epidermal reconstructed model to mimic the consequences of external stressors associated with extrinsic ageing. An overnight application of VOCs on reconstructed human epidermis was associated with a decrease of OR2AT4 (-33%) observed 48 hours after VOCs application. When SW extract was applied post VOCs application for 48 hours, the return to the basal OR2AT4 content was observed.

A reconstructed epidermal model mimicking intrinsic ageing was also used to study the expression of OR2AT4 in this context of a senescent epidermis and the modulatory effect of SW extract (Figure 4).

When compared with normal reconstructed epidermis, the reconstructed senescent epidermal model exhibited a lower OR2AT4 expression (-19 to -30%, according to the experiment). The topical application of 1% and 2% SW extract on reconstructed senescent epidermal model showed an increase in OR2AT4 content after 48 hours (+46% and +96%, compared to respective controls).

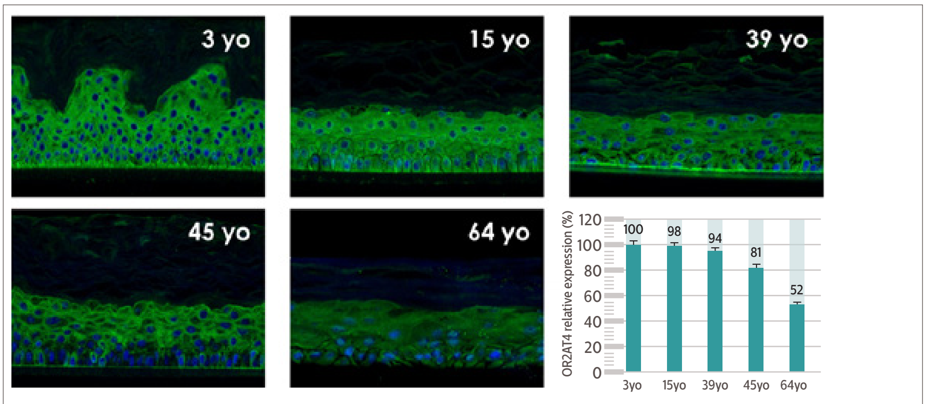

Figure 4. Immunodetection of OR2AT4 in human reconstructed epidermis obtained with keratinocytes from donors of increasing age.

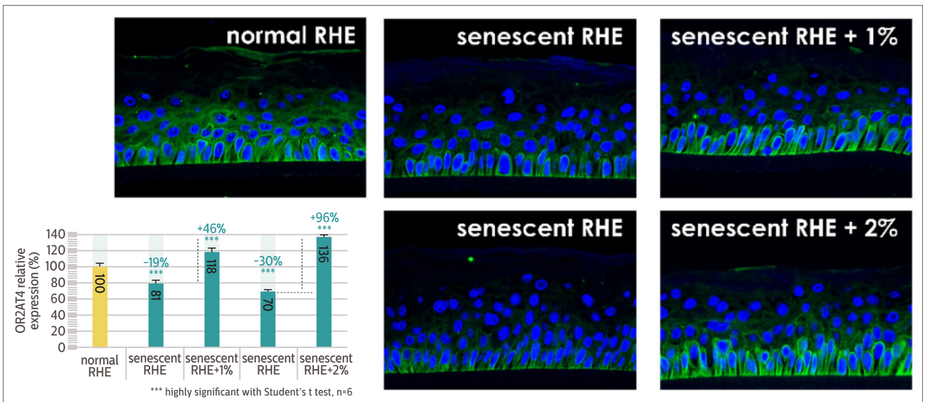

Figure 5: Reconstructed senescent epidermal model showed a decreased expression of OR2AT4, that could be reversed by SW topical application for 48 hours.

Conclusion

Inspired by wood therapy, SW, the trade name of which is Santalwood™ biofunctional, reduces the skin olfactory signature of ageing. It has clinically proven benefits on skin regeneration, firmness and wrinkles. Additionally, the bioinformatic network analysis of Santalwood™ revealed concealed skin biological pathways providing Santalwood™ with possible additional skin benefits and new horizons in future beauty products. **PC**

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Ashland
500 Hercules Road,
Wilmington, DE 19808,
USA