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Beta-Hydroxy-Beta-Methyl Butyrate (HMB) and 2-Hydroxy-Benzyl Amine (2-HOBA) for Treatment of Inflammatory Skin Conditions

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Abstract: ***Background: β-hydroxy β-methylbutyrate (HMB) and 2-hydroxybenzylamine (2-HOBA) represent promising natural compounds for addressing inflammatory skin conditions through complementary mechanisms. HMB, a leucine metabolite, enhances protein synthesis and collagen integrity via mTOR pathway activation, while 2-HOBA functions as a potent electrophile scavenger that reduces oxidative stress and inflammatory damage. This study evaluated the clinical efficacy of topical HMB and 2-HOBA formulations in ameliorating various inflammatory skin conditions. Methods: Nine female participants (ages 27-43) with diverse skin conditions including acne vulgaris, rosacea, and sunburn damage were treated with three topical formulations: HMB Rescue Mask (2% HMB), 2-HOBA Refresh Cream (0.2% 2-HOBA), or 2-HOBA Repair Balm (0.2% 2-HOBA with Nicotiana benthamiana Polypeptide Complex). Treatment duration ranged from 5-30 days depending on condition severity. Clinical improvements were documented through standardized photography and visual assessment. Results: Photographic documentation demonstrated significant improvements across all treated conditions. Key findings included: reduction in inflammatory acne lesions with improved skin texture, decreased post-inflammatory hyperpigmentation, complete resolution of compromised skin barriers, enhanced skin brightness and hydration, visible reduction in acne scarring appearance, improved overall skin tone uniformity, resolution of cystic acne without scarring, and successful sunburn recovery without skin damage. Participants with rosacea showed marked reduction in erythema and improved skin hydration. No adverse effects were reported during the treatment periods. Conclusions: Topical application of HMB and 2-HOBA demonstrated promising therapeutic potential for inflammatory skin conditions through their complementary mechanisms addressing both structural protein synthesis and oxidative stress reduction. The observed clinical improvements support the hypothesis that targeting both immune dysfunction and structural deterioration can effectively treat various dermatological conditions. However, these preliminary findings require validation through randomized controlled trials with objective biomarker assessments, diverse demographic populations, and standardized outcome measures to establish optimal therapeutic protocols and confirm long-term safety and efficacy.***

Keywords: β-hydroxy β-methylbutyrate (HMB), 2-hydroxybenzylamine (2-HOBA), skin health, oxidative stress, collagen synthesis, inflammation, acne treatment, rosacea, antioxidant intervention, protein synthesis

1. Introduction

The skin is the body's largest organ and primary defensive barrier. It requires a delicate balance of immune function and structural integrity to maintain optimal health [Penzer, Eraser, 2010]. Growing evidence suggests that natural compounds may offer significant advantages in supporting these complex biological systems, particularly through their ability to work in harmony with the body's innate mechanisms. The skin's architecture comprises three distinct layers—epidermis, dermis, and hypodermis—each containing specialized immune cells and structural components that contribute to both protective and aesthetic functions. Of particular importance is the dermis, which contains a rich network of collagen fibers, elastic tissue, and underlying muscular components that collectively determine skin turgor and resilience. The panniculus carnosus, a specialized layer of striated muscle fibers within the hypodermis, plays a crucial role in maintaining skin tension and supporting vascular function. This muscular foundation, combined with the dermal matrix of collagen and elastin, creates the structural framework necessary for healthy, resilient skin [Penzer, Eraser, 2010].

Common skin concerns present complex challenges in cosmetic formulation. For example, acne vulgaris involves hormonal dysregulation of pilosebaceous units, leading to inflammation and potential scarring through either excessive collagen deposition or tissue loss. If left unchecked, this condition could lead to scarring through either excessive collagen deposition (hypertrophic scars) or tissue loss (atrophic scars), highlighting the need for compounds that balance inflammation control and tissue repair [Penzer, Eraser, 2010; Paiva-Santos, 2023; Semenescu, 2024]. Additionally, various forms of dermatitis manifest through concurrent skin barrier dysfunction and immune dysregulation [Abreu, 2021; Ong 2022]. Treatments that can restore both structural integrity and immune balance would be especially useful for these conditions. The use of natural compounds supporting the skin's innate immune responses while maintaining proper tissue architecture are particularly valuable in these conditions as well. Previous studies have

identified multiple natural compounds, botanicals, and topical compounds [Vaughn, 2017], and collagen [Pu, 2023] when taken orally lead to improvement in inflammatory skin conditions.

Environmental damage and age-related skin changes lead to reduced skin elasticity, decreased collagen integrity, and impaired barrier function [Abreu, 2021; Ong 2022]. These changes affect the superficial layers, the deeper muscular tissues, and vascular networks, requiring interventions that can penetrate and support multiple tissue layers. In this context, two natural compounds—HMB [Holeček, 2017; Courel-Ibáñez 2019; Su, 2024; Rathmacher, 2025] and 2-HOBA [Williams, 2002; Davies 2019; Rathmacher 2023; Gobert 2023] emerge as particularly promising candidates for comprehensive skin care. These compounds are derived from natural metabolic processes and plant sources respectively, offering complementary mechanisms that support both the immune and structural aspects of skin health.

HMB, a metabolite of the essential amino acid leucine, naturally found in alfalfa, avocado, grapefruit, and asparagus, shows strong potential for improving structural skin integrity through (a) enhancement of protein synthesis via mTOR pathway activation, supporting both dermal collagen and underlying muscular tissue [Holeček, 2017; Courel-Ibáñez 2019; Su, 2024, Rathmacher, 2025]; (b) protection against protein degradation through the ubiquitin-proteasome system inhibition [Rathmacher, 2024; Su, 2024]; (c) support of collagen integrity and boosting deposition in the dermal matrix [Williams, 2002]; (d) promotion of tissue repair and regeneration across multiple skin layers and (e) maintenance of underlying muscular tissue health, contributing to improved skin turgor [Williams, 2002]. The above mechanisms led us to hypothesize that the use of topical HMB might amplify collagen stimulation, enhancing skin elasticity and alleviating dermatologic conditions such as acne and eczema. Previous studies have identified multiple topical natural compounds [Vaughn, 2017] in inflammatory skin conditions.

2-HOBA, naturally present in buckwheat, shows exceptional promise in supporting skin immune function [McMaster, 2015; Davies, 2019; Rathmacher, 2023; Gobert, 2023]; through (a) rapid neutralization of harmful dicarbonyl electrophiles that can damage skin proteins and DNA (b) prevention of protein and DNA modification; (c) reduction of inflammatory cascade activation while preserving normal immune responses. As a potent antioxidant, 2-HOBA mitigates damage from sunlight, UV radiation, environmental toxins, and infections while counteracting aging-related oxidative processes.

In this study we present evidence that topical application of HMB and 2-HOBA demonstrated promising therapeutic potential for inflammatory skin conditions through their complementary mechanisms addressing both structural protein synthesis and oxidative stress reduction.

2. Methods

We present photographic evidence collected from nine participants using three formulations: (a) HMB Rescue Mask, a clay-based wash-off mask containing 2% HMB; (b) 2-HOBA Refresh Cream, a lightweight, serum-like moisturizer formulated for hydration with 0.2% 2-HOBA and plant-based squalane; or (c) 2-HOBA Repair Balm, a thicker facial cream designed for skin barrier repair with 0.2% 2-HOBA and Nicotiana benthamiana, an innovative-polypeptide complex. Participants represented diverse skin conditions (including mild to severe acne, sunburn damage, and rosacea) and ethnicities, documenting progress over 5–30 days, providing visual qualitative and photographic data assessing the products' impact.

3. Results

Clinical Photography Analysis

The photographic documentation (Figures 1–9) demonstrates visible improvements in various skin conditions following treatment with HMB and 2-HOBA. There was reduction in inflammatory acne lesions with notable improvement in skin texture (**Fig.1**); decreased appearance of post-inflammatory hyperpigmentation (**Fig.2**); complete resolution of damaged skin barrier (**Fig.3**); enhanced skin brightness evidenced by improved hydration and reduced redness (**Fig.4**); visible reduction in the appearance of acne scarring (**Fig.5**); improved skin tone and texture (**Fig.6**); resolution of cystic acne and reduction in acne scarring (**Fig.7**); recovery of sunburn without damage to the skin barrier (**Fig.8**); and fully healed acne with overall improvement in skin tone uniformity and texture (**Fig.9**). These visual results support the potential efficacy of combining HMB's protein-preserving properties with 2-HOBA's anti-inflammatory effects in treating various skin conditions.

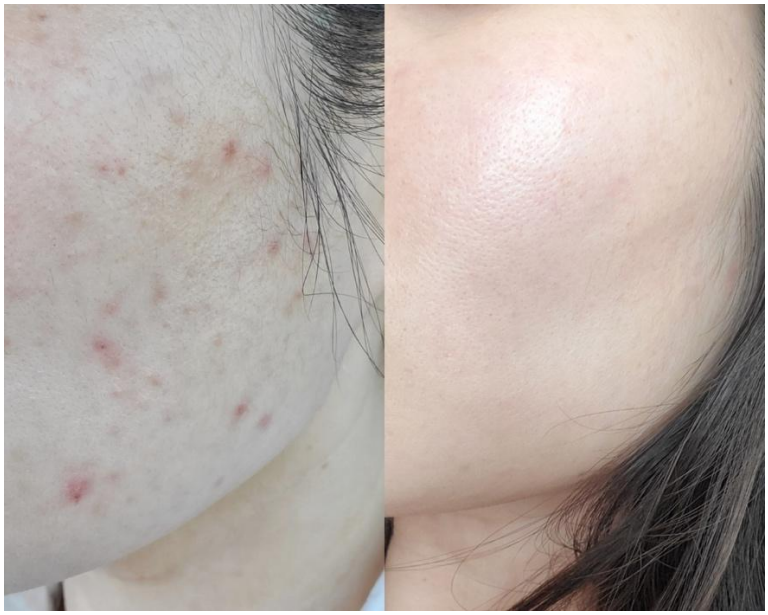

Figure 1: 35-year-old Asian female. Representative photos of a participant with acne and inflammation from acne scars achieved fully healed skin barrier after using HMB Rescue Mask once a week and 2-HOBA Repair Balm once nightly for 28 days. *Left panel represents condition before and right panel after topical application – for all figures.*

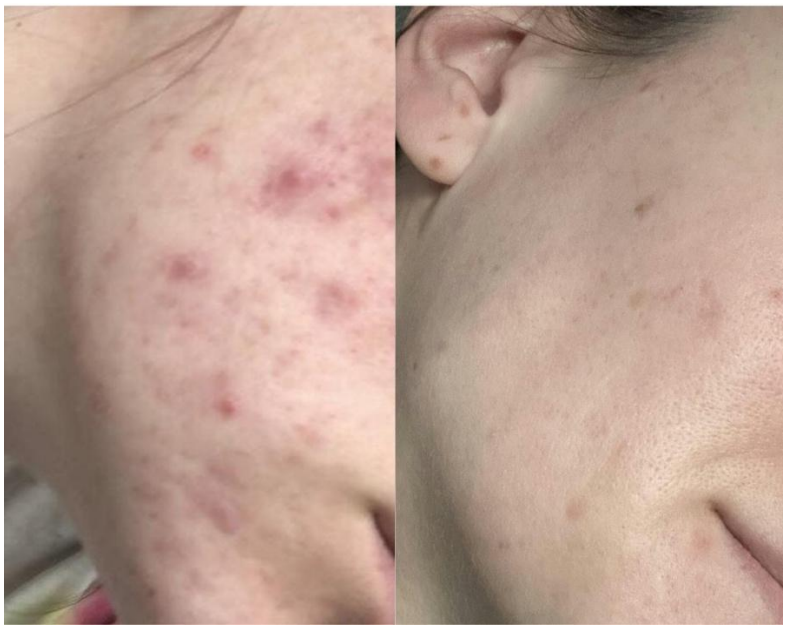

Figure 2: 27-year-old Caucasian female. Photos of participant with deep cystic acne, hyperpigmentation, and redness from acne scars showed significantly reduced post-acne inflammation by using HMB Rescue Mask twice a week and 2-HOBA Repair Balm twice daily (AM and PM) for 30 days.

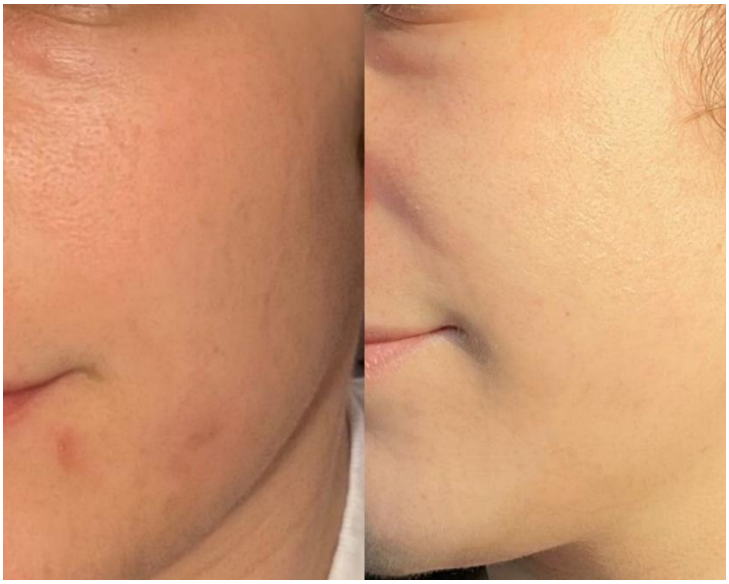

Figure 3: 30-year-old Hispanic female. Photos of participant with acute hormonal acne breakout who used 2-HOBA Repair Balm twice daily (AM and PM) for 14 days and fully healed damaged skin barrier.

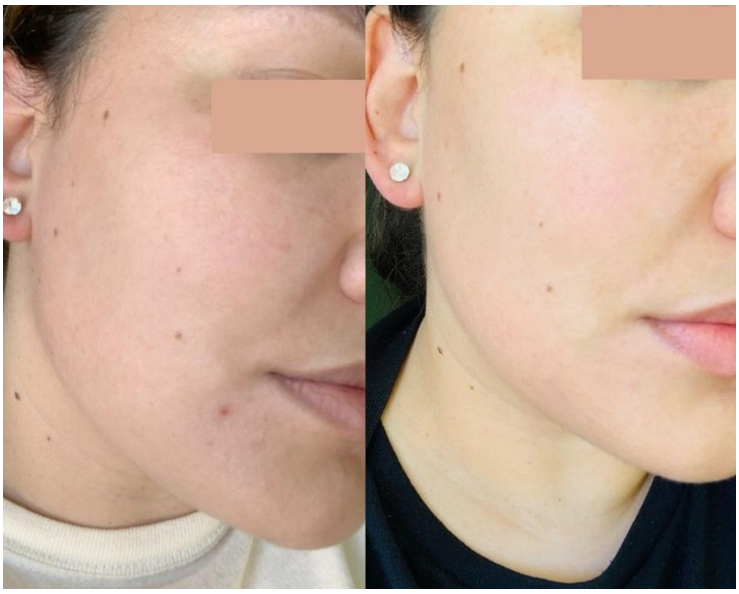

Figure 4: 35-year-old Hispanic female. Participant with redness caused by mold rosacea used 2-HOBA Repair Balm nightly for 21 days significantly reduced redness and improved skin hydration.

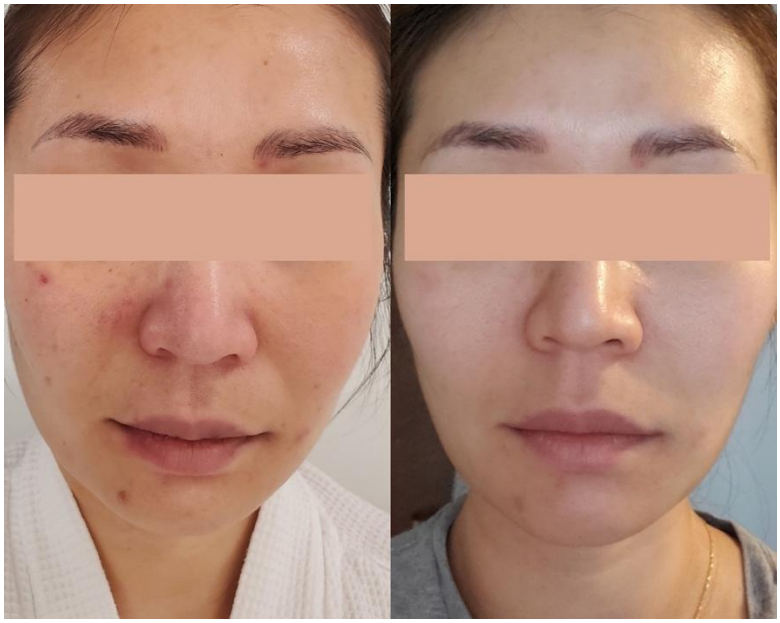

Figure 5: 37-year-old Asian female. Participant with moderate acne breakouts, inflamed acne scars, and damaged skin barrier used HMAB Rescue Mask once a week and 2-HOBA Refresh Cream once daily for 30 days.

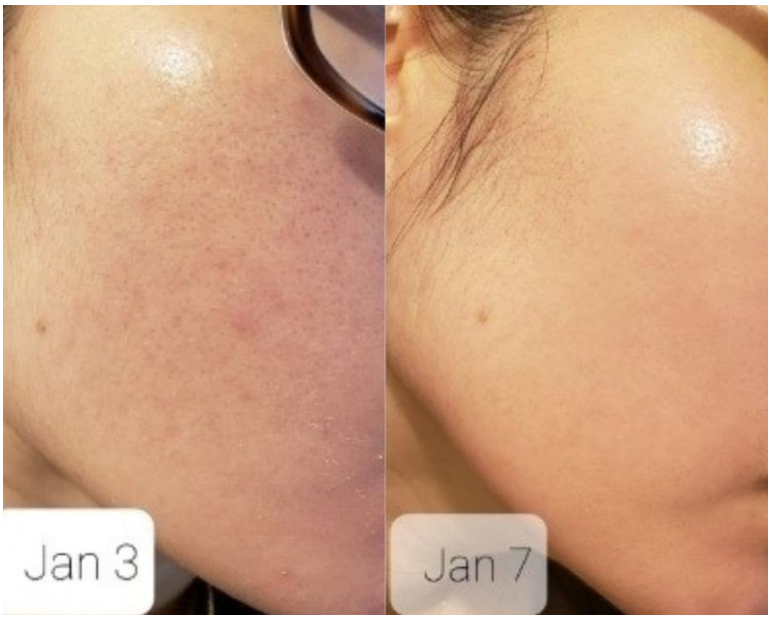

Figure 6: 29-year-old Asian female. Participant with sensitive skin presenting with redness caused by mold rosacea used 2-HOBA Refresh Cream for five days and noticed decreased redness and achieved overall smoother skin tone and texture.

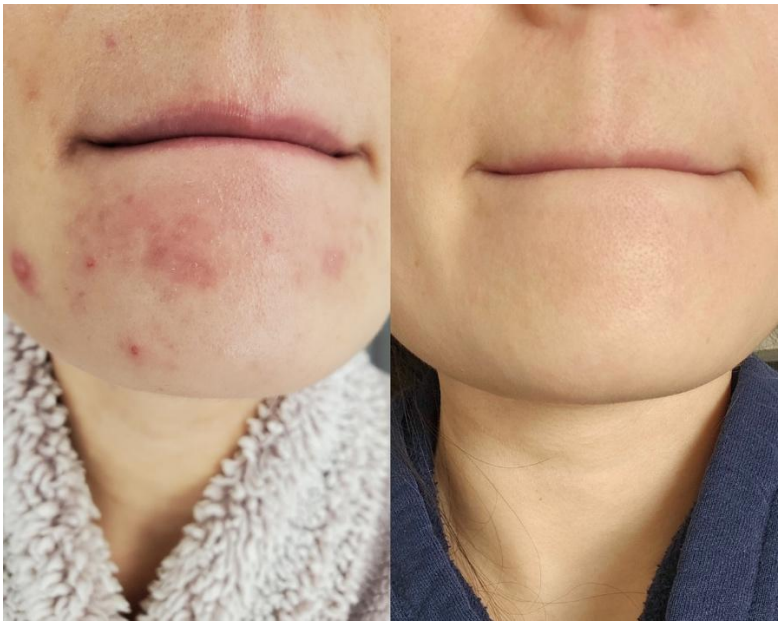

Figure 7: 35-year-old Asian female. Participant with cystic acne breakouts, inflamed acne scars and redness, and damaged skin barrier used HMB Rescue Mask twice a week for 30 days and fully healed skin barrier without scarring.

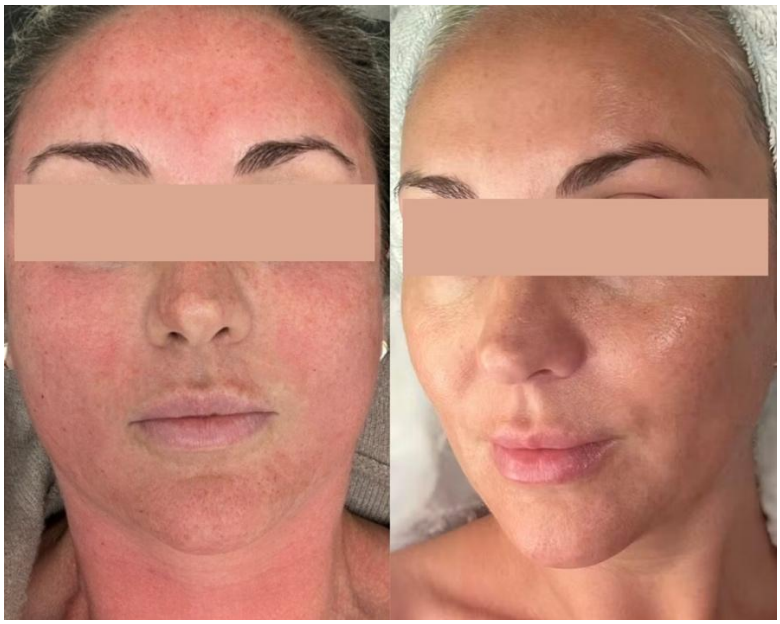

Figure 8: 43-year-old Caucasian female. Participant with sunburn damage, severe redness, and inflammation used 2-HOBA Refresh Cream for 7 days and fully reduced redness while alleviating sunburn without peeling.

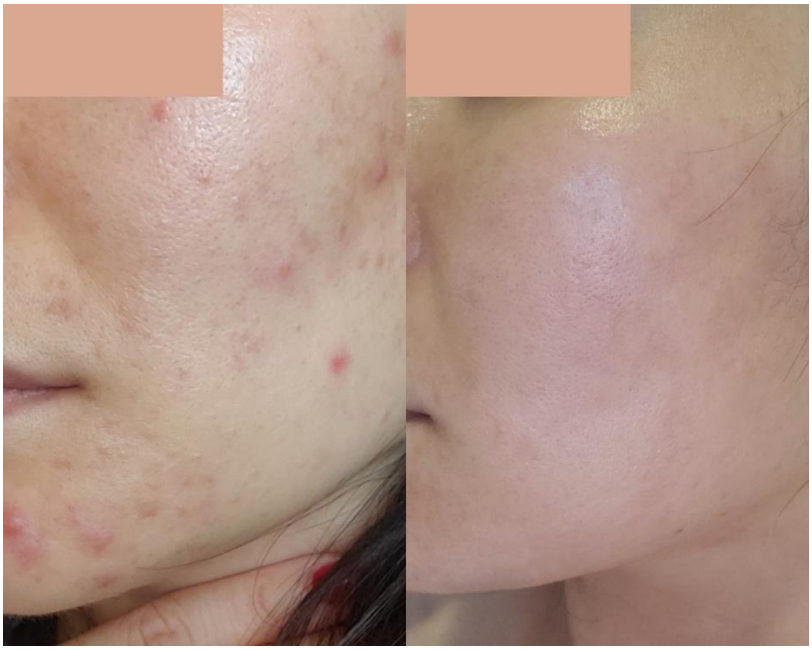

Figure 9: 39-year-old Asian female. Participant with cystic acne, hyperpigmentation, and inflamed acne scars fully healed acne and improved skin texture using HMB Rescue Mask 3-times per week and 2-HOBA Repair Balm nightly for 30 days.

4. Discussion

The significance of this study lies in demonstrating the potential for topical application of HMB and 2-HOBA to address the interconnected pathophysiology of skin "inflammaging" phenotype and inflammatory conditions through complementary biochemical mechanisms. The observed clinical improvements in inflammatory conditions such as acne and rosacea, along with enhanced skin texture and appearance, can be explained through mechanistic pathways that target both immune dysfunction and structural deterioration characteristic of compromised skin health

Chronic inflammation leads to upregulation of matrix metalloproteinases (MMPs) that degrade collagen and elastin, while structural protein damage generates damage-associated molecular patterns (DAMPs) that further activate inflammatory cascades [Lee, 2022]. The topical application of HMB and 2-HOBA represents a mechanistically complementary approach to address the dual pathophysiology. Both HMB and 2-HOBA have been found to be safe with no toxicity (Holeček, 2017; Courel-Ibáñez, 2019; Pitchford, 2018 and 2020; Rathmacher, 2025).

2-HOBA functions as a selective dicarbonyl electrophile scavenger preferentially reacting with very highly reactive isolevuglandins (IsoLGs) and other reactive aldehydes generated during lipid peroxidation. This prevents highly reactive species from forming covalent adducts with structural proteins such as collagen and elastin [Tao, 2020; Davies, 2019; Rathmacher, 2023; Gobert, 2023], preserving their functional integrity and preventing the cross-linking and fragmentation that characterize inflammatory skin conditions. Simultaneously, 2-HOBA modulates inflammatory biomarkers by increasing beneficial immune mediators (CCL19, IL-12β, TNFβ) while decreasing pro-inflammatory factors (TWEAK), potentially interrupting the inflammaging cycle [Rathmacher, 2023].

HMB, as a leucine metabolite with established protein synthesis-promoting properties, complements this protective effect by supporting regeneration and maintenance of dermal structural proteins, particularly collagen types I and III essential for dermal integrity [Williams, 2002]. Additionally, HMB's anti-catabolic properties may prevent degradation of existing structural proteins by inhibiting the ubiquitin-proteasome pathway [Rathmacher, 2025]. Together, these compounds address interconnected mechanisms of skin aging: 2-HOBA reduces oxidative protein modification and chronic inflammation, while HMB supports biosynthesis of new structural proteins, resulting in improved skin flexibility, enhanced structural organization, and decreased inflammation through modulation of immune biomarkers.

At the cellular level, the observed improvements reflect enhanced fibroblast function and reduced keratinocyte stress responses. HMB's activation of protein synthesis pathways support fibroblast production of extracellular matrix components, while 2-HOBA's protection against electrophile-mediated damage likely preserves fibroblast functionality. The reduction in inflammatory lesions may result from 2-HOBA's ability to prevent isolevuglandin-mediated activation of inflammatory pathways while HMB's support of barrier protein synthesis enhances epidermal integrity.

The photographic evidence of improved skin health in acne and rosacea can be explained through converging mechanisms. In acne vulgaris, the combination addresses both inflammatory components through 2-HOBA's anti-inflammatory effects and tissue repair through HMB's support of collagen synthesis for post-inflammatory healing. In rosacea, where vascular inflammation and barrier dysfunction are prominent, 2-HOBA's protection against oxidative damage to endothelial proteins combined with HMB's support of barrier protein synthesis addresses both underlying pathophysiological mechanisms.

Several limitations must be acknowledged. The visual assessment methodology lacks quantitative biomarker analysis that would provide objective measures of inflammatory mediators, collagen synthesis rates, and oxidative stress markers. The study population was limited to females aged 27-43, restricting generalizability across different demographic groups and age ranges. Additionally, the absence of standardized photographic protocols and comparative studies with established treatments limits the ability to quantify improvement magnitude.

Future research should incorporate objective biomarker assessments including measurement of inflammatory cytokines, collagen synthesis markers, and oxidative stress indicators. Mechanistic studies utilizing skin biopsies or non-invasive imaging techniques could provide direct evidence of proposed pathways. Randomized controlled trials comparing the HMB/2-HOBA combination to established treatments would strengthen the clinical evidence base.

In conclusion, this study provides preliminary evidence supporting the therapeutic potential of topical HMB and 2-HOBA combination therapy for inflammatory skin conditions and skin health optimization. The observed clinical improvements can be mechanistically explained through HMB's support of protein synthesis and 2-HOBA's protection against oxidative protein damage, addressing both structural and immune components of skin pathophysiology. The natural origin, established safety profiles, and complementary mechanisms position this combination as a promising candidate for evidence-based formulations. However, rigorous clinical trials with objective outcome measures, diverse populations, and mechanistic biomarker assessments are essential to validate these findings and establish optimal therapeutic protocols.

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