

Modulation of the fibroblast epigenome by plant-derived actives

Arthur CHERVET¹, Shalina HASSANALY¹, Jean-Christophe CHOULOT¹, Jean-Marc LEMAITRE², Paul BENSADOUN², Marc BESSOLES², Mathilde THOMAS³

¹ Laboratoires Caudalie, Gidy, France , ² Skinomix, Montpellier, France, ³ Laboratoires Caudalie, Paris, France

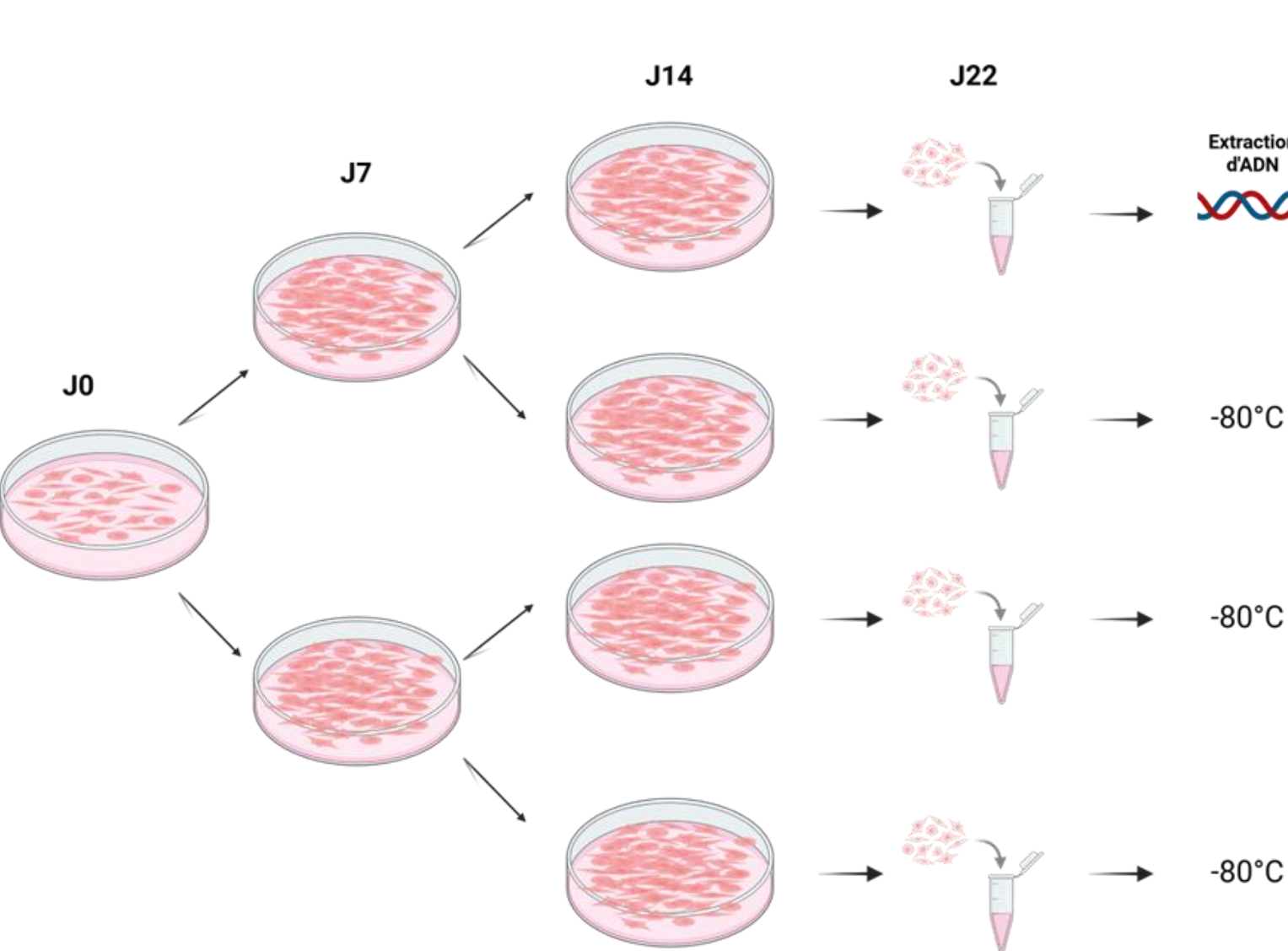
INTRODUCTION

Cutaneous aging results from both lifelong environmental exposures and epigenetic regulation, especially changes in DNA methylation that progressively alter gene expression. Age-related methylation drift is associated with alterations in pathway essential for keratinocyte function, dermal fibroblast activity, extracellular matrix maintenance, and antioxidant defenses (1). These molecular shifts contribute to hallmark aging features such as reduced regeneration, collagen degradation, impaired barrier integrity, and heightened inflammation (2). Epigenetic clocks, built on predictable methylation patterns at specific CpG sites, have emerged as powerful biomarkers of biological age (3). Models such as the Horvath clock estimate epigenetic age from DNA methylation patterns, while deviations from chronological age may reflect differences in biological aging (4). As biological age may reflect the cumulative effects of lifelong stressors, epigenetic clocks may thus represent valuable tools for evaluating lifestyle influences, disease burden, and the effects of targeted interventions.(5).

The objective of this study was to evaluate the ability of a blend of plant-derived bioactive compounds (Vine resveratrol extract, Magnolia Bark extract, and Rosewood extract) to modulate the epigenomic landscape of human dermal fibroblasts cultured *in vitro*.

MATERIALS & METHODS

Cellular model and culture



Primary human fibroblasts were cultured in 100-cm² dishes, passaged weekly, and split into two dishes at each passage. On Day 0, complete untreated medium was added, and on Day 1 it was replaced with medium containing the active compounds. Treated medium was renewed every two to three days for a total of three weeks. Untreated fibroblasts served as negative controls, while positive controls consisted of fibroblasts transiently infected with Sendai virus (SeV-4F) expressing the Yamanaka factors OSKM (Oct4, Sox2, Klf4, c-Myc) to induce transient reprogramming and associated epigenetic effects.

Tested compounds and concentrations

Active compounds	Acronym	Final Concentration
Negative control (ethanol mock)	Untreated	0.040%
Positive control (SeV-4F) in fibroblast culture medium	Transient reprogramming	—
Vine Resveratrol extract	OR	0.0005%
Magnolia extract	MG	0.0200%
Rosewood extract	BR	0.0100%
Vine Resveratrol extract+ Magnolia extract + Rosewood extract	OR + MG + BR	0.0005% OR + 0.020% MG + 0.010% BR

Genomic DNA Extraction and DNA Methylation Analysis

Genomic DNA was extracted from frozen fibroblast pellets (–80 °C) using the Qiagen DNeasy Blood & Tissue Kit, bisulfite-converted, and hybridized to the Illumina EPIC v2.0 BeadChip (>935,000 CpGs). IDAT files were processed with SeSAMe (v1.22.2) using the QCDBP workflow, including probe masking, dye-bias correction, detection-p-value calculation, and noob normalization. β -values (0–1) were computed for each CpG. Epigenetic age was determined using the proprietary Skinomix Clock (Ben Sadoun P, Lemaitre JM, 2025), a 94-CpG fibroblast-specific predictor trained on the laboratory's biobank (18–72 years; unpublished).

The parameters analyzed included:

- CpG Methylation profiles
- Epigenetic age: biological age estimated by epigenetic clocks.
- DeltaAge: difference in epigenetic age between paired treated and control samples (Treated – Control)

RESULTS

Active ingredients effect on fibroblasts methylome

The analysis revealed that resveratrol induced significant modulation of 15,319 CpG sites, including 9,385 hypermethylated and 5,934 hypomethylated sites (Figure 1A). Magnolia extract modulated 13,703 CpG sites (with 3,060 hypermethylated and 10,643 hypomethylated) (Figure 1B), while rosewood extract affected 9,188 CpG sites, including 2,801 hypermethylated and 6,387 hypomethylated sites (Figure 1C). The combination of the three extracts exhibited the most extensive effect, modulating 17,313 CpG sites, of which 7,639 were hypermethylated and 9,674 hypomethylated (Figure 1D). Finally, the Venn diagram analysis showed that only 501 CpG sites were shared among the three individual extracts (Figure 1E).

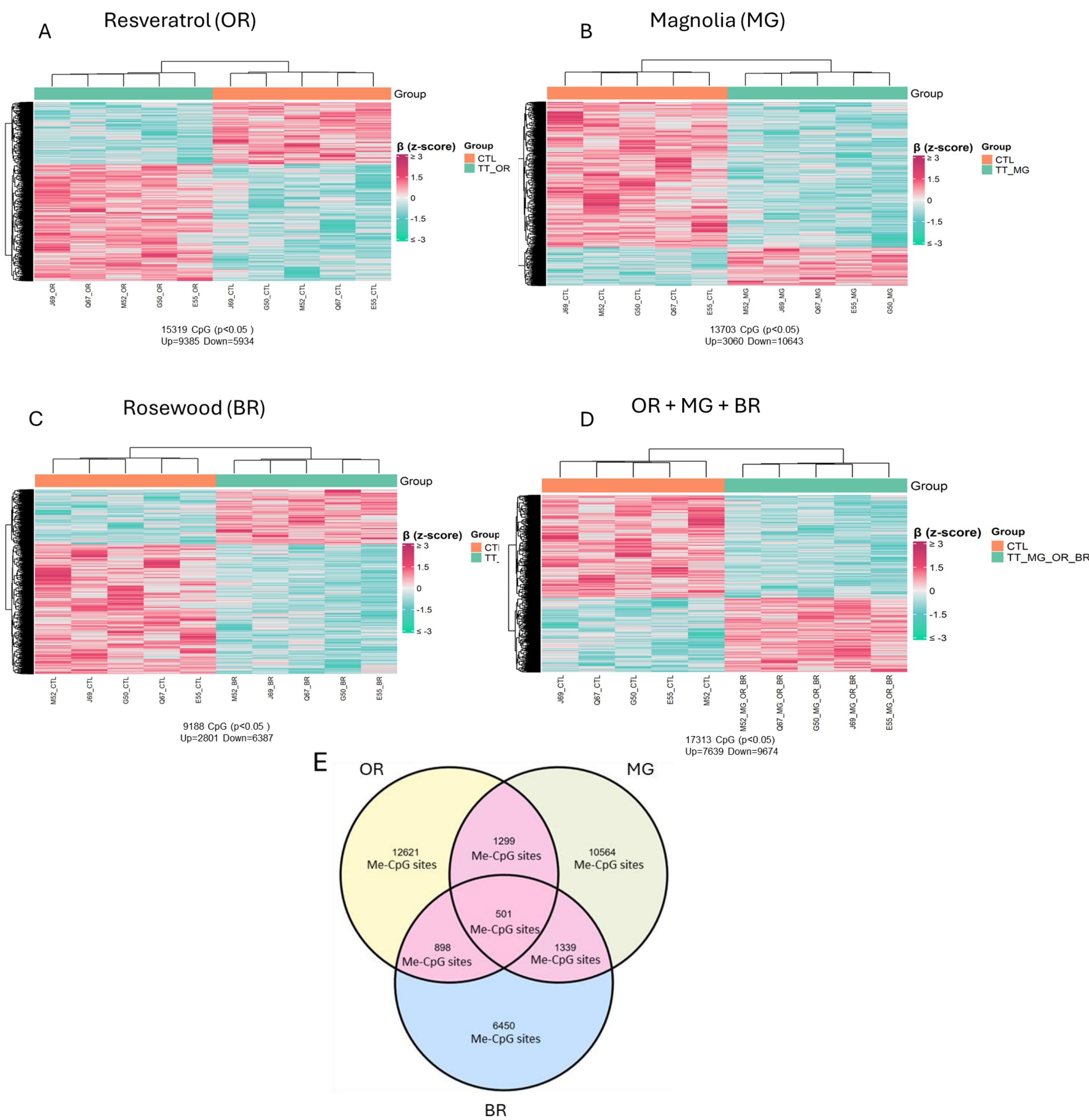


Figure 1. Comparative analysis of CpG methylation profiles between control and treated conditions. Heatmaps showing variations in CpG methylation (β -values, z-scores) between control (CTL) and treated (TT) groups: A) Resveratrol (OR), B) Magnolia (MG), C) Rosewood (BR), and D) OR+MG+BR. Differentially methylated CpG sites are ranked according to the magnitude of methylation changes, allowing identification of hypermethylated (up-methylated) and hypomethylated (down-methylated) CpGs in each treatment conditions. E) Venn diagram illustrating the overlap differentially methylated CpG sites across OR, MG, and BR conditions. Comparisons were performed using a one-way repeated-measures ANOVA with Geisser–Greenhouse correction, followed by Dunnett's post hoc test comparing each treated condition to the untreated control. Statistical significance was set at $p < 0.05$.

Epigenetic age modulation by active ingredients

Transient reprogramming reduced epigenetic age by 3 years, but this effect was not statistically significant ($p = 0.149$) (Figure 2B). A similar trend was observed for resveratrol, which reduced epigenetic age by –1.7 years ($p = 0.096$) (Figure 2B). In contrast, rosewood and magnolia extracts induced reduced epigenetic age of –3.4 years ($p = 0.027$) and –5.5 years ($p = 0.025$), respectively (Figure 2B). Finally, fibroblasts treated with the combination of the three active ingredients showed a significant reduction of epigenetic age by –4.1 years ($p = 0.01$) (Figure 2B).

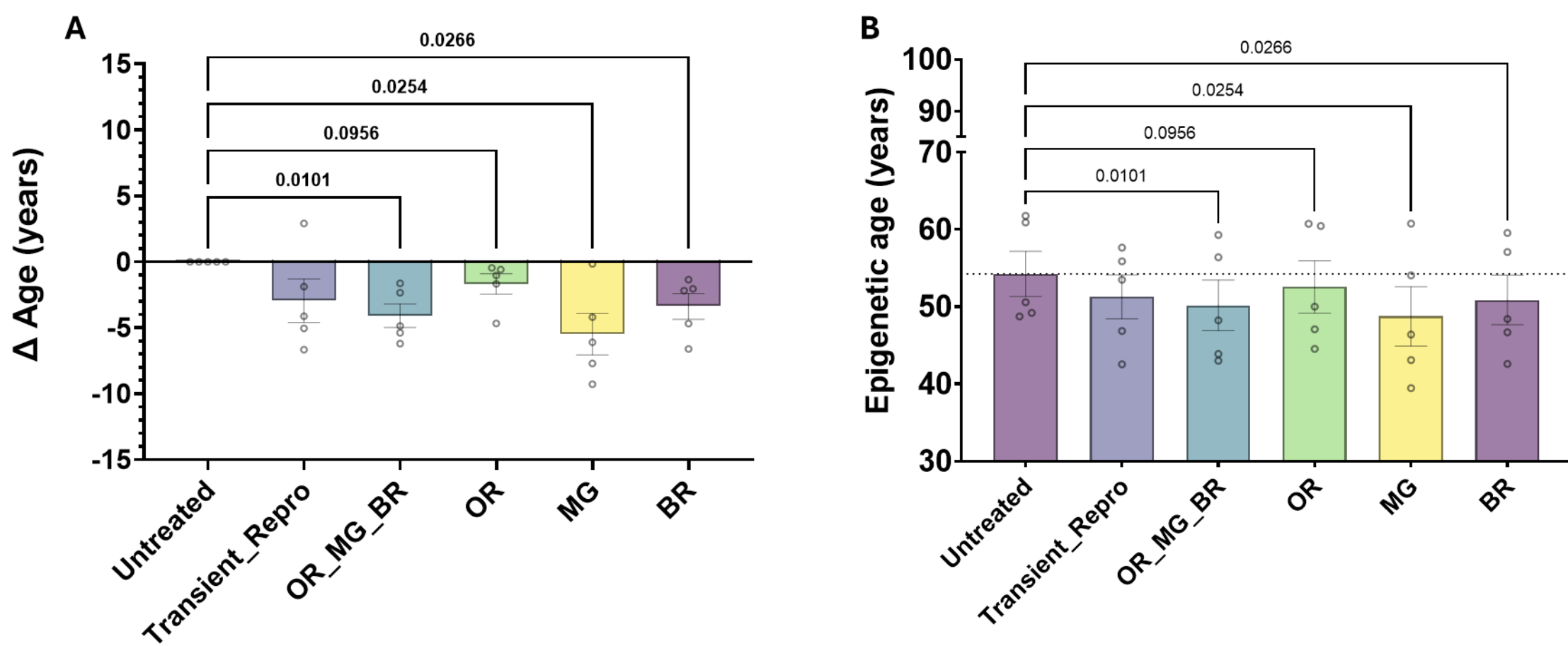


Figure 2. Epigenetic age and deltaAge in vitro. Results are shown as mean $\pm$ S.E.M. Statistical analysis is one-way ANOVA on paired data with Geisser–Greenhouse correction, followed by Dunnett's post-hoc test comparing each treated group to the untreated control group.

CONCLUSION

Together, these findings provide evidence that natural plant extracts can modulate both genome-wide and age-related epigenetic marks in human fibroblasts. By reshaping CpG methylation patterns and reducing epigenetic age, these ingredients may contribute to restoring a more youthful epigenetic profile, supporting their potential use in anti-aging dermocosmetic strategies. Future studies will be needed to identify the specific genes and pathways affected and to determine whether these epigenetic improvements translate into functional rejuvenation at the tissue level.

1. Johnson AA, Akman K, Calimport SRG, Wuttke D, Stolzinger A, de Magalhães JP. The Role of DNA Methylation in Aging, Rejuvenation, and Age-Related Disease. Rejuvenation Res. oct 2012;15(5):483-94.
2. Salameh Y, Bejaoui Y, El Hajj N. DNA Methylation Biomarkers in Aging and Age-Related Diseases. Front Genet. 10 mars 2020;11.
3. Liang R, Tang Q, Chen J, Zhu L. Epigenetic Clocks: Beyond Biological Age, Using the Past to Predict the Present and Future. Aging Dis. 13 déc 2024;16(6):3520-45.
4. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013.
5. Sallih A, Nichols T, Szabo L, Petersen SE, Raisi-Estabragh Z. Conceptual Overview of Biological Age Estimation. Aging Dis. 1 juin 2023;14(3):583-8.