

An evidence-driven classification of nonfiltering ingredients for topical photoprotection

Dear Editor, Sunscreens provide essential protection against ultraviolet (UV) radiation, significantly reducing sunburn, skin cancer and photoageing.¹ However, conventional sunscreen filters have limitations, including inadequate protection against long-wavelength UVA radiation and visible and infrared light.¹ There are also increasing concerns about their impact on the aquatic environment.² This has led to the incorporation of nonfiltering photoprotective ingredients (PINGs) into sunscreen formulations, which are designed to enhance photoprotection by modulating the skin's biological response to solar radiation. Despite their increasing use, no objective efficacy-based classification of PINGs exists.

To address this gap, we performed a systematic review of the published literature up to December 2022. We identified 2380 relevant publications, from which a total of 1750 PINGs were identified. Each PING was then assigned an evidence score based on the strength and volume of experimental support regarding its ability to prevent oxidative stress, DNA damage, cell death, immunosuppression, erythema, pigmentation, inflammation and photoageing. This score considered the specific type of experimental support for each PING and broadly followed the hierarchy or levels of evidence used in classical evidence-based medicine. To generate scores, a tiered scoring system was employed using the highest form of evidence as its starting point, with all

other equivalent and lower forms of evidence subsequently summed to generate the final evidence score (Figure 1). To avoid overweighting PINGs that were supported by numerous studies of low validity, the maximum theoretical score for a specific study type was restricted (Figure 1). Each PING was then assigned an evidence classification based on its score (Figure 1). A full description of the methods is available upon request.

The results showed that 85% of PINGs were supported only by weak or very weak evidence, with only 148 PINGs supported by any form of clinical study. Notably, only 48 PINGs (2.7%) were supported by strong (21, 0.9%) and very strong (27, 1.5%) evidence. The top-performing ingredients included the following:

- L-ascorbic acid (vitamin C), which was identified as the most effective against oxidative stress;
- Photolyase, a DNA repair enzyme, which demonstrated strong evidence in reducing DNA damage and preventing apoptosis;
- Nicotinamide (vitamin B3), which was most effective at reducing UV-induced immunosuppression;
- Epigallocatechin gallate, a green-tea polyphenol, which showed anti-inflammatory properties;
- Tocopheryl acetate (vitamin E), which was most effective at limiting erythema;
- Isobutylamido thiazolyl resorcinol, which was the best-supported depigmenting agent for reducing UV-induced hyperpigmentation;

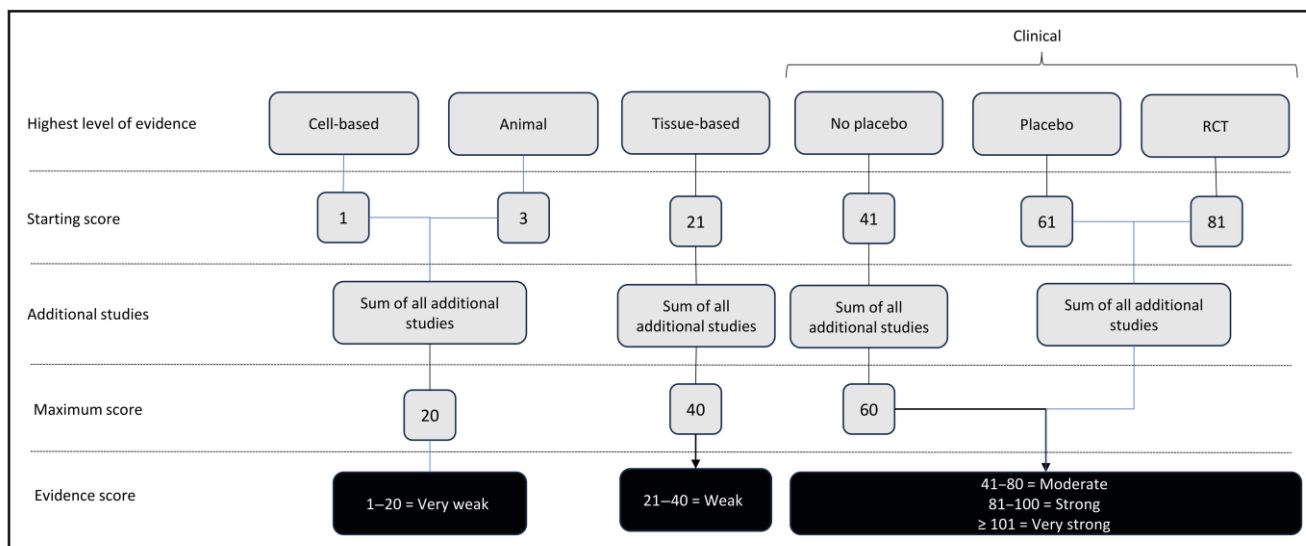


Figure 1 Algorithm for calculation of evidence scores.

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- n-acetyl-L-cysteine, which demonstrated the strongest evidence for preventing photoageing through reactive oxygen species scavenging.

A complete list of all PINGs identified in this study and their associated evidence scores is available upon request.

Our findings support the growing concept of 'biological photoprotection', in which traditional sunscreen filters are supplemented with ingredients that enhance the skin's intrinsic defense mechanisms against solar radiation in addition to other exposome factors. However, our results revealed that no single substance is capable of effectively protecting the skin from all the biological effects of sunlight, suggesting that it will be necessary to supplement sunscreens with more than one PING with complementary mechanisms to achieve full-spectrum photoprotection.

The data also suggested that clinical studies involving PINGs are being performed less frequently; the peak number of trials (10 per year) was performed in 2004 and 2005, and most of the studies supporting the top-ranking ingredients were performed between 1995 and 2010. We speculate that this may reflect the increasing commercialization of PINGs, rather than a lack of research interest in investigating the photoprotective effects of PINGs per se; ingredient suppliers may be less likely to publish their research in peer-reviewed journals for commercial reasons.

In conclusion, the lack of high-quality evidence supporting the use of PINGs for photoprotection currently limits their utility in sunscreens. For most PINGs, the level of evidence is very poor and additional studies with robust methodology must be conducted to assess the potential usefulness of these additive agents in sunscreens. Moreover, as no single method is currently capable of objectively measuring the photoprotective capacity of PINGs, a harmonized method for their assessment is required.

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