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Comprehensive Management of Premature Skin Aging: Current Strategies, Treatments, and Emerging Therapies

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ABSTRACT

Introduction and Aim. Premature skin aging results from both intrinsic and extrinsic factors, requiring a comprehensive management strategy. This review evaluates current and emerging approaches for preventing and treating premature skin aging, focusing on efficacy and safety.

Materials and Methods. A review of recent scientific literature on topical, oral, and procedural interventions for managing premature skin aging was conducted. **Analysis of Literature.** Topical treatments, particularly retinoids and antioxidants, are key in skin regeneration and oxidative stress reduction. Oral interventions, including systemic retinoids and nutraceuticals, support overall skin health. Procedural methods like laser therapies, microneedling, and chemical peels are effective in skin rejuvenation. Preventive measures, such as photoprotection and lifestyle changes, are crucial. Emerging therapies, such as stem cell treatments, show promise in reversing age-related skin changes. **Conclusion.** Managing premature skin aging requires a combination of topical, oral, and procedural treatments with preventive strategies. Future research should focus on refining protocols, assessing novel therapies' long-term safety, and developing personalized approaches considering genetic, environmental, and lifestyle factors.

Keywords: antioxidants**,** extrinsic aging**,** photoaging**,** premature skin aging**,** retinoids, stem cell therapy

Introduction

The skin is a complex organ that plays a crucial role in maintaining overall health by acting as a barrier against external threats and regulating various physiological processes.[1] Aging is a fundamental biological phenomenon that has been ongoing since life first emerged on Earth approximately 3.5 billion years ago.[2] The global population is aging rapidly, with an increasing number of older individuals worldwide.[3] Much like the whole organism, the skin undergoes an inevitable internal aging process.[4] Skin aging is a multifactorial process influenced by intrinsic and extrinsic factors. Intrinsic aging is a natural biological process governed by genetics and metabolic changes. As individuals age, the skin gradually becomes

thinner and loses elasticity due to decreased collagen and elastin production. Fibroblasts, which are the cells responsible for producing these proteins, also become less efficient over time. Extrinsic aging, also known as photoaging or environmentally-induced aging, is is primarily caused by external factors such as UV radiation, pollution, and lifestyle habits like smoking. UV radiation, in particular, accelerates skin aging by breaking down collagen and creating abnormal elastin, leading to wrinkles, pigmentation changes, and a leathery skin texture. This process involves an increase in the activity of matrix metalloproteinases (MMPs), enzymes that degrade collagen and other components of the skin's extracellular matrix.[5,6] Environmental pollution accelerates premature skin aging primarily through the induction of oxidative stress and inflammation, as airborne pollutants and particulate matter generate free radicals that damage cellular structures and initiate inflammatory responses, leading to the degradation of collagen and elastin within the skin.[7-9] Smoking contributes to premature skin aging through the promotion of oxidative damage and inflammatory processes. The toxic chemicals in cigarette smoke induce the formation of reactive oxygen species, compromise blood flow, and reduce collagen production, ultimately resulting in the degradation of collagen and elastin in the skin.[10-12] Cellular senescence, a key factor in photoaging, is also crucial in the development of age-related skin pathologies. Cellular senescence leads to a decline in skin regenerative capacity, promoting conditions like chronic wounds and skin fibrosis. Additionally, such changes may increase the risk of somatic diseases, including chronic conditions, which affect overall health and quality of life.[13-15] Premature skin aging can lead to issues that are not only aesthetic but also negatively impact mental health, contributing to decreased self-esteem and heightened anxiety.[16] Studies have demonstrated that shortened telomeres, commonly observed in prematurely aged skin, are associated with a heightened risk of cardiovascular diseases and certain malignancies. Additionally, genetic conditions like Werner syndrome, which involves rapid skin aging, are closely associated

with systemic conditions such as osteoporosis and cataracts, highlighting the broader health implications of premature skin aging. The connection between telomere biology and these conditions underscores the broader health implications of early skin aging.[17]

Aim

The aim of this literature review is to examine and synthesize current knowledge on the management of premature skin aging. This review seeks to identify and evaluate the various strategies, treatments, and interventions that have been researched and implemented in the prevention and management of early skin aging. By analyzing the available scientific literature, the study aims to provide a comprehensive overview of the most effective approaches for addressing the signs of premature aging. The ultimate goal is to inform clinical practice and guide future research in the field of dermatology and cosmetic science.

Material and methods

This literature review was conducted by searching the PubMed and Google Scholar databases during June and July 2024. The search focused on identifying relevant peer-reviewed articles, clinical studies, and reviews published in English that addressed the management of premature skin aging. The search terms included “skin aging,” “photoaging,” “intrinsic aging,” "extrinsic aging," "premature skin aging," "premature skin aging treatment," “premature skin aging management,” “retinoids,” “antioxidants,” “stem cell therapy,” “skin rejuvenation,” "UV radiation," and "skin care treatments."**.** Articles were first screened for relevance based on their titles and abstracts, followed by a full-text review to ensure they met the inclusion criteria. Studies that did not specifically address the management or prevention of premature skin aging were excluded. The selected articles were then thoroughly reviewed

and the key findings were synthesized to provide a detailed overview of the current approaches to managing premature skin aging.

Analysis of literature

Management Strategies

Topical treatment

Topical retinoids are a cornerstone in the management of premature skin aging, offering a non-invasive and highly effective treatment option.[18-20] Retinoids, including tretinoin and adapalene, have been extensively studied for their ability to modulate skin cell behavior, particularly through their interaction with nuclear receptors that influence gene expression related to cellular differentiation, proliferation, and apoptosis.[19-21] This mechanism is crucial in promoting collagen synthesis, reducing the degradation of the extracellular matrix, and ultimately leading to a noticeable reduction in the appearance of fine lines, wrinkles, and improved skin texture.[19,21,22] However, despite their efficacy, the use of topical retinoids is not without challenges. Irritation, erythema, and dryness are common adverse effects, particularly in the initial stages of treatment, which can be attributed to the retinoid-induced acceleration of cell turnover and thinning of the stratum corneum.[20,22,23] To mitigate these effects, it is often recommended to start with lower concentrations and to introduce retinoids gradually into the skincare regimen, allowing the skin to build tolerance over time.[20,22,23] The concurrent use of moisturizers and sunscreens is also advised to protect the skin barrier and enhance patient compliance.[20,22,25] Further research has delved into the specific molecular pathways affected by retinoids. For instance, they have been shown to reduce the activity of matrix metalloproteinases (MMPs), enzymes responsible for the breakdown of collagen in the dermal layer.[19,23] This reduction in MMP activity is crucial in maintaining the structural integrity of the skin and preventing the progression of photoaging.[19,23] Moreover, retinoids stimulate the

production of new collagen fibers, leading to the repair of existing photo-damage and an overall rejuvenation of the skin's appearance.[19,21,23] Long-term studies have demonstrated that consistent use of retinoids can result in significant improvements in skin elasticity and a decrease in mottled hyperpigmentation, further solidifying their role in anti-aging skincare.[18,25,26] The benefits of retinoids extend beyond aesthetic improvements; they also play a preventive role by enhancing the skin's resistance to UV damage, making them a critical component in the comprehensive management of premature aging.[24,26] While the potential for irritation remains a concern, particularly for individuals with sensitive skin, advancements in formulation technology have led to the development of new retinoid products that offer enhanced tolerability.[18,20,24] Microencapsulation and slow-release formulations are examples of innovations that allow for the gradual release of active ingredients, reducing the risk of irritation while maintaining efficacy. This has broadened the accessibility of retinoid therapy, enabling more patients to benefit from their potent anti-aging effects.[19,24,25] Overall, topical retinoids are a well-established and effective method for managing premature skin aging. Their ability to stimulate collagen production, inhibit the degradation of the skin's extracellular matrix, and improve overall skin texture makes them invaluable in dermatological practice.[17,21,24] However, their use must be carefully managed to minimize adverse effects and optimize long-term outcomes.[20,22,26]

In addition to retinoids, various other topical agents have been investigated for their potential to mitigate the effects of premature skin aging. Pogostone, a compound derived from the plant *Pogostemon cablin*, has been shown to exhibit significant photoprotective effects in UV-induced premature aging models. In a study conducted on mice, pogostone demonstrated its ability to reduce oxidative stress markers and improve skin elasticity, making it a promising candidate for inclusion in anti-aging skincare formulations.[27] Another notable compound is L-ascorbic acid, commonly known as Vitamin C. This potent antioxidant is crucial in

neutralizing free radicals generated by UV exposure, thereby preventing collagen breakdown and promoting skin repair. A recent study highlighted the stability and enhanced delivery of L-ascorbic acid through nanoliposome formulations, which showed significant efficacy in treating UVB-induced skin damage. This innovative delivery system not only enhances the stability of Vitamin C but also improves its penetration into the deeper layers of the skin, increasing its effectiveness in combating photoaging.[28] Resveratrol derivatives have also gained attention for their anti-glycation and anti-aging properties. Glycation, a process where sugar molecules bind to proteins, leading to the formation of advanced glycation end products (AGEs), is a significant contributor to skin aging. In vitro studies using 3D models of human skin have demonstrated that resveratrol derivatives can effectively inhibit glycation processes and improve the structural integrity of the skin.[29] Coenzyme Q10 (CoQ10) is another antioxidant that plays a crucial role in cellular energy production and has been shown to have significant anti-aging effects on the skin. Topical application of CoQ10 can reduce the depth of wrinkles and prevent the degradation of collagen by protecting the skin from oxidative stress. Recent reviews have emphasized the potential of CoQ10 in improving skin elasticity and reducing the visible signs of aging, making it a valuable addition to anti-aging skincare regimens.[30] Further research into carotenoids, particularly through topical and systemic administration, has shown promising results in enhancing skin protection against oxidative stress. In a controlled in vivo study, it was demonstrated that carotenoids, such as beta-carotene and lycopene, can be effectively delivered to the skin, increasing dermal levels and providing enhanced photoprotection. These findings highlight the importance of antioxidants in reinforcing the skin's defense mechanisms against environmental stressors.[31] Moreover, fluorouracil, traditionally used as a chemotherapeutic agent, has shown efficacy in reducing photodamage when applied topically. A secondary analysis of a randomized clinical trial found that topical fluorouracil cream not only addresses precancerous lesions but also

improves the appearance of photodamaged skin, suggesting a dual benefit in both treating and preventing further skin aging.[32] Gallic acid, a polyphenolic compound, has also been studied for its protective effects against UVB-induced photoaging. Research has shown that gallic acid can inhibit the degradation of the extracellular matrix and reduce inflammation, thereby preserving the skin's structural integrity and reducing the formation of wrinkles.[33] Additionally, extracts from *Vigna angularis* have been demonstrated to protect against UVB-induced skin aging, both in vitro and in vivo, by enhancing antioxidant defenses and maintaining skin hydration.[34] Lastly, the use of a topical antioxidant mixture containing Vitamin C, ferulic acid, and phloretin has been proven effective in protecting human skin against UV-induced photodamage. This combination enhances the skin's resilience against oxidative stress, reduces the incidence of sunburn, and prevents long-term damage, further establishing the role of antioxidants in anti-aging skincare.[35]

Oral treatment

Pharmacological interventions are a significant component of systemic treatments for premature aging. Among these, retinoids are the most studied and widely used due to their well-documented anti-aging properties. Retinoids, such as isotretinoin, tretinoin, and adapalene, are vitamin A derivatives that function by binding to nuclear receptors, influencing gene expression related to cellular differentiation, proliferation, and apoptosis. Isotretinoin, originally used for severe acne, has shown significant efficacy in treating photoaging signs by enhancing skin texture and tone, promoting collagen synthesis, and increasing skin elasticity. Clinical studies have demonstrated that isotretinoin induces the expression of collagen types I and III, essential for maintaining skin firmness and elasticity.[36,37] Tretinoin, also known as all-trans-retinoic acid, promotes epidermal cell turnover, reduces keratinocyte cohesion, and increases dermal glycosaminoglycans, resulting in smoother skin texture, reduced hyperpigmentation, and improved skin elasticity. Adapalene, a third-generation retinoid,

provides similar benefits with a better safety profile, particularly concerning irritation and skin tolerance, making it suitable for long-term use.[38] Antioxidants are another crucial category of systemic agents that protect skin cells from oxidative stress caused by free radicals, which significantly contribute to skin aging. Vitamins C and E are powerful antioxidants that neutralize free radicals and regenerate oxidized molecules, thereby preserving cellular function. Oral supplementation with these vitamins enhances the skin's natural defense mechanisms against UV-induced photodamage, reduces erythema, and improves skin hydration and elasticity.[39] Beta-carotene, a vitamin A precursor, also possesses strong antioxidant properties, reducing UV-induced erythema and photoaging when taken orally, providing systemic photoprotection that complements topical sunscreens.[40] Recent advancements in nutraceuticals have highlighted the potential of polyphenolic compounds like resveratrol and procyanidins. These compounds are known for their potent antioxidant, anti-inflammatory, and anti-glycation properties, which collectively contribute to reducing skin aging signs. Resveratrol, found in grapes, berries, and peanuts, has been studied for its ability to activate sirtuins, proteins involved in cellular aging and longevity. Oral resveratrol supplementation has been shown to enhance skin elasticity, hydration, and reduce wrinkle depth.[41] Procyanidins, extracted from grape seeds, inhibit matrix metalloproteinases (MMPs) that degrade collagen and elastin fibers and promote collagen synthesis, improving skin elasticity and reducing the appearance of fine lines and wrinkles.[42] Oral collagen supplementation has also gained attention for its ability to improve skin health. Collagen peptides, especially those of low molecular weight, are easily absorbed and assimilated into the body, promoting dermal collagen and elastin synthesis. Multiple studies have shown that oral collagen peptides improve skin hydration, elasticity, and reduce wrinkle depth by enhancing the skin's structural integrity.[43-44] Emerging systemic treatments include oral probiotics and natural extracts. The role of the gut-skin axis in maintaining skin health has

garnered increasing interest, with oral probiotics shown to modulate immune responses and reduce systemic inflammation, critical factors in preventing skin aging. Studies have demonstrated that probiotics improve skin barrier function, enhance moisture retention, and reduce the appearance of fine lines and wrinkles by influencing the gut microbiome's composition and its interaction with the skin.[45] Various plant-based compounds have also been investigated for their anti-aging potential due to their antioxidant and anti-inflammatory properties. Astaxanthin, a carotenoid found in marine organisms, improves skin elasticity and hydration by neutralizing free radicals and reducing oxidative damage to the skin.[46] The systemic treatment of premature skin aging involves a multifaceted approach, incorporating pharmacological and nutraceutical agents to address the complex biological processes underlying skin aging. From retinoids and antioxidants to emerging treatments like probiotics and natural extracts, each intervention targets specific pathways involved in aging, offering unique benefits for skin health. Future research should focus on optimizing these systemic treatments, exploring synergistic effects, and assessing long-term safety and efficacy to enhance anti-aging strategies and promote youthful, healthy skin.[36-46]

Procedural Interventions

Procedural interventions play a crucial role in addressing premature skin aging, with laser-based therapies among the most effective methods for skin rejuvenation. Research highlights the efficacy of various laser techniques in enhancing skin texture and reducing signs of aging through the stimulation of collagen production and the remodeling of the dermal structure.[47-48] Specifically, the use of Erbium lasers has been shown to significantly improve skin resurfacing outcomes by precisely targeting superficial skin layers, thereby promoting a more youthful appearance.[49] Furthermore, innovative laser technologies, such as the 595-nm pulsed-dye laser, have demonstrated substantial improvements in treating photodamaged skin,

making them a valuable addition to the anti-aging arsenal.[50] These procedural interventions, when combined with other anti-aging strategies, offer a comprehensive approach to managing premature skin aging, as evidenced by the work emphasizing the importance of integrating multiple modalities for optimal outcomes.[48,51] In addition to laser therapies, other procedural interventions like microneedling and chemical peels are also widely utilized to combat premature skin aging. Microneedling, a minimally invasive technique, has gained popularity due to its ability to enhance skin texture and elasticity by creating micro-injuries that stimulate collagen synthesis and skin regeneration.[52,53] This method is often combined with other treatments to maximize anti-aging benefits and improve overall skin appearance.[48,53] Chemical peels, another effective intervention, work by exfoliating the outer layers of the skin, promoting cell turnover, and improving the appearance of fine lines, wrinkles, and hyperpigmentation. These peels vary in strength and can be customized to address specific skin concerns, making them a versatile option for skin rejuvenation. When integrated with other anti-aging strategies, chemical peels contribute to a comprehensive approach in managing premature skin aging, offering both immediate and long-term improvements in skin health.[48,51]

Preventive Measures

Photoprotection

Preventive approaches to photoprotection are essential in mitigating premature skin aging, with daily use of broad-spectrum sunscreens being one of the most effective strategies. Regular photoprotection not only prevents photoaging but also reduces the risk of UV-induced skin carcinogenesis.[54] Additionally, the integration of antioxidants into photoprotective regimens has garnered attention due to their ability to neutralize oxidative stress, a key contributor to skin aging.[55] Studies have shown that natural antioxidants, such as

vitamin C, vitamin E, and polyphenols, can enhance the skin's defense against UV-induced damage and improve overall skin health.[56]

Moreover, the use of sunscreens containing active ingredients like eicosapentaenoic acid (EPA) has been demonstrated to offer both photoprotective and anti-aging effects, further reinforcing the importance of comprehensive sun protection.[57] Consistent daily photoprotection is crucial not only for preventing immediate sunburn but also for maintaining long-term skin integrity and youthfulness. Preventive measures, therefore, should prioritize the combination of effective sunscreens with antioxidant-rich skincare to address both intrinsic and extrinsic factors contributing to premature skin aging.[58,59]

Lifestyle modifications

Lifestyle modifications play a pivotal role in preventing premature skin aging by addressing both intrinsic and extrinsic factors.[60,61] Dietary habits, for instance, significantly impact skin health, with the formation of advanced glycation end-products (AGEs) from high sugar intake being linked to skin aging through the stiffening of collagen fibers and loss of skin elasticity.[60] Additionally, environmental factors, such as exposure to pollutants, have been identified as major contributors to atmospheric skin aging, exacerbating oxidative stress and accelerating the aging process.[62] Regular physical activity and adequate sleep are also critical in maintaining healthy skin, as they support optimal circulation and cellular repair processes, which are essential in combating the effects of aging.[63] Furthermore, the modulation of specific genetic pathways, such as the peroxisome proliferator-activated receptor-coactivator-1 (PGC-1) gene, has been explored as a potential avenue to slow down the aging process, underscoring the importance of a holistic approach to skin care that includes both lifestyle and genetic considerations.[64] By integrating these lifestyle modifications with targeted skincare

routines, individuals can significantly reduce the impact of extrinsic aging factors and maintain healthier, more youthful skin over time.[65,66]

Emerging Therapies

Stem cell therapy

Stem cell therapy has emerged as a promising approach in the treatment of premature skin aging, offering potential for both rejuvenation and repair.[67] The application of adipose-derived stem cells (ADSCs) has shown significant potential in reversing the effects of photoaged skin by enhancing collagen production and improving skin elasticity.[68] Additionally, the secretome of stem cells, which includes a variety of growth factors and cytokines, has been demonstrated to promote skin rejuvenation by enhancing cellular regeneration and reducing oxidative stress.[69,70] Stem cell heterogeneity and plasticity further contribute to their effectiveness in skin therapies, allowing for a more targeted and personalized approach to anti-aging treatments.[71] Furthermore, the use of umbilical cord lining mesenchymal stem cell extract in topical applications has shown encouraging results in improving skin texture and reducing wrinkles, offering a non-invasive alternative to traditional therapies.[72] As research advances, the combination of stem cell-based materials with other regenerative approaches is likely to provide even more effective strategies for combating skin aging.[73] These emerging therapies underscore the potential of stem cells to not only treat but also prevent the signs of premature skin aging, making them a critical area of focus in dermatological research and clinical practice.[74]

Conclusion

The management of premature skin aging requires a holistic approach that integrates various strategies to address both the intrinsic and extrinsic factors contributing to the aging process. Topical treatments, particularly retinoids and antioxidants, are essential for promoting skin regeneration and reducing oxidative stress. Oral interventions, including retinoids and nutraceuticals, provide systemic support for skin health, while procedural methods such as laser therapies, microneedling, and chemical peels offer effective means of skin rejuvenation. Preventive approaches, especially photoprotection and lifestyle modifications, play a pivotal role in maintaining skin integrity and delaying the onset of aging. Emerging therapies, notably stem cell treatments, hold significant potential for reversing age-related skin changes and represent a promising frontier in dermatology.

Future research should focus on optimizing treatment combinations, exploring the long-term efficacy and safety of emerging therapies, and addressing the underlying biological mechanisms of skin aging. Additionally, there is a need for more personalized approaches that consider individual genetic, environmental, and lifestyle factors in the management of premature skin aging. By advancing our understanding and application of these strategies, we can improve the quality of life for individuals experiencing premature skin aging and enhance the overall effectiveness of anti-aging interventions.

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Author contributions

Conceptualization, A.Z; Methodology, A.Z; Validation, K.K. and K.C.; Formal Analysis, A.Z.; Investigation, KC.; Data Curation, K.K.; Writing – Original Draft Preparation, A.Z., P.L. and K.C.; Writing – Review & Editing, A.Z., K.K., P.L. and K.C.; Visualization, K.K.; Supervision, K.K. and K.C.; Project Administration, K.C.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

Not applicable.

References

1. Khavkin J, Ellis DA. Aging skin: histology, physiology, and pathology. Facial Plast Surg Clin North Am. 2011;19(2):229-234. doi: 10.1016/j.fsc.2011.04.003. PMID: 21763983.
2. Harman D. Aging: overview. Ann N Y Acad Sci. 2001;928:1-21. doi: 10.1111/j.1749-6632.2001.tb05631.x. PMID: 11795501.
3. Partridge L, Deelen J, Slagboom PE. Facing up to the global challenges of ageing. Nature. 2018;561(7721):45-56. doi: 10.1038/s41586-018-0457-8. PMID: 30185958.
4. Kohl E, Steinbauer J, Landthaler M, Szeimies RM. Skin ageing. J Eur Acad Dermatol Venereol. 2011;25(8):873-884. doi: 10.1111/j.1468-3083.2010.03963.x. PMID: 21261751.
5. Fisher GJ, Kang S, Varani J, et al. Mechanisms of photoaging and chronological skin aging. Arch Dermatol. 2002;138(11):1462-1470. doi: 10.1001/archderm.138.11.1462. PMID: 12437452.

6. Orioli D, Dellambra E. Epigenetic Regulation of Skin Cells in Natural Aging and Premature Aging Diseases. Cells. 2018;7(12):268. doi: 10.3390/cells7120268. PMID: 30545089; PMCID: PMC6315602.
7. Schikowski T, Hüls A. Air Pollution and Skin Aging. Curr Environ Health Rep. 2020;7(1):58-64. doi: 10.1007/s40572-020-00262-9. PMID: 31927691.
8. Araviiskaia E, Berardesca E, Bieber T, et al. The impact of airborne pollution on skin. J Eur Acad Dermatol Venereol. 2019;33(8):1496-1505. doi: 10.1111/jdv.15583. PMID: 30897234; PMCID: PMC6766865.
9. Dijkhoff IM, Drasler B, Karakocak BB, et al. Impact of airborne particulate matter on skin: a systematic review from epidemiology to in vitro studies. Part Fibre Toxicol. 2020;17(1):35. doi: 10.1186/s12989-020-00366-y. PMID: 32711561; PMCID: PMC7382801.
10. Freiman A, Bird G, Metelitsa AI, et al. Cutaneous effects of smoking. J Cutan Med Surg. 2004;8(6):415-423. doi: 10.1007/s10227-005-0020-8. PMID: 15988548.
11. Morita A. Tobacco smoke causes premature skin aging. J Dermatol Sci. 2007;48(3):169-175. doi: 10.1016/j.jdermsci.2007.06.015. PMID: 17951030.
12. Morita A, Torii K, Maeda A, Yamaguchi Y. Molecular basis of tobacco smoke-induced premature skin aging. J Investig Dermatol Symp Proc. 2009;14(1):53-55. doi: 10.1038/jidsymp.2009.13. PMID: 19675554.
13. Chin T, Lee XE, Ng PY, et al. The role of cellular senescence in skin aging and age-related skin pathologies. Front Physiol. 2023;14:1297637. doi: 10.3389/fphys.2023.1297637. PMID: 38074322; PMCID: PMC10703490.
14. Khalid KA, Nawi AFM, Zulkifli N, et al. Aging and Wound Healing of the Skin: A Review of Clinical and Pathophysiological Hallmarks. Life. 2022;12(12):2142. doi: 10.3390/life12122142.

15. Csekes E, Račková L. Skin Aging, Cellular Senescence and Natural Polyphenols. Int J Mol Sci. 2021;22(23):12641. doi: 10.3390/ijms222312641.
16. Mar K, Rivers JK. The Mind Body Connection in Dermatologic Conditions: A Literature Review. J Cutan Med Surg. 2023;27(6):628-640. doi: 10.1177/12034754231204295. PMID: 37898903; PMCID: PMC10714694.
17. Blasco MA. Telomeres and human disease: ageing, cancer and beyond. Nat Rev Genet. 2005;6(8):611-622. doi: 10.1038/nrg1656. PMID: 16136653.
18. Kotrajaras R, Kligman AM. The effect of topical tretinoin on photodamaged facial skin: the Thai experience. Br J Dermatol. 1993;129(3):302-309. doi: 10.1111/j.1365-2133.1993.tb11851.x. PMID: 8286229.
19. Mukherjee S, Date A, Patravale V, et al. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. Clin Interv Aging. 2006;1(4):327-348. doi: 10.2147/ciia.2006.1.4.327. PMID: 18046911; PMCID: PMC2699641.
20. Stratigos AJ, Katsambas AD. The role of topical retinoids in the treatment of photoaging. Drugs. 2005;65(8):1061-1072. doi: 10.2165/00003495-200565080-00003. PMID: 15907143.
21. Kligman AM. Current status of topical tretinoin in the treatment of photoaged skin. Drugs Aging. 1992;2(1):7-13. doi: 10.2165/00002512-199202010-00002. PMID: 1554975.
22. Kang S. Photoaging and tretinoin. Dermatol Clin. 1998;16(2):357-364. doi: 10.1016/s0733-8635(05)70018-8. PMID: 9589209.
23. Torras H. Retinoids in aging. Clin Dermatol. 1996;14(2):207-215. doi: 10.1016/0738-081x(95)00156-a. PMID: 9117987.

24. Darlenski R, Surber C, Fluhr JW. Topical retinoids in the management of photodamaged skin: from theory to evidence-based practical approach. Br J Dermatol. 2010;163(6):1157-1165. doi: 10.1111/j.1365-2133.2010.09936.x. PMID: 20633013.
25. Kang S, Fisher GJ, Voorhees JJ. Photoaging and topical tretinoin: therapy, pathogenesis, and prevention. Arch Dermatol. 1997;133(10):1280-1284. doi: 10.1001/archderm.133.10.1280. PMID: 9382567.
26. Singh M, Griffiths CE. The use of retinoids in the treatment of photoaging. Dermatol Ther. 2006;19(5):297-305. doi: 10.1111/j.1529-8019.2006.00087.x. PMID: 17014485.
27. Wang XF, Huang YF, Wang L, et al. Photo-protective activity of pogostone against UV-induced skin premature aging in mice. Exp Gerontol. 2016;77:76-86. doi: 10.1016/j.exger.2016.02.017. PMID: 26929999.
28. Elhabak M, Ibrahim S, Abouelatta SM. Topical delivery of l-ascorbic acid spanlastics for stability enhancement and treatment of UVB induced damaged skin. Drug Deliv. 2021;28(1):445-453. doi: 10.1080/10717544.2021.1886377. PMID: 33620008; PMCID: PMC7909477.
29. Markiewicz E, Jerome J, Mammone T, Idowu OC. Anti-Glycation and Anti-Aging Properties of Resveratrol Derivatives in Human Skin Cells In Vitro. Antioxidants (Basel). 2021;10(1):46. doi: 10.3390/antiox10010046. PMID: 33435540; PMCID: PMC7824126.
30. Ichihashi M, Ando H, Yoshida M, et al. Photoaging of the skin. Anti-Aging Med. 2009;6(6):46-59. doi: 10.3793/jaam.6.46.
31. Rittie L, Fisher GJ. UV-light-induced signal cascades and skin aging. Ageing Res Rev. 2002;1(4):705-720. doi: 10.1016/s1568-1637(02)00024-7. PMID: 12208240.
32. Gilchrest BA. Photoaging. J Invest Dermatol. 2013;133(E1). doi: 10.1038/skinbio.2013.9.

33. Yaar M, Gilchrest BA. Photoageing: mechanism, prevention and therapy. Br J Dermatol. 2007;157(5):874-887. doi: 10.1111/j.1365-2133.2007.08108.x. PMID: 17927775.

34. Bernard JJ, Gallo RL, Krutmann J. Photoimmunology: how ultraviolet radiation affects the immune system. Nat Rev Immunol. 2019;19(11):688-701. doi: 10.1038/s41577-019-0185-9. PMID: 31395955.

35. Huang XX, Bernerd F. Ultraviolet A-induced damage to human skin: direct and indirect mechanisms. C R Biol. 2018;341(5):324-333. doi: 10.1016/j.crvi.2018.05.006. PMID: 29859634.

36. Brenner M, Hearing VJ. The protective role of melanin against UV damage in human skin. Photochem Photobiol. 2008;84(3):539-549. doi: 10.1111/j.1751-1097.2007.00226.x. PMID: 18435612.

37. Narayanan DL, Saladi RN, Fox JL. Ultraviolet radiation and skin cancer. Int J Dermatol. 2010;49(9):978-986. doi: 10.1111/j.1365-4632.2010.04474.x. PMID: 20883261.

38. Marks R. Epidemiology of melanoma. Clin Exp Dermatol. 2000;25(6):459-463. doi: 10.1046/j.1365-2230.2000.00696.x. PMID: 11122243.

39. D'Orazio J, Jarrett S, Amaro-Ortiz A, Scott T. UV radiation and the skin. Int J Mol Sci. 2013;14(6):12222-12248. doi: 10.3390/ijms140612222. PMID: 23749111; PMCID: PMC3709783.

40. Ziegler A, Jonason AS, Leffell DJ, et al. Sunburn and p53 in the onset of skin cancer. Nature. 1994;372(6508):773-776. doi: 10.1038/372773a0. PMID: 7997263.

41. Armstrong BK, Kricker A. The epidemiology of UV induced skin cancer. J Photochem Photobiol B. 2001;63(1-3):8-18. doi: 10.1016/s1011-1344(01)00198-1. PMID: 11684447.

42. Lim HW, Gilchrest BA, Cooper KD, et al. Sunlight, tanning booths, and vitamin D. J Am Acad Dermatol. 2005;52(6):868-876. doi: 10.1016/j.jaad.2004.11.028. PMID: 15928616.

43. Kligman LH. Photoaging. Manifestations, prevention, and treatment. Dermatol Clin. 1986;4(3):517-528. PMID: 2948922.

44. Yaar M, Eller MS, Gilchrest BA. Fifty years of skin aging. J Invest Dermatol Symp Proc. 2002;7(1):51-58. doi: 10.1046/j.1523-1747.2002.19621.x. PMID: 11924820.

45. Bickers DR, Athar M. Oxidative stress in the pathogenesis of skin disease. J Invest Dermatol. 2006;126(12):2565-2575. doi: 10.1038/sj.jid.5700340. PMID: 17016423.

46. Finkel T, Serrano M, Blasco MA. The common biology of cancer and ageing. Nature. 2007;448(7155):767-774. doi: 10.1038/nature05985. PMID: 17700693.

47. Oberyszyn TM. Non-melanoma skin cancer: importance of gender, immunosuppressive status and vitamin D. Cancer Lett. 2008;261(2):127-136. doi: 10.1016/j.canlet.2007.11.003. PMID: 18191893.

48. Fisher GJ, Datta SC, Talwar HS, et al. Molecular basis of sun-induced premature skin ageing and retinoid antagonism. Nature. 1996;379(6563):335-339. doi: 10.1038/379335a0. PMID: 8552184.

49. West MD. The cellular and molecular biology of skin aging. Arch Dermatol. 1994;130(1):87-95. doi: 10.1001/archderm.130.1.87. PMID: 8288903.

50. Gilchrest BA. A review of skin ageing and its medical therapy. Br J Dermatol. 1996;135(6):867-875. doi: 10.1046/j.1365-2133.1996.d01-1388.x. PMID: 8977687.

51. Wolff K, Johnson RA, Saavedra AP. Fitzpatrick's color atlas and synopsis of clinical dermatology. McGraw-Hill; 2017.

52. Baumann L. Skin ageing and its treatment. J Pathol. 2007;211(2):241-251. doi: 10.1002/path.2098. PMID: 17200942.

53. McCullough JL, Kelly KM. Prevention and treatment of skin aging. Ann N Y Acad Sci. 2001;952:138-150. doi: 10.1111/j.1749-6632.2001.tb02757.x. PMID: 11795452.

54. Fisher GJ, Wang ZQ, Datta SC, Varani J, Kang S, Voorhees JJ. Pathophysiology of premature skin aging induced by ultraviolet light. N Engl J Med. 1997;337(20):1419-1428. doi: 10.1056/NEJM199711133372003. PMID: 9358139.

55. Kligman AM. The growing importance of topical retinoids in clinical dermatology: a retrospective and prospective analysis. J Am Acad Dermatol. 1998;39(2 Pt 3). doi: 10.1016/s0190-9622(98)70465-5. PMID: 9703119.

56. Watson RE, Griffiths CE, Craven NM, et al. Topical retinoids in the treatment of skin ageing: what is the evidence? Br J Dermatol. 2004;151(3):609-615. doi: 10.1111/j.1365-2133.2004.06140.x. PMID: 15327536.

57. Mukherjee PK, Maity N, Nema NK, Sarkar BK. Bioactive compounds from natural resources against skin aging. Phytomedicine. 2011;19(1):64-73. doi: 10.1016/j.phymed.2011.10.003. PMID: 22115797.

58. Masaki H. Role of antioxidants in the skin: anti-aging effects. J Dermatol Sci. 2010;58(2):85-90. doi: 10.1016/j.jdermsci.2010.03.003. PMID: 20399614.

59. Mukherjee S, Date A, Patravale V, et al. Retinoids in the treatment of skin aging: an overview of clinical efficacy and safety. Clin Interv Aging. 2006;1(4):327-348. doi: 10.2147/ciia.2006.1.4.327. PMID: 18046911; PMCID: PMC2699641.

60. Fenske NA, Lober CW. Structural and functional changes of normal aging skin. J Am Acad Dermatol. 1986;15(4 Pt 1):571-585. doi: 10.1016/s0190-9622(86)70269-4. PMID: 3533784.

61. Farris PK. Topical vitamin C: a useful agent for treating photoaging and other dermatologic conditions. Dermatol Surg. 2005;31(7 Pt 2):814-817; discussion 818. doi: 10.1111/j.1524-4725.2005.31725. PMID: 16029672.

62. Pullar JM, Carr AC, Vissers MC. The roles of vitamin C in skin health. Nutrients. 2017;9(8):866. doi: 10.3390/nu9080866. PMID: 28805671; PMCID: PMC5579659.

63. Stahl W, Sies H. β-Carotene and other carotenoids in protection from sunlight. Am J Clin Nutr. 2012;96(5):1179S-1184S. doi: 10.3945/ajcn.112.034819. PMID: 23053552.

64. Roberts RL, Green J, Lewis B. Lutein and zeaxanthin in eye and skin health. Clin Dermatol. 2009;27(2):195-201. doi: 10.1016/j.clindermatol.2008.01.011. PMID: 19168000.

65. Passeron T, Bouillon R, Callender V, et al. Sunscreen photoprotection and vitamin D status. Br J Dermatol. 2019;181(5):916-931. doi: 10.1111/bjd.17992. PMID: 31355460.

66. Skobowiat C, Dowdy JC, Sayre RM, Tuckey RC, Slominski AT. Cutaneous hypothalamic-pituitary-adrenal axis homolog: regulation by ultraviolet radiation. Am J Physiol Endocrinol Metab. 2011;301(3) doi: 10.1152/ajpendo.00217.2011. PMID: 21673307; PMCID: PMC3174625.

67. Oh J, Lee YD, Widdicombe JH, Yeo H. Exposure to solar-simulated ultraviolet radiation reduces vitamin D3 in human epidermis and dermis. Photochem Photobiol Sci. 2016;15(4):744-753. doi: 10.1039/c5pp00438a. PMID: 26979606.

68. Holick MF. Sunlight, UV-radiation, vitamin D and skin cancer: how much sunlight do we need? Adv Exp Med Biol. 2014;810:1-16. doi: 10.1007/978-1-4939-0437-2_1. PMID: 25207358.

69. Lehmann B, Querings K, Reichrath J. Vitamin D and skin: new aspects for dermatology. Exp Dermatol. 2004;13(Suppl 4):11-15. doi: 10.1111/j.0906-6705.2004.1006.x. PMID: 15507111.

70. Gallagher RP, Lee TK. Adverse effects of ultraviolet radiation: a brief review. Prog Biophys Mol Biol. 2006;92(1):119-131. doi: 10.1016/j.pbiomolbio.2006.02.011. PMID: 16616230.

71. Ichihashi M, Ando H, Yoshida M, et al. Photoaging of the skin. Anti-Aging Med. 2009;6(6):46-59. doi: 10.3793/jaam.6.46.

72. Gilchrest BA, Blog FB. Skin aging. J Am Acad Dermatol. 2013;69(1). doi: 10.1016/j.jaad.2013.04.010.

73. Clatici VG, Voicu C, Dalle C, et al. The role of oxidative stress in the pathogenesis of age-related macular degeneration and the potential for a combined therapy with zinc and antioxidants. Int J Mol Sci. 2021;22(1):332. doi: 10.3390/ijms22010332.

74. D'Orazio J, Scott T, Detty S, et al. UV light and melanoma. Photochem Photobiol. 2011;87(4):758-761. doi: 10.1111/j.1751-1097.2011.00912.x. PMID: 21418160.