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## Multi-omics analysis and integrative approach to evaluate pharmaco-clinical efficacy of a novel combination of active ingredients on senescence and causes of aging

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## INTRODUCTION

Skin aging is the consequence of two biological process: intrinsic genetically programmed factors and extrinsic environmental factors. At the cellular level, accumulation of senescent cells (SC) is also involved in skin aging. SC stop to proliferate but remain metabolically active (Bulbiantkova et al., 2023). The secretome of SC (Senescence Associated Secretory Phenotype: SASP), is a cocktail of mediators, like chemokine (eg CXCL9) or oxylipin (eg 15 deoxy-delta-12, 14 prostaglandin J2) involved in skin aging (Sayed et al., 2021; Wiley et al., 2021). The reduction of SASP by using senotherapeutics is a promissis strategy to reduce skin aging. Our aim was to demonstrate, by using our interactomic expertise, the senomorphic and anti-aging properties, of a unique cosmetic formulation composed of, among others, 6% Niacinamide, 0.1% High Molecular Weight Hyaluronic Acid (HMW HA) and 0.1% Hyaluronic Acid Fragment intermediate (HAFi).

## MATERIALS AND METHODS

We developed an original pharmaco-clinical approach based on multi-omics, combining transcriptomic and epigenetic (mRNA-miRNA network), metabolomic (metabolites network) and metagenomic (microbiota identification) integrated analyses (Fig. 1). Metabolomics profiles were performed with NMR and UHPLC-HRMS. Data were processed with XCMS using W4M. Identified discriminant metabolites according to in-house databases were mapped on metabolic pathways using Metexplore software. Metagenomics analyses were performed from genomic DNA extract samples. Intergenic spacers 1 (ITS1) of the ribosomal RNA gene, or of the V1-V3 region of 16S gene was sequenced by high-speed sequencing. Analysis of the sequences by comparison with international data bases and differential analysis was used to identify genus or species. We included 30 female subjects between 42 and 55 years old. Formulation was used once a day, for 2 months. Biological skin samples were collected to correlate the clinical signs of aging with biological networks before and after treatment.

## interactome expertise

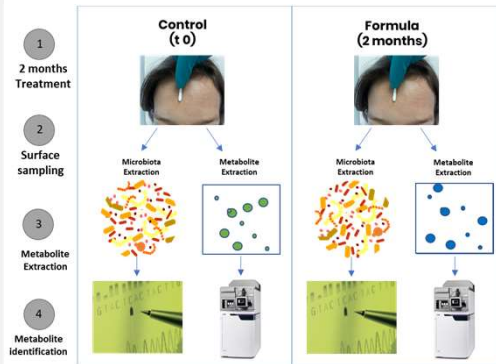


Figure 1 : Experimental procedure

## RESULTS

We demonstrated that the formulation regulates mRNA, miRNA (Bogdanowicz et al., 2023) and metabolites networks (Fig. 2), and positively modulate skin microbiota diversity (Fig. 3) to counterbalance the skin aging hallmarks, correlated with skin aging signs. In particular, the formula showed a senomorphic effect by decreasing SASP-mediators-like (CXCL9 and Oxylipin) (Wiley et al., 2021). Moreover, by studying the interactions and regulations of the cutaneous ecosystem, we showed that these variations are correlated with a decrease of the oxidative stress and inflammatory biomarkers, and the recovery of mitochondrial activity, involving specific microbiota changes, in particular *Lactobacillus* and lactate increase (Li et al., 2020) (Fig. 3). These benefits are associated with improved clinical sign of aging: wrinkles, firmness and plump (data not shown).

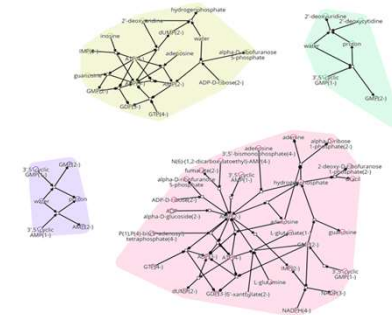


Figure 2 : Metabolites networks regulated by formula.

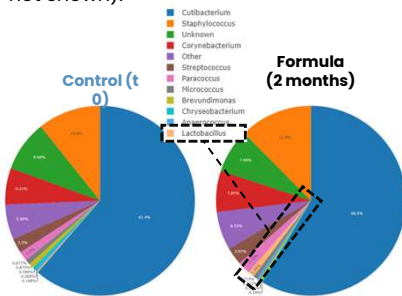


Figure 3 : Effect of formula on skin microbiota

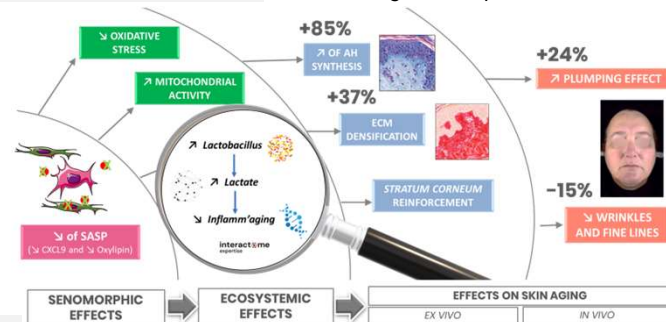


Figure 4 : Interactome expertise: from senomorphic activity to clinical efficacy

## CONCLUSIONS

By using our Interactome Expertise, we showed for the first time, that a formula is acting on senescence and signs of aging, from a pharmacological to a clinical level.

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