

The Concentration Paradox: When Dose-Response Logic Collapses in a Photoaging Study [Letter]

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Dear editor

We read with interest the article by Feng et al on idebenone against UVB-induced photoaging in HaCaT cells.¹ The authors are commended for their multi-pathway investigation. However, we have identified critical logical contradictions and statistical and methodological inconsistencies that fundamentally undermine the reported conclusions and warrant clarification.

A direct logical contradiction exists in the wound healing assay results. The authors explicitly state that following IDE treatment, the “wound healing rate was enhanced in a concentration-dependent manner,” yet immediately conclude that “the 0.5 nM IDE treatment group exhibited the most pronounced effect.” These statements are mathematically mutually exclusive; a concentration-dependent enhancement inherently dictates that 5 nM > 1 nM > 0.5 nM. Asserting both suggests either an inversion of the quantitative data or a severe statistical misrepresentation, rendering the migration data uninterpretable.

Invalid statistical approach to multiple comparisons. The authors used one-way ANOVA followed by Tukey's post-hoc test across numerous independent endpoints (cell viability, migration, proliferation, senescence, SOD, MDA, ROS, MMP, ATP, three inflammatory cytokines, and two proteins), yet no correction for the total number of comparisons was applied. With over 30 separate hypothesis tests, the family-wise error rate substantially exceeds 0.05. The authors present numerous “significant” differences at $P < 0.05$ without acknowledging the high probability of false-positive findings inherent in such an uncorrected exploratory analysis. Given that many between-group differences are marginal (eg., Figure 4D–F shows modest SOD recovery with wide error bars), the robustness of these findings is questionable.

RNA-seq sample size falls below acceptable standards. Transcriptomic analysis was performed with only three biological replicates per group. While this meets minimum requirements for differential expression analysis, the field standard recommends at least 4–6 replicates per group to achieve adequate statistical power and reproducibility, particularly when fold changes are modest.² With only $n=3$, the DEGs identified (221 upregulated, 126 downregulated) are highly susceptible to outliers and technical variability, and the lack of independent validation cohorts further weakens the generalizability of the IL-3RA and TUBA8 mechanistic claims.

The authors' proposed causal mechanism is directly contradicted by their own data. They hypothesize that “oxidative stress often leads to mitochondrial dysfunction.” However, their own results show that 10 and 20 mJ/cm² UVB induced significant oxidative stress (decreased SOD, increased MDA in Figure 4D–I), yet explicitly note these sub-30 mJ/cm² doses did not cause mitochondrial damage, recording an MMP maintenance rate >90%. If oxidative stress was the primary driver of mitochondrial dysfunction, these intermediate doses should have exhibited dose-dependent membrane depolarization. Their own dose-response data refutes their mechanistic premise.³

In summary, the wound healing data contain a mutually exclusive contradiction regarding concentration dependence, the mechanistic premise is refuted by the authors' own dose-response findings, uncorrected multiple testing inflates false-positive risk, and the RNA-seq sample size falls below field standards. These are not minor clarifications—they strike at the core of the efficacy claims and proposed mechanisms. We urge the authors to re-analyze their data, apply appropriate statistical corrections, and provide transparent explanations for these inconsistencies.

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