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Research Article

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Advanced Glycation End Products (AGEs) in Non-Alcoholic Fatty Liver Disease (NAFLD) and Their Contribution to Skin Aging

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Abstract

Advanced glycation end products (AGEs), formed through the non-enzymatic glycation of proteins and lipids, are emerging as critical mediators of systemic inflammation and oxidative stress in non-alcoholic fatty liver disease (NAFLD). The accumulation of AGEs in NAFLD patients not only exacerbates hepatic steatosis and fibrosis but also extends its detrimental effects to the skin, accelerating processes associated with skin aging. Elevated levels of AGEs in this population disrupt collagen cross-linking and impair extracellular matrix remodeling, leading to decreased skin elasticity, increased wrinkling, and compromised dermal resilience. Additionally, AGEs enhance skin susceptibility to photodamage by amplifying oxidative stress and promoting the release of matrix metalloproteinases, which degrade structural proteins essential for maintaining skin integrity. Evidence suggests that systemic inflammation and insulin resistance, hallmarks of NAFLD, further contribute to AGE-mediated skin changes by sustaining a pro-inflammatory and pro-oxidative environment. Targeting AGEs through dietary modification, pharmacological inhibitors, and antioxidant supplementation has shown potential in mitigating both hepatic and dermatological complications. Understanding the bidirectional relationship between AGE accumulation in NAFLD and skin aging highlights the need for integrated therapeutic approaches aimed at reducing AGE burden, improving skin health, and addressing the systemic implications of this metabolic disorder.

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Introduction

AGEs are groups of proteins, lipids, and other organic compounds that are formed after being non-enzymatically modified by direct contact with reducing sugars [1]. The non-enzymatically modified compounds accumulate within tissues over time, contributing to the pathogenesis and progression of various metabolic diseases. Among these, non-alcoholic fatty liver disease (NAFLD) has emerged as a significant global health concern, with a prevalence estimated at nearly 25% worldwide [2]. Unlike alcohol-induced liver damage, NAFLD is characterized by hepatic fat often driven by metabolic disturbances such as obesity, insulin resistance, and diabetes [1]. This interplay illustrates a feedback loop wherein metabolic dysfunction exacerbates NAFLD progression, while NAFLD itself perpetuates systemic metabolic imbalance. NAFLD if not adequately controlled can lead to non-alcoholic steatohepatitis and then ultimately progress to cirrhosis. NAFLD has been shown to have many extrahepatic systemic manifestations and has been frequently associated with cardiovascular disease, kidney disease, dyslipidemia, and diabetes [3,4]. Recent studies have attempted to track all cause mortality of patients with NAFLD. A recent study of 646 patients with NAFLD showed that the most common cause of death for patients with NAFLD were cardiovascular events with 36.9%, closely followed by extrahepatic malignancies at 25.7% [5]. This study reinforces the idea that the effects of NAFLD are systemic in nature and do not stay confined to hepatic tissue.

AGEs have recently been identified as significant contributors to skin aging and various dermatologic concerns. This relationship becomes particularly concerning when compounded with NAFLD, as the production of AGEs not only accelerates skin damage but also exacerbates hepatic inflammation and fat accumulation [6]. This bidirectional influence emphasize the systemic nature of AGEs, positioning them as pivotal agents in the intersection of liver dysfunction and cutaneous health. At the cellular level, AGEs are known to amplify the aging process by promoting the generation of reactive oxygen species (ROS), which accumulate within tissues and create a pro-oxidative environment [7]. The elevated ROS levels can damage the skin, decrease elasticity, delay skin healing, and contribute to skin aging. Moreover, the production of free radicals such as ROS has the ability to trigger inflammatory signaling cascades which can ultimately lead to reduced cellular proliferation, apoptosis, and cellular necrosis [8]. This reduced regenerative capacity further compounds tissue damage, as fewer healthy cells are available to replace compromised skin. These findings suggest a cyclical mechanism in which AGE accumulation perpetuates both the initial insult and the subsequent failure of tissue repair.

The hepatic implications of AGEs are equally detrimental, with these compounds driving an inflammatory response in liver tissue and contributing to fat deposition. The parallel impact on skin and liver health demonstrate the systemic burden imposed by AGE accumulation. For instance, the degradation of collagen and elastin within cutaneous tissues mirrors the disruptions seen in the extracellular matrix (ECM) of hepatic tissue, revealing a shared vulnerability to AGE-induced damage [9]. This interconnectedness between NAFLD, AGE-related oxidative stress, and skin aging suggests that addressing one component may have ripple effects on the others.

The overarching aim of this review is to explore the systemic impact of AGEs on both liver and skin health, highlighting their interconnected roles in NAFLD progression and skin aging. By examining the shared mechanisms through which AGEs drive inflammation, oxidative stress, and structural degradation, this review underscores the necessity of integrated therapeutic approaches to address these multifaceted challenges. Strategies should focus on targeting the root causes of NAFLD, while simultaneously mitigating AGE-induced damage through interventions like AGE inhibitors, antioxidant supplementation, and lifestyle modifications. Additionally, therapies aimed at restoring collagen and elastin integrity in the skin could complement broader efforts to alleviate tissue dysfunction. By addressing the shared pathways underlying hepatic and cutaneous damage, these innovative approaches hold the potential to improve outcomes holistically and mitigate the systemic burden of AGE-related diseases.

Mechanisms of AGEs in NAFLD

To fully understand how such integrated therapeutic strategies can be developed, it is essential to examine the underlying mechanisms through which AGEs contribute to the pathogenesis and progression of NAFLD. AGEs are a result of non-enzymatic Maillard reactions during metabolism, where reducing sugars form reactive carbonyl groups that interact with proteins, lipids, and nucleic acids, leading to the formation of irreversible covalent bonds with amino groups [10]. This process generates reactive carbonyl intermediates, whose accumulation is driven by prolonged metabolic activity and catalyzed by transition metals. Interestingly, reducing agents such as ascorbate can inhibit these reactions, suggesting potential avenues for therapeutic intervention [10]. The accumulation of AGEs is further exacerbated by oxidative stress, with ROS playing a central role in amplifying liver damage. Elevated serum AGE levels under conditions of oxidative or inflammatory stress reveal their significant role in liver pathology ROS-induced oxidative stress promotes hepatic steatosis and fibrosis, creating a cycle of inflammation and tissue damage that accelerates NAFLD progression [11]. For instance, AGE products have been shown to stimulate hepatic C-reactive protein production in Hep3B cells and upregulate vascular endothelial growth factor expression, enhancing the angiogenic potential of these cells [12]. This angiogenesis-driven tissue remodeling may further exacerbate liver dysfunction, suggesting that targeting these pathways could attenuate disease progression.

In addition to promoting oxidative damage, AGEs influence inflammatory responses that contribute to the dual nature of inflammation in NAFLD. For example, complement proteins C3 and C5 aggravate steatosis but also play a protective role by promoting liver regeneration and reducing bacterial infections [13]. Similarly, interleukin-17 enhances liver fibrosis while simultaneously limiting bacterial translocation, illustrating the complex interplay between inflammatory mediators and liver homeostasis [13]. Macrophages and neutrophils, key inflammatory cells, detrimentally produce ROS which induce hepatic injury and beneficially remove debris and dead cells while promoting liver fibrosis resolution and liver regeneration, respectively [13,14]. Both hepatic and systemic inflammation play a crucial role in the development and exacerbation of NAFLD. Specifically in severe cases, the systemic inflammatory response syndrome progresses the disease and induces multiorgan failure, thus shifting treatment options to focus on hepatic and extrahepatic mechanisms [15]. The accumulation of AGEs, by perpetuating oxidative stress and dysregulated inflammation, serves as a pivotal factor in the pathogenesis of NAFLD. Due to the variety of NAFLD mediators and immune cells, which vary in harmful and positive effect, it is important to further investigate which components provide higher beneficial potential in order to create tailored lifestyle adjustments and therapeutic options.

AGEs are also credited with the ability to disrupt lipid metabolism and contribute to fibrotic progression. Both endogenous AGEs, formed through normal metabolic processes, and exogenous AGEs, derived from Western-like diets rich in processed foods, sugars, and unhealthy fats, contribute to adipocyte hypertrophy and metabolic dysregulation [16]. This source of AGEs exacerbates their systemic impact, with accumulation occurring in various organs, including the liver, where they stimulate the release of pro-inflammatory cytokines, thereby intensifying oxidative stress and chronic inflammation [16]. Within hepatic stellate cells, AGEs play a pivotal role in promoting fibrosis by inducing transdifferentiation into myofibroblasts, a process characterized by the upregulation of smooth muscle actin alpha, transforming growth factor-beta 1 (TGF-β1), and monocyte chemoattractant protein-1 [17]. This cascade of inflammatory and fibrotic signaling not only accelerates liver damage but also establishes a feedback loop that perpetuates metabolic dysfunction. Additionally, AGEs are implicated in worsening insulin resistance, a key driver of NAFLD pathogenesis, by impairing insulin signaling pathways. In the liver, this resistance limits gluconeogenesis and lipolysis of adipose tissue, contributing to increased lipid accumulation and further metabolic strain [18].

The persistent activation of these pathways and the cumulative burden of AGE products result in the progressive stiffening of liver tissue, impairing its normal function and worsening conditions such as NAFLD. The ability of AGEs to disrupt normal metabolic processes and accelerate fibrosis highlights their role as critical mediators of liver pathology and metabolic disease. Strategies aimed at reducing dietary AGE intake, alongside interventions to enhance insulin sensitivity, are emerging as promising approaches to slow or halt the progression of liver fibrosis. As the mechanisms driving AGE-induced liver damage become better understood, these interventions may pave the way for more targeted therapies, offering hope for mitigating the systemic burden of NAFLD.

Mechanisms of AGEs in Skin Aging

While AGEs play a central role in liver pathology through their contributions to inflammation, oxidative stress, and fibrosis, their deleterious effects are not confined to the liver. These compounds also significantly contribute to skin aging by

disrupting collagen structure and remodeling the ECM. Collagen, a key structural protein in the dermis, becomes stiffer and less elastic as AGEs form cross-links between its fibers, reducing the skin's ability to recover from mechanical stress [19]. This AGE-induced cross-linking interferes with the natural turnover and repair of the ECM, weakening its structural integrity over time [20,21]. The resulting decline in elasticity leads to visible signs of aging, such as sagging and the formation of fine lines and wrinkles [22]. Furthermore, AGEs activate inflammatory pathways through receptors like RAGE (Receptor for Advanced Glycation End Products), amplifying oxidative stress and promoting matrix metalloproteinase (MMP) activity. These enzymes degrade collagen and elastin, accelerating the loss of dermal resilience and exacerbating skin aging. Fibroblasts, the primary producers of ECM components, are particularly affected, as their function is impaired in the presence of AGEs, further reducing collagen synthesis. Chronic AGE accumulation also induces apoptosis in fibroblasts, compounding the degradation of the ECM and hindering its ability to support skin structure [23]. In diabetic patients, elevated levels of systemic AGEs correlate with heightened MMP and lysyl oxidase activity, which disrupt collagen and elastin cross-links, leading to premature aging [24]. Over time, the cumulative effects of these processes weaken the skin's ability to maintain its structural and functional integrity, making it more prone to visible aging.

The decline in dermal resilience due to AGE accumulation is multifaceted and involves both biochemical and mechanical disruptions. AGEs impair fibroblast activity, which is critical for maintaining ECM turnover and collagen homeostasis [25]. Reduced fibroblast function limits the production of new collagen, while existing collagen becomes increasingly resistant to enzymatic breakdown due to AGE-induced cross-linking. This imbalance in ECM remodeling creates a stiffer and less adaptable dermal environment, reducing the skin's ability to recover from damage and maintain elasticity [23,26]. Additionally, chronic inflammation driven by AGE-RAGE interactions exacerbates oxidative stress, which further damages ECM components and disrupts fibroblast signaling pathways [27]. The presence of AGEs also affects keratinocytes in the epidermis, reducing their ability to proliferate and migrate, which delays wound healing and affects the skin's regenerative capacity. These cumulative effects diminish the skin's resilience, resulting in a loss of firmness, increased wrinkling, and overall structural decline. In diabetic and aging populations, these processes are often accelerated due to heightened systemic inflammation and oxidative stress, which exacerbate the detrimental effects of AGEs on skin health.

UV radiation, the most significant external factor in skin aging, synergizes with AGEs to amplify photodamage. UV exposure increases ROS production and activates the nuclear factor-kappa B signaling pathway, which promotes inflammation and further elevates MMP levels [28,29]. MMPs degrade collagen and elastin, weakening the ECM while simultaneously inhibiting the TGF-β pathway necessary for collagen synthesis. The combination of AGE accumulation and UV-induced oxidative stress creates a feedback loop that accelerates collagen breakdown and inhibits its repair [19]. Additionally, UV exposure promotes AGE formation by saccharifying fiber networks and altering the composition of the ECM. AGEs accumulate at higher levels in UV-exposed areas of the skin, exacerbating structural damage and contributing to photoaging [30]. This manifests as increased wrinkling, uneven pigmentation, and reduced skin elasticity, further diminishing the skin's ability to resist environmental damage. Fibroblasts exposed to both AGEs and UV radiation show heightened apoptosis and reduced ECM production, leading to faster degradation of dermal structures. Moreover, AGEs influence pigmentation by stimulating melanocyte activity, contributing to the formation of dark spots and uneven skin tone [31]. Together, these processes underline the critical role of AGEs in amplifying the effects of UV-induced damage, indicating the need for interventions that target both intrinsic and extrinsic factors to mitigate skin aging effectively.

Interconnection Between NAFLD and Skin Aging

Insulin resistance, a hallmark of NAFLD, is intricately linked to the formation of AGEs, which significantly impact skin health. In insulin-resistant states, inefficient glucose utilization leads to chronic hyperglycemia, a key driver of the non-enzymatic glycation of proteins and lipids that results in AGE production [32]. Within the skin, AGEs target long-lived structural proteins like collagen and elastin, causing crosslinking that reduces their flexibility and mechanical resilience. These cross-links also hinder the liver's ability to repair itself and contribute to cirrhosis, particularly in individuals with elevated AGE levels due to metabolic conditions [33]. As a result, the progressive accumulation of AGEs in the liver not only impairs cellular regeneration but also accelerates the onset of fibrosis, ultimately compromising liver function and increasing the risk of liver-related complications. Furthermore, insulin resistance disrupts glucose uptake in dermal cells, depriving them of the energy necessary for effective repair and cellular turnover. This dysfunction exacerbates the effects of AGE accumulation and impairs the production of glycosaminoglycans, essential molecules critical for maintaining skin hydration and firmness [34,35]. Together, these processes create a metabolic environment that not only fosters the initiation of AGE-mediated damage but perpetuates its progression, significantly impacting skin integrity.

The chronic inflammation associated with NAFLD amplifies the detrimental effects of insulin resistance by fostering a pro-inflammatory and pro-oxidative environment that accelerates AGE formation and skin damage. Elevated cytokines, including tumor necrosis factor alpha and interleukin-6 which are hallmark key mediators of systemic inflammation in NAFLD, interact with RAGE on skin cells, triggering intracellular signaling cascades that exacerbate oxidative stress and promote the generation of ROS [36,37]. This surge in ROS not only increases AGE formation but damages cellular components, including DNA, proteins, and lipids, further compromising the skin's structural integrity [38]. Additionally, inflammation-induced disruption of fibroblast function impairs the production of healthy collagen and elastin, thereby reducing the skin's regenerative capacity. The inflammatory milieu also stimulates the release of MMPs, enzymes that degrade collagen and elastin in the extracellular matrix, contributing to dermal thinning and premature aging [39-42]. This cascade of inflammation and oxidative damage further compromises the skin's barrier, leaving it vulnerable to environmental aggressors and accelerating visible signs of damage, including dryness, redness, and fine lines.

The interaction between AGEs and their receptor, RAGE, establishes a self-reinforcing cycle of insulin resistance, inflammation, and skin degradation. AGEs bind to RAGE, a receptor expressed on keratinocytes, fibroblasts, and endothelial cells in the skin, activating pathways such as NF-κB, a transcription factor that drives the production of pro-inflammatory cytokines and ROS [43,44]. This perpetuates systemic inflammation and oxidative stress, creating a feedback loop that promotes further AGE formation. The AGE-RAGE axis also enhances the activity of MMPs, which weaken the dermal matrix over time, diminishing the skin's resilience and regenerative potential [45]. Moreover, the interaction disrupts the normal function of dermal cells, reducing their ability to synthesize essential components like hyaluronic acid, a molecule crucial for maintaining skin hydration and elasticity [46]. This self-reinforcing cycle ensures that AGE-mediated skin damage continues unchecked unless systemic inflammation and AGE levels are controlled, emphasizing the importance of targeted intervention.

NAFLD exacerbates AGE-related skin damage by contributing to systemic inflammation and impairing metabolic clearance mechanisms. As the liver becomes dysfunctional in NAFLD, its ability to clear circulating AGEs diminishes, leading to their accumulation in the bloodstream and subsequent deposition in peripheral tissues, including the skin [47]. Simultaneously, NAFLD-induced insulin resistance and chronic inflammation enhance the systemic production of AGEs and pro-inflammatory cytokines, compounding tissue damage. Cytokines released by the liver intensify inflammation in the skin, further exacerbating oxidative stress and accelerating the degradation of collagen. Additionally, oxidative stress in NAFLD promotes lipid peroxidation [48,49], which damages cellular membranes in dermal cells and weakens the skin's barrier function. Disrupted lipid metabolism due to liver dysfunction also impairs the production of essential fatty acids, vital for maintaining skin barrier integrity [50]. These cumulative effects manifest as visible signs of premature skin aging, including increased wrinkles, loss of elasticity, and a dull complexion. Thus, NAFLD serves as both a source and amplifier of systemic metabolic dysfunctions that sustain AGE-mediated skin damage.

Therapeutic Approaches to Mitigate AGE Effects

Minimizing the intake of AGEs through dietary adjustments offers a proactive strategy to counteract systemic inflammation and oxidative stress, which are pivotal drivers of aging and chronic disease progression. Cooking methods such as steaming and boiling, which avoid dry heat, significantly lower dietary AGE levels and have been shown to reduce systemic markers of inflammation [51]. This points to the critical link between dietary habits and biochemical health, offering an accessible, low-cost intervention to mitigate the burden of chronic diseases. Such approaches are particularly valuable for populations with limited access to advanced medical care, where dietary modifications can serve as an effective first-line defense. Dietary strategies to reduce AGEs are further validated by findings that adherence to a low-AGE diet restores AGE receptor-1 function, which plays an essential role in neutralizing oxidative stress and mitigating AGE-related damage [52]. This suggests that diet-induced restoration of AGER1 could enhance resilience to inflammation, particularly in aging populations prone to degenerative diseases.

Moreover, caloric restriction, another dietary approach, extends lifespan in animal models by reducing oxidative stress and lipid peroxidation, processes tightly linked to AGE accumulation [53]. Combining caloric restriction with a low-AGE diet may provide synergistic benefits, potentially slowing age-related conditions and improving healthspan. Beyond individual health benefits, promoting awareness and adoption of low-AGE cooking practices has implications for public health. By reducing AGE intake, inflammatory pathways such as NF-κB activation are curtailed, reducing risks like vascular stiffness and impaired tissue repair [4]. This emphasizes the need for broader public health initiatives to educate communities about AGE-rich foods and encourage healthier cooking techniques. The incorporation of these strategies into dietary guidelines could reduce the prevalence of AGE-related diseases globally, offering a scalable, preventive approach to improving population health outcomes and longevity. With the growing recognition of AGEs' role in chronic diseases, this dietary intervention represents a promising avenue for enhancing public health at a global scale.

Inhibition of AGE formation has emerged as a promising strategy to counteract both skin aging and liver pathology. Pharmacological agents, including plant-derived compounds and synthetic inhibitors, target AGE formation by preventing its initial development or disrupting the cross-linking process. For example, aminoguanidine and pyridoxamine have been shown to reduce AGE accumulation in both the skin and liver. These inhibitors improve tissue resilience by decreasing collagen stiffness and promoting ECM remodeling, which may delay signs of skin aging and liver fibrosis. Additionally, AGE inhibitors reduce inflammation and oxidative stress, which are key contributors to aging. By modulating RAGE and interrupting its associated inflammatory pathways, these compounds mitigate the chronic inflammation that accelerates aging [54]. AGE inhibitors, by improving tissue integrity and modulating inflammation, present a promising therapeutic avenue for both external and internal aging processes. Their ability to complement existing therapies offers potential benefits in dermatology for photoaging and in hepatology for slowing the progression of NAFLD and cirrhosis in diabetic patients.

In addition to AGE inhibitors, antioxidant therapies play a vital role in mitigating oxidative stress, a key driver of AGE-related damage, thereby enhancing therapeutic potential against both external and internal aging processes. For instance, skin antioxidants like vitamins C and E protect against collagen oxidation and limit AGE formation, which are critical for maintaining ECM stability and improving skin elasticity while reducing wrinkles [55]. These findings are particularly relevant in the context of AGE-mediated skin changes in NAFLD, as reduced ECM integrity is a hallmark of both hepatic and dermal complications. In parallel, antioxidants in the liver preserve ECM structure, attenuating fibrosis and supporting hepatic function by counteracting oxidative damage [56]. This preservation of liver health may indirectly benefit systemic conditions associated with NAFLD, such as skin aging, by reducing the pro-inflammatory environment that exacerbates AGE accumulation. Mitochondrial-targeted antioxidants, like MitoQ, further expand the therapeutic landscape by addressing mitochondrial oxidative stress, a key contributor to AGE-related vascular and tissue damage. By accumulating within mitochondria, MitoQ enhances mitochondrial function, which has been associated with improved vascular health and reduced

arterial stiffness in aging models [57]. These findings underscore the relevance of antioxidant therapies in promoting a balanced redox environment, fostering tissue resilience, and addressing the systemic interplay between oxidative stress, AGE accumulation, and aging-related tissue damage in both the skin and liver.

Future Directions

Emerging advancements in AGE-targeted therapies hold significant promise to transform the management of aging-related skin conditions and metabolic diseases, paving the way for personalized and innovative approaches to address these interconnected challenges. Since AGEs produce oxidative stress which impacts a cascade of systems, it allows anti-oxidants to be the major therapeutic approach for reduction in AGE-related diseases. Recent advancements have paved the way for novel pharmaceuticals, including the promising retinoid, astaxanthin, a marine xanthophyll carotenoid produced by *haematococcus pluvialis* [58]. Astaxanthin spans cell membranes to scavenge ROS, effectively targeting AGEs and enhances insulin-mediated glucose uptake by regulating GLUT4 in skeletal muscle and boosting insulin receptor substrate 1 and Akt signaling, inhibiting insulin resistance pathways [59]. This mechanism of action adds a protective role to diabetes-related issues. It also acts dermatologically, preventing UV-induced damage by neutralizing ROS, preventing DNA oxidation and reducing MMPs, which will decrease the risk of skin damage, and decrease the rate of wrinkle formation [59]. As AGE-targeted therapies continue to evolve, the integration of combination approaches emerges as a complementary strategy that can help address aging-related skin conditions through synergistic mechanisms and innovative drug delivery methods.

Combination therapies are an emerging pharmacological treatment for reduction of AGEs in anti-aging. In a study done in 2021 on leukemia cells, combination therapy increased efficacy in anti-aging than single independent treatments [60]. The use of combination medications appears highly effective in reducing the effects of skin aging. This approach is not limited to the selection of drugs but also extends to how they are administered. For instance, a 2023 study demonstrated increased efficacy in reducing wrinkles and skin aging through the combined use of oral and topical retinoids [61]. This highlights the potential of multimodal treatments in addressing complex dermatological concerns. Among emerging combination therapies, a promising example is the pairing of hyaluronic acid (HA) with trehalose, which not only addresses existing skin damage but also prevents further deterioration by stabilizing HA and mitigating glycation-induced stress [62]. Biochemically HA is polysaccharide known for its anti-inflammatory and antioxidant properties as well as its ability to increase collagen production to maintain skin elasticity. While, trehalose is a disaccharide that targets glycation and oxidative stress. According to Chmiekewski et. al., 2024, trehalose is included to protect HA from being broken down allowing for lasting effects. Unlike most antioxidants, which primarily target existing damage, this innovative therapy incorporates preventive measures, offering a more comprehensive approach to skin health.

Efficient treatment of AGE-related diseases is hindered by gaps in knowledge regarding personalized approaches tailored to specific metabolic processes and skin conditions. This lack of targeted research represents a valuable opportunity to generate impactful insights that address these unmet needs. Curating individualized treatment plans could enhance the efficacy and precision of interventions by accounting for a patient's unique characteristics. Personalized approaches also hold the potential to reduce adverse reactions by considering factors such as skin sensitivity and metabolic abnormalities, which are often overlooked in generalized treatment strategies. Given the diversity in skin types, conditions, and metabolic profiles, a one-size-fits-all approach to reducing AGE production may offer limited benefits compared to a tailored, patient-specific strategy. There is substantial potential to address this gap through research that establishes a foundation for improving patient care and outcomes. Advancements in AGE-targeted therapies hold transformative potential to revolutionize the management of aging-related skin conditions and metabolic diseases. Emerging pharmaceuticals like astaxanthin and combination therapies highlight the growing promise of synergistic and innovative treatment strategies. Despite this progress, further research is necessary in AGE-targeted treatments, setting a new standard for aging and metabolic health while significantly enhancing patient care.

Conclusion

AGEs play a critical role in the pathogenesis of metabolic diseases like NAFLD and in the acceleration of skin aging by driving oxidative stress, chronic inflammation, and structural tissue damage. In NAFLD, AGEs exacerbate fibrosis, metabolic dysregulation, and hepatic inflammation, while in the skin, they impair collagen integrity, disrupt extracellular matrix remodeling, and activate inflammatory pathways that degrade dermal resilience, leading to visible signs of aging. UV radiation further amplifies AGE-related damage in the skin, revealing the interplay between intrinsic and extrinsic aging processes. Therapeutic strategies aimed at mitigating the effects of AGEs, including dietary modifications to reduce AGE intake, pharmacological inhibitors, and antioxidants, offer significant promise for addressing these multifaceted challenges. These approaches not only target the molecular pathways contributing to skin and liver dysfunction but also provide a foundation for managing broader age-related conditions. By addressing the systemic and localized effects of AGEs, these interventions represent a crucial step toward improving overall health and longevity. Further research integrating dermatologic and hepatologic perspectives is essential to refine these strategies and develop holistic, evidence-based solutions for combating AGE-related tissue damage and promoting healthspan.

References

1. Prasad, C., Davis, K. E., Imrhan, V., Juma, S., & Vijayagopal, P. (2017). Advanced Glycation End Products and Risks for Chronic Diseases: Intervening Through Lifestyle Modification. *American journal of lifestyle medicine*, *13*(4), 384–404. https://doi.org/10.1177/1559827617708991
2. Younossi, Z. M., Koenig, A. B., Abdelatif, D., Fazel, Y., Henry, L., & Wymer, M. (2016). Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology (Baltimore, Md.)*, *64*(1), 73–84. https://doi.org/10.1002/hep.28431
3. Li, A. A., Ahmed, A., & Kim, D. (2020). Extrahepatic Manifestations of Nonalcoholic Fatty Liver Disease. *Gut and liver*, *14*(2), 168–178. https://doi.org/10.5009/gnl19069

4. Luevano-Contreras, C., & Chapman-Novakofski, K. (2010). Dietary advanced glycation end products and aging. *Nutrients*, *2*(12), 1247–1265. https://doi.org/10.3390/nu2121247
5. Hagström, H., Nasr, P., Ekstedt, M., Hammar, U., Stål, P., Hultcrantz, R., & Kechagias, S. (2017). Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. *Journal of hepatology*, *67*(6), 1265–1273. https://doi.org/10.1016/j.jhep.2017.07.027
6. Pereira, E. N. G. D. S., Paula, D. P., de Araujo, B. P., da Fonseca, M. J. M., Diniz, M. F. H. S., Daliry, A., & Griep, R. H. (2021). Advanced glycation end product: A potential biomarker for risk stratification of non-alcoholic fatty liver disease in ELSA-Brasil study. *World journal of gastroenterology*, *27*(29), 4913–4928. https://doi.org/10.3748/wjg.v27.i29.4913
7. Cepas, V., Collino, M., Mayo, J. C., & Sainz, R. M. (2020). Redox Signaling and Advanced Glycation Endproducts (AGEs) in Diet-Related Diseases. *Antioxidants (Basel, Switzerland)*, *9*(2), 142. https://doi.org/10.3390/antiox9020142
8. Day, R. M., & Suzuki, Y. J. (2006). Cell proliferation, reactive oxygen and cellular glutathione. *Dose-response : a publication of International Hormesis Society*, *3*(3), 425–442. https://doi.org/10.2203/dose-response.003.03.010
9. Zheng, W., Li, H., Go, Y., Chan, X. H. F., Huang, Q., & Wu, J. (2022). Research Advances on the Damage Mechanism of Skin Glycation and Related Inhibitors. *Nutrients*, *14*(21), 4588. https://doi.org/10.3390/nu14214588
10. Singh, R., Barden, A., Mori, T., & Beilin, L. (2001). Advanced glycation end-products: a review. *Diabetologia*, *44*(2), 129–146. https://doi.org/10.1007/s001250051591
11. Takeuchi, M., Takino, J. I., Sakasai-Sakai, A., Takata, T., & Tsutsumi, M. (2017). Toxic AGE (TAGE) Theory for the Pathophysiology of the Onset/Progression of NAFLD and ALD. *Nutrients*, *9*(6), 634. https://doi.org/10.3390/nu9060634
12. Takino, J., Yamagishi, S., & Takeuchi, M. (2012). Glycer-AGEs-RAGE signaling enhances the angiogenic potential of hepatocellular carcinoma by upregulating VEGF expression. *World journal of gastroenterology*, 18(15), 1781-1788. https://doi.org/10.3748/wjg.v18.i15.1781
13. Gao, B., & Tsukamoto, H. (2016). Inflammation in Alcoholic and Nonalcoholic Fatty Liver Disease: Friend or Foe? *Gastroenterology*, *150*(8), 1704–1709. https://doi.org/10.1053/j.gastro.2016.01.025
14. Ramaiah, S. K., & Jaeschke, H. (2007). Role of neutrophils in the pathogenesis of acute inflammatory liver injury. *Toxicologic pathology*, *35*(6), 757–766. https://doi.org/10.1080/01926230701584163
15. Michelena, J., Altamirano, J., Abraldes, J. G., Affò, S., Morales-Ibanez, O., Sancho-Bru, P., Dominguez, M., García-Pagán, J. C., Fernández, J., Arroyo, V., Ginès, P., Louvet, A., Mathurin, P., Mehal, W. Z., Caballería, J., & Bataller, R. (2015). Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. *Hepatology (Baltimore, Md.)*, *62*(3), 762–772. https://doi.org/10.1002/hep.27779
16. Ruiz, H. H., Ramasamy, R., & Schmidt, A. M. (2020). Advanced Glycation End Products: Building on the Concept of the "Common Soil" in Metabolic Disease. *Endocrinology*, *161*(1), bqz006. https://doi.org/10.1210/endocr/bqz006
17. Priken, K., Tapia, G., Cadagan, C., Quezada, N., Torres, J., D'Espessailles, A., & Pettinelli, P. (2022). Higher hepatic advanced glycation end products and liver damage markers are associated with nonalcoholic steatohepatitis. *Nutrition research (New York, N.Y.)*, *104*, 71–81. https://doi.org/10.1016/j.nutres.2022.04.005
18. Portero-Otin, M., de la Maza, M. P., & Uribarri, J. (2023). Dietary Advanced Glycation End Products: Their Role in the Insulin Resistance of Aging. *Cells*, *12*(13), 1684. https://doi.org/10.3390/cells12131684
19. Lyu, J.-L., Liu, Y.-J., Wen, K.-C., Chiu, C.-Y., Lin, Y.-H., Chiang, H.-M., Elansary, H. O., & Mahmoud, E. A. (2022). Protective Effect of Djulis (Chenopodium formosanum) Extract against UV- and AGEs-Induced Skin Aging via Alleviating Oxidative Stress and Collagen Degradation. *Molecules*, *27*(7). https://doi.org/10.3390/molecules27072332
20. Rosenberg JL, Woolley W, Elnunu I, Kamml J, Kammer DS, Acevedo C. (2023). Effect of non-enzymatic glycation on collagen nanoscale mechanisms in diabetic and age-related bone fragility. *Biocell : Official Journal of the Sociedades Latinoamericanas de Microscopia Electronica ... Et. Al*, *47*(7), 1651–1659. https://doi.org/10.32604/biocell.2023.028014
21. Snelson, M., & Coughlan, M. T. (2019). Dietary Advanced Glycation End Products: Digestion, Metabolism and Modulation of Gut Microbial Ecology. *Nutrients*, *11*(2). https://doi.org/10.3390/nu11020215
22. Yoo, J. H., Lee, J. S., Jang, J. H., Jung, J. I., Kim, E. J., & Choi, S.-Y. (2023). AGEs Blocker™ (Goji Berry, Fig, and Korean Mint Mixed Extract) Inhibits Skin Aging Caused by Streptozotocin-Induced Glycation in Hairless Mice. *Preventive Nutrition and Food Science*, *28*(2), 134–140. https://doi.org/10.3746/pnf.2023.28.2.134
23. Dai, J., Chen, H., & Chai, Y. (2019). Advanced Glycation End Products (AGEs) Induce Apoptosis of Fibroblasts by Activation of NLRP3 Inflammasome via Reactive Oxygen Species (ROS) Signaling Pathway. *Medical science monitor: international medical journal of experimental and clinical research*, *25*, 7499–7508. https://doi.org/10.12659/MSM.915806
24. Añazco, C., Riedelsberger, J., Vega-Montoto, L., Rojas, A., & Trackman, P. C. (2023). Exploring the Interplay between Polyphenols and Lysyl Oxidase Enzymes for Maintaining Extracellular Matrix Homeostasis. *International Journal of Molecular Sciences*, *24*(13). https://doi.org/10.3390/ijms241310985
25. Varani, J., Dame, M. K., Rittie, L., Fligiel, S. E., Kang, S., Fisher, G. J., & Voorhees, J. J. (2006). Decreased collagen production in chronologically aged skin: roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. *The American journal of pathology*, *168*(6), 1861–1868. https://doi.org/10.2353/ajpath.2006.051302
26. Zhong, W., Wang, L.-l., Cui, H., & Li, S. (2005). [Targeted AGEes and AGEs cross-link in drug discovery: preventing and reversing arterial sclerosis in aging and diabetes]. *Yao Xue Xue Bao = Acta Pharmaceutica Sinica*, *40*(1), 91–96.

27. Wang, L., Jiang, Y., & Zhao, C. (2024). The effects of advanced glycation end-products on skin and potential anti-glycation strategies. *Experimental dermatology*, *33*(4), e15065. https://doi.org/10.1111/exd.15065
28. Pittayapruek, P., Meephansan, J., Prapapan, O., Komine, M., Ohtsuki, M., & Maki, M. (2016). Role of Matrix Metalloproteinases in Photoaging and Photocarcinogenesis. *International Journal of Molecular Sciences*, *17*(6). https://doi.org/10.3390/ijms17060868
29. Tam, E. M., Wu, Y. I., Butler, G. S., Stack, M. S., & Overall, C. M. (2002). Collagen binding properties of the membrane type-1 matrix metalloproteinase (MT1-MMP) hemopexin C domain. The ectodomain of the 44-kDa autocatalytic product of MT1-MMP inhibits cell invasion by disrupting native type I collagen cleavage. *The Journal of biological chemistry*, *277*(41), 39005–39014.
30. Crisan, M., Taulescu, M., Crisan, D., Cosgarea, R., Parvu, A., Cãtoi, C., Drugan, T., & Karagiannis, S. N. (2013). Expression of Advanced Glycation End-Products on Sun-Exposed and Non-Exposed Cutaneous Sites during the Ageing Process in Humans. *PLoS ONE*, *8*(10). https://doi.org/10.1371/journal.pone.0075003
31. Lee, E. J., Kim, J. Y., & Oh, S. H. (2016). Advanced glycation end products (AGEs) promote melanogenesis through receptor for AGEs. *Scientific Reports*, *6*, 27848. https://doi.org/10.1038/srep27848
32. Singh, V. P., Bali, A., Singh, N., & Jaggi, A. S. (2014). Advanced glycation end products and diabetic complications. *The Korean journal of physiology & pharmacology: official journal of the Korean Physiological Society and the Korean Society of Pharmacology*, *18*(1), 1–14. https://doi.org/10.4196/kjpp.2014.18.1.1
33. Leung, C., Herath, C. B., Jia, Z., Andrikopoulos, S., Brown, B. E., Davies, M. J., Rivera, L. R., Furness, J. B., Forbes, J. M., & Angus, P. W. (2016). Dietary advanced glycation end-products aggravate non-alcoholic fatty liver disease. *World journal of gastroenterology*, *22*(35), 8026–8040. https://doi.org/10.3748/wjg.v22.i35.8026
34. Gowd, V., Gurukar, A., & Chilkunda, N. D. (2016). Glycosaminoglycan remodeling during diabetes and the role of dietary factors in their modulation. *World journal of diabetes*, *7*(4), 67–73. https://doi.org/10.4239/wjd.v7.i4.67
35. Williams, A. S., Kang, L., & Wasserman, D. H. (2015). The extracellular matrix and insulin resistance. *Trends in endocrinology and metabolism: TEM*, *26*(7), 357–366. https://doi.org/10.1016/j.tem.2015.05.006
36. Rafaqat, S., Gluscevic, S., Mercantepe, F., Rafaqat, S., & Klisic, A. (2024). Interleukins: Pathogenesis in Non-Alcoholic Fatty Liver Disease. *Metabolites*, *14*(3), 153. https://doi.org/10.3390/metabo14030153
37. Duan, Y., Pan, X., Luo, J., Xiao, X., Li, J., Bestman, P. L., & Luo, M. (2022). Association of Inflammatory Cytokines with Non-Alcoholic Fatty Liver Disease. *Frontiers in immunology*, *13*, 880298. https://doi.org/10.3389/fimmu.2022.880298
38. Nakamura, H., & Takada, K. (2021). Reactive oxygen species in cancer: Current findings and future directions. *Cancer science*, *112*(10), 3945–3952. https://doi.org/10.1111/cas.15068
39. Tanwar, S., Rhodes, F., Srivastava, A., Trembling, P. M., & Rosenberg, W. M. (2020). Inflammation and fibrosis in chronic liver diseases including non-alcoholic fatty liver disease and hepatitis C. *World journal of gastroenterology*, *26*(2), 109–133. https://doi.org/10.3748/wjg.v26.i2.109
40. Shan, L., Wang, F., Zhai, D., Meng, X., Liu, J., & Lv, X. (2023). Matrix metalloproteinases induce extracellular matrix degradation through various pathways to alleviate hepatic fibrosis. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *161*, 114472. https://doi.org/10.1016/j.biopha.2023.114472
41. Widgerow, A. D., Fabi, S. G., Palestine, R. F., Rivkin, A., Ortiz, A., Bucay, V. W., Chiu, A., Naga, L., Emer, J., & Chasan, P. E. (2016). Extracellular Matrix Modulation: Optimizing Skin Care and Rejuvenation Procedures. *Journal of drugs in dermatology: JDD*, *15*(4 Suppl), s63–s71.
42. Feng, C., Chen, X., Yin, X., Jiang, Y., & Zhao, C. (2024). Matrix metalloproteinases on skin photoaging. *Journal of Cosmetic Dermatology*, *23*, 3847–3862. https://doi.org/10.1111/jocd.16558
43. Zhou, M., Zhang, Y., Shi, L., Li, L., Zhang, D., Gong, Z., & Wu, Q. (2024). Activation and modulation of the AGEs-RAGE axis: Implications for inflammatory pathologies and therapeutic interventions - A review. *Pharmacological research*, *206*, 107282. https://doi.org/10.1016/j.phrs.2024.107282
44. Deepu, V., Rai, V., & Agrawal, D. K. (2024). Quantitative Assessment of Intracellular Effectors and Cellular Response in RAGE Activation. *Archives of internal medicine research*, *7*(2), 80–103. https://doi.org/10.26502/aimr.0168
45. Bhattacharya, R., Alam, M. R., Kamal, M. A., Seo, K. J., & Singh, L. R. (2023). AGE-RAGE axis culminates into multiple pathogenic processes: a central road to neurodegeneration. *Frontiers in molecular neuroscience*, *16*, 1155175. https://doi.org/10.3389/fnmol.2023.1155175
46. Draelos, Z. D., Diaz, I., Namkoong, J., Wu, J., & Boyd, T. (2021). Efficacy Evaluation of a Topical Hyaluronic Acid Serum in Facial Photoaging. *Dermatology and therapy*, *11*(4), 1385–1394. https://doi.org/10.1007/s13555-021-00566-0
47. Hyogo, H., & Yamagishi, S. (2008). Advanced glycation end products (AGEs) and their involvement in liver disease. *Current pharmaceutical design*, *14*(10), 969–972. https://doi.org/10.2174/138161208784139701
48. Mayén, A. L., Aglago, E. K., Knaze, V., Cordova, R., Schalkwijk, C. G., Wagner, K. H., Aleksandrova, K., Fedirko, V., Keski-Rahkonen, P., Leitzmann, M. F., Katzke, V., Srour, B., Schulze, M. B., Masala, G., Krogh, V., Panico, S., Tumino, R., Bueno-de-Mesquita, B., Brustad, M., Agudo, A., … Freisling, H. (2021). Dietary intake of advanced glycation endproducts and risk of hepatobiliary cancers: A multinational cohort study. *International journal of cancer*, *149*(4), 854–864. Advance online publication. https://doi.org/10.1002/ijc.33612
49. Martín-Fernández, M., Arroyo, V., Carnicero, C., Sigüenza, R., Busta, R., Mora, N., Antolín, B., Tamayo, E., Aspichueta, P., Carnicero-Frutos, I., Gonzalo-Benito, H., & Aller, R. (2022). Role of Oxidative Stress and Lipid Peroxidation in the Pathophysiology of NAFLD. *Antioxidants (Basel, Switzerland)*, *11*(11), 2217. https://doi.org/10.3390/antiox11112217
50. Pei, K., Gui, T., Kan, D., Feng, H., Jin, Y., Yang, Y., Zhang, Q., Du, Z., Gai, Z., Wu, J., & Li, Y. (2020). An Overview of Lipid Metabolism and Nonalcoholic Fatty Liver Disease. *BioMed research international*, *2020*, 4020249. https://doi.org/10.1155/2020/4020249.

51. Uribarri, J., Woodruff, S., Goodman, S., Cai, W., Chen, X., Pyzik, R., … Vlassara, H. (2010). Advanced glycation end products in foods and a practical guide to their reduction in the diet. *Journal of the American Dietetic Association*, *110*(6), 911–916. https://doi.org/10.1016/j.jada.2010.03.018
52. Vlassara, H., Cai, W., Goodman, S., Pyzik, R., Yong, A., Chen, X., … Uribarri, J. (2009). Protection against loss of innate defenses in adulthood by low advanced glycation end products (AGE) intake: Role of the anti-inflammatory AGE receptor-1. *The Journal of Clinical Endocrinology & Metabolism*, *94*(11), 4483–4491. https://doi.org/10.1210/jc.2009-0089
53. Yu, B. P. (1996). Aging and oxidative stress: Modulation by dietary restriction. *Free Radical Biology and Medicine*, *21*(5), 651–668. https://doi.org/10.1016/0891-5849(96)00162-1
54. Fan, R., Zhang, Y., Liu, R., Wei, C., Wang, X., Wu, X., Yu, X., Li, Z., Mao, R., Hu, J., Zhu, N., Liu, X., & Li, Y. (2024). Exogenous nucleotides improve the skin aging of SAMP8 mice by modulating autophagy through MAPKs and AMPK pathways. *Nutrients*, *16*, 1907. https://doi.org/10.3390/nu16121907
55. Fusco, R., Jolly, C. A., & Muthuswamy, K. (2007). Antioxidants and skin aging: An overview of the mechanisms involved in the prevention of oxidative stress-induced skin damage. *Biology of Aging*, *21*(3), 157-164. https://doi.org/10.1016/j.jdsci.2021.04.010
56. Tan, B. L., Norhaizan, M. E., Liew, W. P. P., & Sulaiman Rahman, H. (2018). Antioxidants and oxidative stress: A mutual interplay in age-related diseases. *Frontiers in Pharmacology*, *9*, 1162. https://doi.org/10.3389/fphar.2018.01162
57. Murray, K. O., Berryman-Maciel, M., Darvish, S., Coppock, M. E., You, Z., Chonchol, M., Seals, D. R., & Rossman, M. J. (2022). Mitochondrial-targeted antioxidant supplementation for improving age-related vascular dysfunction in humans: A study protocol. *Frontiers in Physiology*, *13*, 980783. https://doi.org/10.3389/fphys.2022.980783.
58. Debnath T, Bandyopadhyay TK, Vanitha K, Bobby MN, Nath Tiwari O, Bhunia B, Muthuraj M. Astaxanthin from microalgae: A review on structure, biosynthesis, production strategies and application. Food Res Int. 2024 Jan;176:113841. doi: 10.1016/j.foodres.2023.113841. Epub 2023 Dec 10. PMID: 38163732.
59. Sztretye, M., Dienes, B., Gönczi, M., Czirják, T., Csernoch, L., Dux, L., Szentesi, P., & Keller-Pintér, A. (2019). Astaxanthin: A Potential Mitochondrial-Targeted Antioxidant Treatment in Diseases and with Aging. *Oxidative Medicine and Cellular Longevity*, *2019*, 1–14. https://doi.org/10.1155/2019/3849692Kim SK, Goughnour PC, Lee EJ, Kim MH, Chae HJ, Yun GY, et al. (2021) Identification of drug combinations on the basis of machine learning to maximize anti-aging effects. PLoS ONE 16(1): e0246106. https://doi.org/10.1371/journal.pone.0246106.
60. Kim, S. K., Goughnour, P. C., Lee, E. J., Kim, M. H., Chae, H. J., Yun, G. Y., Kim, Y. R., & Choi, J. W. (2021). Identification of drug combinations on the basis of machine learning to maximize anti-aging effects. *PLoS ONE*, *16*(1), e0246106. https://doi.org/10.1371/journal.pone.0246106
61. Milani, M., & Colombo, F., on behalf of the To-Re Trial Study Group. (2023). Skin Anti-Aging Effect of Oral Vitamin A Supplementation in Combination with Topical Retinoic Acid Treatment in Comparison with Topical Treatment Alone: A Randomized, Prospective, Assessor-Blinded, Parallel Trial. *Cosmetics*, *10*(5), 144. https://doi.org/10.3390/cosmetics10050144
62. Chmielewski, R., & Lesiak, A. (2024). Mitigating Glycation and Oxidative Stress in Aesthetic Medicine: Hyaluronic Acid and Trehalose Synergy for Anti-AGEs Action in Skin Aging Treatment. *Clinical, Cosmetic and Investigational Dermatology*, *17*, 2701–2712. https://doi.org/10.2147/CCID.S476362