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Orange Peel Bioactives for Skin Exposome Defense: A Review of Transferosomal Dermaceuticals Against UV Radiation, Blue Light and Air Pollution

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Abstract: The skin exposome represents a multifactorial burden of environmental stressors, including ultraviolet (UV) radiation, high-energy visible (HEV) blue light, and airborne particulate pollution, that collectively contribute to oxidative stress, inflammation, DNA damage, matrix metalloproteinase activation, collagen degradation, pigmentation, and premature skin aging. Sweet-orange peel (*Citrus sinensis*) contains a diverse profile of flavonoids, phenolics, polymethoxylated flavones, carotenoids, and volatile constituents that have been investigated for several skin-relevant biological activities. However, the limited aqueous solubility, chemical instability, and restricted penetration of several phytochemicals across the stratum corneum may limit their topical effectiveness. Transferosomes, ultra-deformable phospholipid vesicles incorporating edge activators, offer a promising delivery platform by improving vesicular flexibility. This review integrates current evidence concerning skin exposome stressors, orange peel phytochemistry, biological activities relevant to environmental skin damage, and transferosomal drug-delivery strategies. Particular emphasis is placed on the proposed development of an orange peel extract-loaded transferosomal lotion and the potential application of Quality-by-Design and Box–Behnken experimental design for formulation optimization. Although individual components demonstrate promising biological activities, direct evidence for an integrated formulation against combined UV, blue-light, and pollution exposure remains limited. Standardization of botanical extracts, vesicle stability, characterization, scalability, dermal safety, and clinical validation therefore remain important translational challenges. Overall, transferosomal delivery represents a rational approach for converting citrus waste-derived bioactives into sustainable, multifunctional dermaceutical systems targeting the skin exposome.

Keywords: *Citrus sinensis*; skin exposome; transferosomes; dermaceuticals; UV radiation; blue light; air pollution.

1. INTRODUCTION

The skin is the body's largest organ and its primary interface with the external environment, continuously mediating exposure to solar radiation, airborne pollutants, and microbial agents while maintaining systemic homeostasis. Solar radiation itself is a double-edged phenomenon: it drives essential physiological processes such as vitamin D3 photosynthesis and is even harnessed therapeutically, such as narrowband UVB in psoriasis and vitiligo and far-UVC (222 nm) for pathogen inactivation, including recent applications against SARS-CoV-2. Yet the same electromagnetic spectrum that enables these benefits

spanning UVC (100–280 nm), UVB (280–320 nm), UVA (320–400 nm), and high-energy visible (HEV) blue light (400–500 nm) is also the principal driver of cutaneous pathology when exposure becomes chronic or excessive.^[1,2]

Environmental exposure to these stressors has intensified in recent decades. Rising atmospheric chlorofluorocarbon (CFC) emissions and consequent stratospheric ozone depletion have increased surface-level UV intensity, while urbanization has raised ambient particulate matter (PM_{2.5}) concentrations and prolonged screen-based blue light exposure. Together, these factors constitute what is now termed the "skin exposome," the cumulative, lifetime burden of external stressors that drives oxidative stress, chronic inflammation, DNA damage, and premature senescence in cutaneous tissue.^[1,2,3,4,5,6]

Addressing this multifactorial burden requires more than single-mechanism intervention. Conventional sunscreens and antioxidant cosmetics typically target UV filtration or isolated free-radical scavenging, leaving blue-light- and pollution-driven pathways inadequately addressed. This has motivated growing interest in multifunctional, plant-derived bioactive systems capable of intervening across several exposome pathways simultaneously.^[1,2,7,8]

Orange peel (*Citrus sinensis*) is a phytochemically complex residue of citrus processing, containing multiple constituent classes that have attracted interest for their potential antioxidant, inflammation-modulating, and skin-protective effects.^[9] Valorizing this waste stream aligns dermatological innovation with circular-economy principles.^[10] However, the clinical translation of these phytochemicals is constrained by their limited solubility and poor penetration across the lipophilic stratum corneum.^[11] Transferosomes, ultra-deformable phospholipid vesicles incorporating edge activators, offer a promising delivery platform by improving vesicular flexibility and enhancing cutaneous localization of encapsulated bioactives.^[12]

This review aims to synthesize current evidence on orange peel phytochemistry, exposome-stressor biology, and transferosomal delivery science, and to critically evaluate the rationale, formulation strategy, and translational gaps surrounding an orange peel extract-loaded transferosomal lotion as a multifunctional exposome-protective dermatological.^[9,12,13]

2. SKIN EXPOSOME AND ENVIRONMENTAL STRESSORS

The skin serves as the primary biological interface against microbes, particulates, and radiation, maintaining systemic homeostasis through a tightly regulated barrier function. However, it remains the principal target of the "exposome" the cumulative external factors that induce molecular damage across an individual's lifetime.^[1,11]

2.1 Concept of the Skin Exposome

The skin exposome encompasses the total environmental burden of radiation, pollution, temperature, humidity, and lifestyle factors that drives cutaneous pathology. These stressors act cumulatively and synergistically, inducing molecular and cellular imbalances that disrupt barrier integrity and accelerate chronological and extrinsic aging.^[1,2,6]

2.2 Ultraviolet Radiation and Cutaneous Damage

UV effects are strongly wavelength-dependent. Researchers now distinguish narrowband UVB (311–313 nm), UVA₂ (320–340 nm), and UVA₁ (340–400 nm) as clinically relevant sub-bands. UVA penetrates into the dermis, exciting endogenous chromophores and generating ROS indirectly, while UVB is absorbed predominantly in the epidermis and basal layer, causing direct DNA photodamage. Both pathways converge on a common cascade: ROS generation, cyclobutane pyrimidine dimer (CPD) and 6-4 photoproduct (6-4PP) formation, collagen degradation via MMP activation, photoaging, and dysregulated pigmentation. Chronic exposure particularly to narrowband UVB also triggers acute erythema and long-term photo-immunosuppression.^[1,13]

2.3 Blue Light and Oxidative Skin Stress

HEV blue light (400–500 nm), with dermatologically relevant peaks near 452 and 456 nm, originates from both solar and digital-screen sources. Unlike UV, blue light exposure is not confined to daylight hours, and evidence suggests it may disrupt dermal circadian rhythms in addition to degrading cutaneous carotenoids and stimulating melanogenesis contributing to hyperpigmentation and photoaging through oxidative pathways distinct from, but overlapping with, UV damage.^[2,6]

2.4 Air Pollution and Particulate Matter

Particulate matter (PM_{2.5}) acts synergistically with radiation to amplify oxidative burden. Radiation-induced barrier disruption facilitates deeper penetration of chemical pollutants, while pollutants themselves catalyze additional ROS formation on the skin surface - an additive rather than merely independent insult.^[5]

2.5 Combined Effects of Exposome Stressors

The cumulative interaction of UV, blue light, and pollution results in a degraded extracellular matrix (ECM), persistent low-grade inflammation, and compounded oxidative injury that exceeds what any single stressor produces in isolation. Understanding these synergistic interactions is the strategic prerequisite for developing multifunctional shields that provide more than simple UV filtration, establishing the problem that the proposed formulation is intended to address.^[1,5]

3. ORANGE PEEL AS A SOURCE OF DERMACEUTICAL BIOACTIVES

Waste valorization transforms citrus byproducts into high-value pharmaceutical assets, framing orange peel as a concentrated reservoir of defensive bioactives.^[10]

3.1 Botanical Profile and Waste Valorization

Citrus sinensis peel residues constitute a substantial fraction of the material generated during sweet-orange processing and can serve as a renewable source of phytochemical ingredients. Recovery of these constituents provides an opportunity to convert processing residues into value-added materials for pharmaceutical and topical applications.^[10]

3.2 Phytochemical Composition of Orange Peel

The phytochemical profile of orange peel comprises several classes, with flavanones, polymethoxylated flavones, phenolics, carotenoids, and volatile compounds being among the principal reported constituents.^[14] Collectively, these molecules act as DNA-protective agents, mitigating the formation of mutagenic photoproducts under solar radiation exposure.^[15]

3.3 Major Bioactive Flavonoids

Hesperidin, naringin, and the polymethoxylated flavone nobiletin are among the orange-peel constituents that have received considerable attention in biological and dermatological research. These compounds function as potent antioxidants and anti-inflammatory agents, neutralizing ROS and inhibiting pro-inflammatory cytokines including IL-1, IL-6, and TNF- α .^[16]

3.4 Biological Activities Relevant to Skin Health

By acting as radical scavengers and, in some contexts, natural photosensitizers, orange peel bioactives prevent lipid peroxidation and protein degradation, and demonstrate antioxidant, anti-inflammatory, photoprotective, anti-photoaging, and antimelanogenic potential — exploiting industrial waste for molecular defense in a manner that represents a paradigm shift toward resource-efficient, sustainable pharmacology.^[8,10]

4. ORANGE PEEL BIOACTIVES AGAINST THE SKIN EXPOSOME

Modern dermaticals must provide multifactorial protection against the complex, overlapping pathways of environmental stress.

Antioxidant Defense Against UV-Induced Oxidative Stress

Orange peel bioactives neutralize superoxide anions (O₂^{•-}), singlet oxygen (1O₂), and hydroxyl radicals (•OH), intercepting oxidative stress before it triggers cellular senescence or apoptosis.^[8]

Protection Against Blue-Light-Induced Oxidative Damage

These compounds mitigate HEV-induced oxidative stress, which otherwise degrades cutaneous carotenoids and stimulates melanogenesis.^[6]

Potential Protection Against Pollution-Induced Skin Damage

Bioactives reinforce antioxidant defense partly by supporting catalase activity. This is mechanistically significant because oxidative stressors can alter catalase function, contributing to hydrogen peroxide accumulation — a vulnerability that flavonoid-mediated antioxidant activity may help offset.^[8]

Anti-Inflammatory and Anti-Photoaging Effects

By inhibiting NF- κ B and MAPK signaling, orange peel bioactives may suppress upregulation of MMP-1, MMP-3, and MMP-9 — enzymes responsible for degrading structural extracellular matrix proteins and contributing to visible photoaging.^[17]

Potential Skin Barrier and Collagen Protection

Bioactives may limit collagen fragmentation and support Type I collagen synthesis, helping preserve the mechanical resilience of the extracellular matrix.^[17]

Evidence Gap in Multifactorial Exposome Protection

It is important to distinguish three tiers of evidence:

- (i) Activity demonstrated directly for whole orange peel extract
- (ii) Activity demonstrated for isolated orange-peel compounds, such as purified hesperidin or nobiletin, rather than the crude extract.
- (iii) Activity that remains hypothetical or extrapolated for the complete transferosomal formulation, where direct experimental data are not yet available. Notably, there is a critical lack of studies combining UV, blue light, and pollution in a single integrated "triple-stressor" model. Most existing work isolates one stressor at a time, and bridging this evidence gap is essential for validating the real-world clinical efficacy of multifactorial protective formulations.^[11,15,16]

5. TRANSFEROSOMES AS ADVANCED TOPICAL DELIVERY SYSTEMS

The stratum corneum acts as a lipophilic barrier that hinders penetration of hydrophilic and moderately lipophilic phytochemicals alike. Advanced delivery systems are therefore a strategic necessity for effective dermal bioactive delivery.^[11]

Structure and Composition of Transferosomes

Transferosomes are ultra-deformable, lipid-based vesicles composed of a phospholipid bilayer combined with an edge activator (surfactant) component.^[18]

Role of Phospholipids and Edge Activators

Phospholipids such as soy lecithin form the structural bilayer, while edge activators impart high membrane curvature and elasticity, allowing the vesicle to deform without rupturing.^[18]

Deformability and Skin Penetration

Driven by the transepidermal moisture/osmotic gradient, transferosomes squeeze through intercellular pores substantially smaller than their own diameter, enabling deeper penetration than conventional liposomes.^[18]

Mechanisms of Transferosomal Skin Delivery

Penetration proceeds via a combination of intercellular lipid pathway diffusion and vesicle self-deformation in response to the hydration gradient, ultimately localizing the payload within the epidermis and upper dermis.^[18]

Advantages Over Conventional Liposomes and Topical Systems

Relative to liposomes and free extract formulations, transferosomes offer potentially improved entrapment, deformability, and cutaneous deposition, although the magnitude of these advantages depends on formulation composition and experimental conditions.^[18]

Limitations of Transferosomal Delivery

Stability during storage and manufacturing scalability remain significant hurdles, along with sensitivity to formulation variables such as lipid-to-surfactant ratio and hydration method.^[18]

6. ORANGE PEEL EXTRACT-LOADED TRANSFEROSOMAL SYSTEM

Standardization at every formulation stage is important for therapeutic consistency and potency across batches.

Selection and Standardization of Orange Peel Extract

Bioactive markers such as hesperidin content should be quantified through appropriate analytical fingerprinting to ensure batch-to-batch reproducibility.^[16]

Extraction Approaches

Green extraction methods are preferred where possible to preserve phytochemical integrity while maintaining the sustainability profile of the overall system.^[10]

Selection of Transferosomal Components

Key components include a phospholipid source such as soy lecithin, an edge activator such as Tween 20, an aqueous phase, and other formulation excipients selected to balance stability and deformability.^[18]

Preparation Approaches

Commonly reported methods include thin-film hydration, hand-shaking, and sonication, each offering trade-offs in vesicle size control, scalability, and entrapment efficiency.^[18]

Formulation Optimization

Precise lipid-to-surfactant ratios must be optimized to balance vesicle stability against deformability and entrapment efficiency.^[18]

Quality-by-Design and Box–Behnken Design

Systematic optimization using Quality-by-Design (QbD) principles and statistical designs such as Box–Behnken enables predictive control over vesicle size, PDI, and entrapment efficiency, reducing empirical trial-and-error and providing a systematic framework for formulation development.^[13]

7. CHARACTERIZATION AND EVALUATION OF TRANSFEROSOMES

Rigorous analytical characterization is essential for establishing the physicochemical quality and functional performance of the system.

Vesicle Size and Polydispersity Index

Nanometer-range vesicle size may facilitate cutaneous delivery, while a low PDI indicates a more uniform vesicle population and improved formulation reproducibility.^[12]

Zeta Potential

Zeta potential provides information concerning surface charge and colloidal stability. Higher absolute zeta-potential values are generally associated with greater electrostatic repulsion and reduced aggregation, although stability also depends on the dispersion medium and formulation composition.^[12]

Entrapment Efficiency

Entrapment efficiency quantifies the proportion of the bioactive extract incorporated within the vesicular system relative to the total amount initially added.^[18]

Morphology

Morphological characterization using techniques such as transmission electron microscopy (TEM) or field-emission scanning electron microscopy (FESEM) can provide information concerning vesicle shape, integrity, surface characteristics, and aggregation.^[12]

Extract/Drug Content

Quantitative extract or marker-compound assay confirms the actual bioactive content relative to the intended formulation concentration.^[12]

Deformability Index

The deformability index provides an important indication of vesicle elasticity and the ability of transferosomes to pass through constricted pathways without complete structural disruption.^[18]

In Vitro Release

In vitro release studies provide information concerning the release behavior of encapsulated bioactives. Release profiles may be analyzed using mathematical kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models, to provide insight into the predominant release mechanism.^[12]

Stability

Long-term physical and chemical stability, including vesicle leakage, aggregation, changes in particle size, and bioactive degradation, should be assessed under relevant storage conditions.^[12]

8. TRANSFEROSOMAL LOTION AS A MULTIFUNCTIONAL DERMACEUTICAL

User-centric formulation bridges the gap between advanced nanotechnology and practical topical application.

Rationale for Lotion-Based Delivery

A lotion base provides a practical vehicle for broad-area topical application and may improve ease of application compared with a plain transferosomal dispersion.^[7]

Incorporation of Transferosomes into Lotion

Transferosomes may be incorporated into a suitable lotion base under conditions designed to preserve vesicle integrity while ensuring uniform distribution of the encapsulated bioactives.^[18]

Physicochemical and Cosmetic Characteristics

Key parameters include appearance, homogeneity, pH, spreadability, viscosity, skin feel, and overall cosmetic acceptability. These characteristics should be optimized for compatibility with normal skin physiology and consumer use.^[7]

Potential Advantages of the Transferosomal Lotion

Combining nanocarrier-enhanced delivery with a cosmetically acceptable vehicle may provide the dual advantages of improved cutaneous localization and practical topical application. However, the efficacy of the complete formulation requires direct experimental and clinical validation.^[12]

9. PROPOSED MECHANISM OF SKIN EXPOSOME PROTECTION

This section presents a proposed mechanistic framework based on evidence reported for individual orange-peel bioactives and transferosomal delivery systems.

Antioxidant and ROS-Scavenging Mechanisms

Transferosomal delivery is proposed to enhance the cutaneous localization of orange peel bioactives at sites of free-radical generation. These compounds may neutralize reactive oxygen species such as superoxide and hydroxyl radicals and contribute to restoration of antioxidant balance.^[8]

Anti-Inflammatory Pathways

Orange peel bioactives are proposed to modulate inflammatory signaling pathways, including NF- κ B and MAPK, thereby potentially reducing the expression of pro-inflammatory mediators such as IL-1, IL-6, and TNF- α .^[16,17]

Protection Against Matrix Metalloproteinase Activation

Bioactives may suppress pathways associated with AP-1 activation and MMP expression, particularly MMP-1, MMP-3, and MMP-9. Reduction of oxidative and inflammatory signaling may consequently limit extracellular matrix degradation and photoaging.^[17] Protection against UV-associated DNA photoproduct formation, including CPDs and 6-4PPs, represents a further proposed protective mechanism.^[1,15]

Protection of Collagen and Skin Barrier

Modulation of signaling pathways involved in extracellular matrix homeostasis, including TGF- β /Smad signaling, may contribute to maintenance of collagen and skin structural integrity. These mechanisms remain to be directly established for the complete orange peel transferosomal system.^[17]

Integrated Multifactorial Exposome Defense

By potentially improving the cutaneous localization of bioactives, transferosomal delivery may enable antioxidant, anti-inflammatory, anti-photoaging, and barrier-supportive mechanisms to act within the same anatomical environment. The integrated protection against UV radiation, blue light, and air pollution therefore represents a scientifically plausible but experimentally testable model rather than an established clinical outcome.^[12,18]

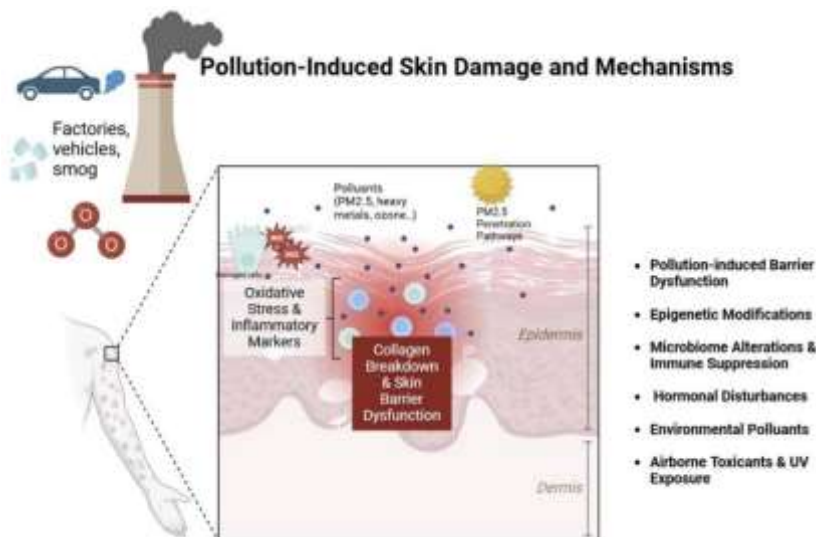


Fig 1: Proposed mechanism of orange peel bioactive-loaded transferosomal protection against UV radiation, blue light, and air-pollution-induced skin damage.

10. CURRENT EVIDENCE, RESEARCH GAPS AND CHALLENGES

Strategic assessment of current evidence is essential for positioning this work as a critical review rather than a descriptive literature summary.

Current Evidence

Existing evidence supports individual components of the proposed system, including antioxidant and anti-inflammatory activities of orange peel-derived bioactives and the potential of transferosomal systems to enhance dermal delivery. However, these components have generally been investigated separately rather than as a single integrated exposome-protective formulation.^[8,16,18]

Limitations of Existing Studies

Much of the supporting evidence derives from in vitro experiments or simplified biological models that do not fully reproduce the structural, biochemical, and immunological complexity of human skin.^[5,12]

Lack of Integrated Exposome-Protection Studies

There remains a critical need for experimental models simultaneously incorporating UV radiation, blue light, and particulate pollution. Such models would better represent real-world environmental exposure and allow assessment of potential additive or synergistic effects.^[1,5]

Extract Standardization and Batch Variability

Natural variability in orange peel feedstock, including cultivar, geographical origin, maturity, processing history, and extraction conditions, can produce meaningful differences in phytochemical composition. Standardized marker-based characterization is therefore essential.^[10,16]

Transferosome Stability

Vesicle leakage, aggregation, phospholipid oxidation, and changes in membrane structure during storage may affect product performance. Appropriate stability studies are necessary before clinical translation.^[12]

Translation from In Vitro to Human Skin

Ex vivo human skin studies and controlled clinical investigations of the complete formulation remain necessary to determine penetration, localization, efficacy, tolerability, and safety.^[12]

Regulatory and Manufacturing Considerations

Scale-up, reproducibility, dermal toxicity assessment, raw-material standardization, quality control, and regulatory classification represent important challenges before commercialization. Failure to validate these systems in complex, human-relevant environments may delay the transition of circular-economy nanomedicine from laboratory research to practical dermatological applications.^[12]

11. FUTURE PERSPECTIVES

Standardized Orange Peel Bioactive Extracts

Development of analytically standardized and reproducible extraction protocols should be prioritized to minimize batch-to-batch variation in bioactive composition.^[10]

Advanced Transferosomal and Hybrid Nanocarriers

Hybrid vesicular systems and combinations with other advanced nanocarriers may provide opportunities to improve penetration, payload stability, and controlled delivery. Such approaches should be evaluated carefully for safety and reproducibility.^[19]

Multifunctional Exposome-Targeted Formulations

Future formulations should be explicitly designed and experimentally validated against combined UV, blue-light, and pollution exposure models rather than relying solely on single-stressor studies.^[5]

Smart and Stimuli-Responsive Delivery

Stimuli-responsive systems, including exposure-responsive release strategies, may provide opportunities for adaptive delivery of antioxidant and protective bioactives in response to environmental stress.^[19]

QbD- and AI-Assisted Optimization

Quality-by-Design combined with computational and machine-learning approaches may facilitate prediction of optimal lipid-surfactant combinations and formulation conditions, potentially accelerating development while reducing empirical experimentation.^[13]

Ex Vivo and Clinical Validation

Future research should incorporate human ex vivo skin models, advanced imaging, molecular profiling, and appropriately designed clinical studies to establish penetration, biological activity, safety, and real-world efficacy of the complete formulation.^[12]

12. CONCLUSION

Orange peel represents a promising and sustainable source of flavonoids, polymethoxylated flavones, phenolic compounds, carotenoids, and other bioactive constituents with potential relevance to the major biological pathways involved in skin exposome-associated damage. Its antioxidant, anti-inflammatory, photoprotective, anti-photoaging, and antimelanogenic properties provide a rational basis for investigating citrus-derived bioactives as multifunctional dermatological ingredients. However, the topical application of these compounds is constrained by limitations including poor aqueous solubility, chemical instability, and restricted penetration through the stratum corneum. Transferosomes provide a promising delivery strategy because their highly deformable phospholipid membranes and edge activators can enhance the cutaneous localization of encapsulated bioactives. Integration of standardized orange peel extracts with transferosomal technology, supported by Quality-by-Design and systematic formulation optimization, may therefore provide a rational platform for developing sustainable exposome-oriented topical formulations. Nevertheless, the proposed ability of the complete system to simultaneously protect against UV radiation, blue light, and air pollution remains a mechanistic hypothesis requiring direct validation. Future research should prioritize standardized extracts, physicochemical and biological characterization, multi-stressor experimental models, ex vivo human skin studies, dermal safety assessment, formulation stability, and ultimately well-designed clinical investigations. Such evidence will determine whether citrus-waste valorization can progress from a promising sustainability concept to a scientifically validated multifunctional dermatological strategy for skin exposome defense.

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