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Moldavian Dragonhead Extract: A Natural Collagen-Booster to Target Skin Aging

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Abstract

The complex process of skin aging results in noticeable changes, including decreased collagen content, reduced elasticity, and decreased hydration. Interventions to preserve or restore collagen, a key structural protein, may help counteract these signs. The concept of "beauty from within" through nutritional supplements is of growing interest, particularly the use of plant-based alternatives to animal-derived or synthetic collagen. This study investigated the anti-aging potential of an extract from Moldavian dragonhead (*Dracocephalum moldavica* L.), a natural plant-based compound. *In vitro* studies have shown that the extract stimulates genes crucial for skin structure. Further, a double-masked, randomized, placebo-controlled clinical trial in female volunteers demonstrated that oral supplementation with the extract significantly improves skin hydration and increases dermal and full-skin thickness. These findings suggest that the Moldavian dragonhead extract is a promising natural alternative to traditional interventions, offering a holistic approach to improve the skin's dermal network and combat skin aging.

Keywords
Dracocephalum moldavica L.; flavonoid-glucuronides; collagen-boosting; dermal thinning; nutricosmetics; beauty from within

1. Introduction

The health and aesthetic appearance of skin are essential concerns for individuals of all ages. As such, there are some notable differences in specific concerns and skin care practices between genders and age groups. For instance, men prioritize issues such as acne and skin irritation whereas women may often focus on anti-aging and hydration, [1]. Particularly during the menopausal transition, female skin undergoes significant functional changes, including a decrease in collagen content, water content, elasticity, and thickness [2, 3]. In the elderly population, thinning skin becomes a significant issue. The reduced production of collagen and the breakdown of existing collagen fibers weaken the skin's structure, making it more susceptible to bruising and impairing the skin barrier function [4]. These aging-related changes are influenced by various intrinsic and extrinsic factors, including hormonal changes, oxidative stress, and environmental exposures [5]. Among the internal factors influencing skin aging, nutrition, sleep, stress, and lifestyle play significant roles. Chronic sleep deprivation can exacerbate signs of aging, such as wrinkles and reduced skin elasticity [6]. Furthermore, prolonged stress can impair the skin's barrier function and accelerate the aging process [7]. Oxidative stress, caused by an imbalance between the production of reactive oxygen species (ROS) and the skin's antioxidant defenses, further plays a significant role [8, 9]. Specifically, ROS can degrade collagen and elastin fibers, which are essential for maintaining skin elasticity and firmness [10, 11]. Additionally, oxidative stress can activate matrix metalloproteinases (MMPs), enzymes that break down collagen and other extracellular matrix components, further contributing to skin aging [12].

Collagen, a key structural protein in the extracellular matrix of the skin [13], plays an integral role in maintaining the skin's elasticity and hydration [14]. Being a crucial protein in the human body, it is present in bones, tendons, ligaments, and particularly the dermal layer of the skin [15]. As collagen levels decrease with age and during menopause [3, 16], the skin structure and resilience declines. Therefore, interventions to preserve or restore collagen levels could be beneficial to combat skin aging. Dermal collagen synthesis, deposition, and extracellular matrix (ECM) remodeling are primarily mediated by fibroblasts, the most abundant cell type in the dermis [17]. The organization of the collagen fibrils contributes to the skin’s structural integrity and resilience [18]. Given its significant role in skin function, it is unsurprising that reduced collagen production and impaired collagen function are hallmarks of skin aging [19]. Indeed, altered collagen levels and changes in the extracellular matrix composition have been frequently observed, both *in vitro* and clinically [20-22]. Therefore, identifying compounds that can stimulate collagen synthesis, enhance collagen signaling, and prevent dermal degradation is of great interest for effectively targeting skin aging. Possible targets for addressing collagen signaling include different collagen subtypes, such as collagen XVI (COL16A1) and collagen VI (COL6A1) [23, 24]. Additionally, small leucine-rich proteoglycans (SLRPs) such as biglycan (BGN) and decorin are promising. These proteoglycans interact with collagen fibrils,

influencing their assembly and stability, and modulating the skin's resilience and repair mechanisms [25].

The concept of "beauty from within" treatments, which explore the benefits of nutritional supplements on the skin, including combating skin aging from within, is of growing interest [26, 27]. Consumers are increasingly recognizing that the health and appearance of the skin are closely linked to overall nutritional status and internal factors [28]. Consequently, supplements containing bioactive compounds that can stimulate collagen production, enhance antioxidant defenses, and support skin barrier function are gaining popularity to slow down the skin aging process [29]. Indeed, collagen supplements have shown significant potential in improving skin texture [30]. Among these, particularly hydrolyzed collagen from marine or bovine sources has been well characterized and highlighted for its safety profile and effectiveness in enhancing skin health [31, 32]. Several randomized placebo-controlled clinical studies have demonstrated that hydrolyzed collagen supplementation can lead to a reduction in wrinkles and improvement in skin firmness, hydration, and elasticity [33-37]. However, in recent years, there has been a noticeable shift in consumer preferences towards more natural, botanical-based supplements as an alternative to products derived from animals [38]. This growing trend reflects an increasing interest in, and demand for, natural, plant-based options.

The Moldavian dragonhead (*Dracocephalum moldavica L.*) is an aromatic herb native to Eastern Europe and Central Asia [39] and listed on various European plant-positive lists, including Belgium, France, Germany, and Italy. Furthermore, in the US, *Dracocephalum moldavica L.* is included in the Old Dietary Ingredient List, a list compiled shortly after the passage of the Dietary Supplement Health and Education Act of 1994 and developed by the American Herbal Product Association (AHPA), Council for Responsible Nutrition (CRN), Natural Products Association (NPA) and the United Natural Products Alliance (UNPA). It is also part of the Korean positive list. The plant is rich in a variety of bioactive compounds, including essential oils such as geranial, neral, and geraniol, as well as terpenoids, glycosides, and flavonoid-glucuronides [39]. These diverse phytochemicals have a range of pharmacological properties, including antioxidant, anti-inflammatory, and wound-healing activities, which may contribute to the plant's reported health benefits [40, 41]. Previous findings have demonstrated that Moldavian dragonhead extract can activate longevity pathways and preserve youthful collagen expression and mass in the model organism *Caenorhabditis elegans* (*C. elegans*) [27]. Notably, studies in *C. elegans* have shown that increased collagen expression is associated with extended longevity [42, 43]. Although research in humans is limited and primarily based on small-scale studies, there is some evidence for genetic mutations in collagens being associated with longevity and healthy aging [44].

With its bioactive properties that enhance collagen production, the Moldavian dragonhead proves to be a suitable candidate to combat skin aging from within. Previously, our open-label, single-arm pilot study showed that daily food supplementation with Moldavian dragonhead dry extract powder improved skin hydration, elasticity, and, importantly, skin density [27]. To follow up on this study, a double-blind, randomized, placebo-controlled study was performed to investigate further the collagen-boosting effects of dietary supplementation with a Moldavian dragonhead extract at a lower dose and with an improved formulation. Furthermore, underlying molecular mechanisms were addressed *in vitro* to identify possible mediators of the skin rejuvenation effects.

2. Methods

2.1 Moldavian Dragonhead Extract Preparation

The Moldavian dragonhead extract (hereafter referred to as MDH Nu sd) was prepared as previously described [27], with some modifications. In short, the dry aerial parts of *Dracocephalum moldavica* L. were extracted with de-ionized water for 1 hour at 85-90°C by percolation. After vacuum concentration, the liquid extract was then spray-dried on 50% maltodextrin as a carrier (DracoBelle™ Nu sd, provided by Mibelle Group Biochemistry, Buchs, Switzerland). This process ensures a content of at least 2.5% of total flavonoid-glucuronides in the extract powder. The detailed nutritional values are found in Table S1.

2.2 UHPLC Extract Analysis

Extract analysis was performed using an ACQUITY C18 column (1.7 µm; 2.1 × 50 mm; Waters AG, Switzerland) connected to an Ultra High-Performance Liquid Chromatography (UHPLC) system (Waters Acquity Classic, Waters AG, Switzerland). The run was performed using solvent A (H_2O + 0.05 trifluoracetic acid) and solvent B (methanol) with a gradient of 15-95% solvent B over 8 minutes with a flow rate of 0.40 mL/min followed by a wash-out with 100% solvent B for 10 minutes. Detection was performed at a fixed 254 nm using a UV detection system (Shimadzu, Kyoto, Japan). Reference substances luteolin-7-O-glucuronide (CAS 29741-10-4, Sigma-Aldrich, USA) and apigenin-7-O-glucuronide (CAS 29741-09-1, Sigma-Aldrich, USA) were used as a standard for calibration and quantification in at least three replicates. Identification of compounds in the extract was based on UV detection and elution order as previously described [45].

2.3 Normal Human Dermal Fibroblast Cell Culture and Treatment

Normal human dermal fibroblasts (NHDF) were seeded in 24-well plates and cultured in DMEM supplemented with 10% fetal calf serum (FCS) (Thermo Fischer Scientific, USA) for 24 hours. After, cells were subjected to DMEM supplemented with 1% FCS as assay medium for a further 24 hours. The medium was then replaced by assay medium containing or not (control) 0.25 mg/mL MDH Nu. and the cells were incubated for 24 hours. All experimental conditions were performed in n = 3. At the end of incubation, the cells were washed in phosphate-buffered saline (PBS, pH 7.4, Gibco™, USA) and immediately frozen at -80°C for mRNA extraction.

2.4 RT-qPCR Analysis

RNA extraction was performed using TriPure™ Isolation Reagent (Roche, Switzerland) according to the manufacturer's instructions. The quality of RNA was evaluated via capillary electrophoresis (4200 TapeStation System, Agilent Technologies, USA). The quantity of RNA was determined by spectrophotometer (Synergy H1, BioTek Instruments), and cDNA was synthesized by reverse transcription of 1 µg RNA using oligo(dT) primers and Transcriptor Reverse Transcriptase (Roche). The SYBR Green I qPCR was performed using 25 ng of cDNA per condition, with primers against COL16A1, COL3A1, COL6A1, BGN, MMP14 and GAPDH in a LightCycler® system (Roche). All data were normalized to GAPDH, and fold changes were calculated based on the comparative ΔΔCt method.

2.5 Clinical Study

2.5.1 Participants

A total of 103 healthy non-smoking female volunteers, Caucasian, aged 35-65 years (54.6 ± 6.5), with noticeable wrinkles were included to test the clinical efficacy of oral supplementation of the Moldavian dragonhead extract, MDH Nu sd. Exclusion criteria were smokers, males, medical history of gastrointestinal, renal, cardiovascular disease or dermatologic disease, current or previous intake of contraceptives, female hormones, obesity drugs, absorption inhibitors, antidepressants or appetite suppressants, evidence of drug and/or alcohol abuse, intake of any kind nutritional supplements (vitamins, antioxidant, herbal, sports enhancing), intake of medication that might affect the study outcome. Before enrolment, all participants were thoroughly informed of the purpose of the study and enrolled subjects provided written, informed consent. The study was conducted in Valencia, Spain, in accordance with the Scientific Committee on Consumer Safety (SCCS) and the Declaration of Helsinki. The standard protocol and test conditions were submitted to and approved by the Ethical Committee of Bionos Biotech (Date 18/07/2023, Code number 0038-2023) and registered in the database for Protocol Registration and Results System ClinicalTrials.gov PRS (NCT 06059534).

2.5.2 Study Design and Product Intake

The study was monocentric, double-masked, randomized, and placebo-controlled. Participants attended an environmentally controlled facility for the evaluation of skin parameters. Following baseline determination (D0) of the skin parameters defined in the sections below, participants were instructed to ingest the test product MDH Nu sd (100 mg Moldavian dragonhead extract) or the corresponding placebo (100 mg maltodextrin) by oral intake once a day, in the morning, for a total 12 weeks. The MDH Nu sd and placebo were provided in the form of capsules (hydroxypropyl methylcellulose) supplied in plastic flasks with 50 capsules per flask. Parameters were measured before treatment (D0, hydration, dermal density), after 4 weeks (D28, hydration), 8 weeks (D56, hydration), and 12 weeks (D84, hydration, dermal density) of oral intake. Subjects were requested to keep a diary and note any observed reactions or discomfort. The study was performed under dermatological surveillance, which monitored for adverse effects and confirmed the safety and tolerance of the interventions.

2.5.3 Skin Measurements

The skin parameters were measured on the face of the participants. Skin hydration was quantified using Corneometer® CM 825 (Courage & Khazaka, Germany). Five measurements were performed on the cheek for each volunteer for each time point (D0, D28, D56 and D84). Additionally, a hydration map of 6 randomly selected volunteers was made to track the global hydration changes over the duration of the study. For this, 30 measurements were made for each volunteer at each time point (D0, D28, D56 and D84). Skin density measurements (full skin, epidermis and dermis) were performed on the face with an echograph ultrasound Ultrascan® UC 22 at 22 MHz (Courage & Khazaka), 3 replicas per timepoint. Ultrasound images were recorded and processed using the provided software.

2.6 Statistical Analysis

Preclinical data were tested by unpaired Student's T-test with homoscedasticity using GraphPad Prism 8 software (GraphPad, USA); results are depicted as mean ± SD. Clinical data were subjected to normality tests using the Shapiro-Wilkinson method. Parametric variables were then analyzed using paired Student's t-test, whilst non-parametric data were analyzed with the Wilcoxon signed-rank test. Results are depicted as mean ± SEM, p values < 0.05 were considered significant.

2.7 Ethics Statement/Institutional Review Board Statement

The study protocol is in accordance with the Scientific Committee on Consumer Safety (SCCS) guidance. It meets all international standards for research studies involving human subjects, the Good Clinical Practices (ICH-GCP), and the World Medical Association. It has been conducted under the Declaration of Helsinki (1864), with the amendments of Tokyo (1975), Venice (1983), Hong Kong (1989), Somerset West (1996), Edinburgh (2000), Washington (2002), Tokyo (2004), Seoul (2008) and Fortaleza (2013). The standard protocol and test conditions were submitted to and approved by the Ethical Committee of Bionos Biotech (Date 18/07/2023 and Code number 0038-2023). **Clinical Trial Registry number:** https://clinicaltrials.gov/study/NCT06059534.

3. Results

3.1 Phytochemical Profile of the Moldavian Dragonhead Extract

A phytochemical analysis of the Moldavian dragonhead extract was performed using ultra-performance liquid chromatography (UHPLC) to elucidate its bioactive constituents. Our analysis based on UV-detection at 254 nm revealed the presence of two prominent peaks corresponding to luteolin-glucuronide and apigenin-glucuronide (peaks 1 and 2 in Figure 1), which are flavonoid-glycosides known for their potent antioxidant and anti-inflammatory activities [46, 47]. Furthermore, different flavonoid-glycosides and flavonoid-glucuronides have been detected to a lesser extent than these specific ones; specifically, acacetin-glucoside, diosmetin-glucuronide, and acacetin-glucuronide (peaks 3-5 in Figure 1). Based on their UV spectra, the unidentified peaks correspond most probably to flavonoids as well. These findings are consistent with previous reports on the phytochemical composition of Moldavian dragonhead, which is a rich source of these phytochemicals [27]. A total content of 9.6 mg flavonoid-glucuronides/g dried extract powder has been quantified.

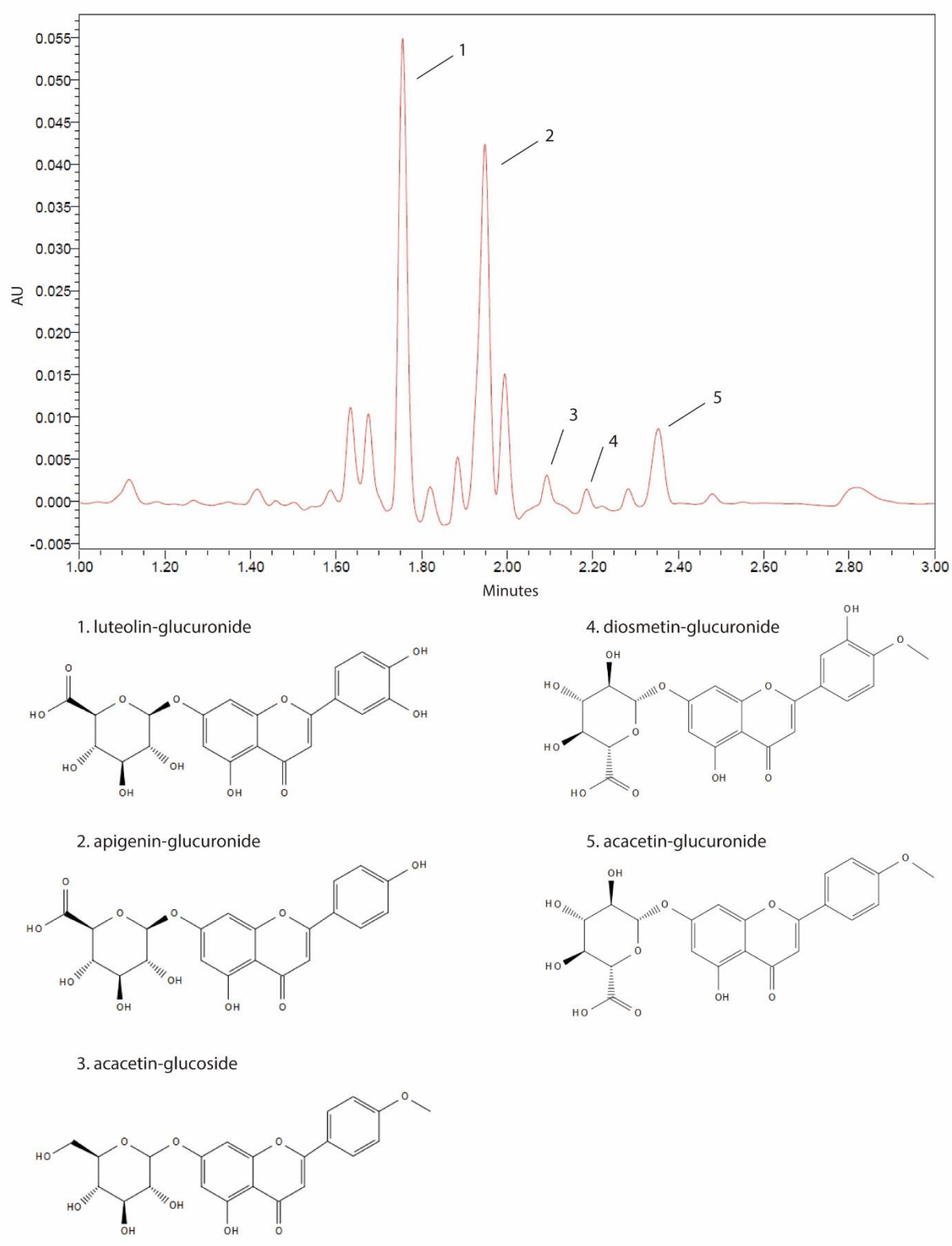

Figure 1 Detection of Flavonoid Glucuronides in Moldavian Dragonhead Extract. UHPLC Fingerprint at fixed wavelength (254 nm) of the Moldavian dragonhead extract identifies peaks corresponding to (1) luteolin-glucuronides, (2) apigenin-glucuronides, (3) acacetin-glucosides, (4) diosmetin-glucuronides and (5) acacetin-glucuronides.

3.2 In Vitro Stimulation of Collagens

To investigate the mechanism underlying the previously observed collagen-boosting effects of Moldavian dragonhead [27], human dermal fibroblasts were treated with the Moldavian dragonhead extract (hereafter termed "MDH Nu sd") and changes in gene expression assessed by RT-qPCR. After 24 h, treatment with MDH Nu sd had a stimulating effect on three collagen genes, COL16A1, COL3A1, and COL6A1, as well as on biglycan (BGN), and the matrix metalloproteinase MMP14. Details on the genes are presented in Table 1.

Table 1 Name and function of genes analyzed by RT-qPCR in human dermal fibroblasts.

Gene symbol	HGNC approved name	Function in skin
COL16A1	collagen type XVI alpha 1 chain	Maintenance of ECM integrity
COL3A1	collagen type III alpha 1 chain	Fibrillar collagen, structural protein, ECM integrity
COL6A1	collagen type VI alpha 1 chain	ECM organization, collagen binding, cell connectivity
BGN	biglycan	Collagen fibril assembly
MMP14	matrix metalloproteinase-14	ECM remodeling, collagen homeostasis

All the five genes analyzed were upregulated, most of them significantly, compared to untreated controls (Figure 2). COL16A1, expressed in fibroblasts and keratinocytes, is a member of the FACIT collagen family (fibril-associated collagens with interrupted helices), which serves to maintain the integrity of the extracellular matrix [23]. COL3A1 is an essential protein and one of the significant fibrillar collagens extensively found in connective tissues such as skin, lungs, and intestine [48]. Collagen 6A1 is a major structural component of microfibrils, expressed in many connective tissues and implicated in ECM organization [24]. BGN encodes a member of the small leucine-rich proteoglycan (SLRP) family of proteins. Being involved in collagen fibril assembly, it is particularly abundant in connective tissues such as bone, cartilage and skin [25]. The matrix metalloproteinases are further essential for ECM organization, and it was found that MMP-14 regulates collagen homeostasis in the adult skin [49]. In summary, MDH Nu sd stimulates genes critical in the maintenance of the extracellular matrix *in vitro*.

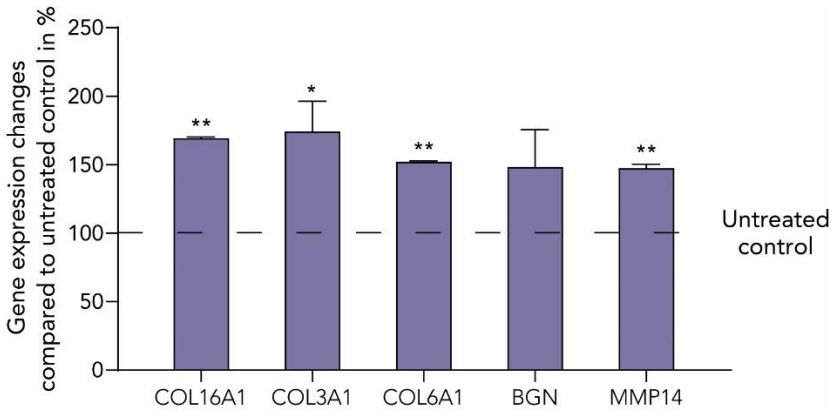

Figure 2 Stimulation of ECM-related genes with Moldavian dragonhead extract. Gene expression changes in treated human dermal fibroblasts after 24 h treatment with MDH Nu sd. Mean ± SD (n = 3), Students t-test, *p < 0.05, **p < 0.01 compared to untreated controls.

3.3 Safe and Well-Tolerated Nutritional Supplement

One hundred-one of the enrolled 103 subjects completed the entire course of treatment and follow-up. Two dropouts occurred for personal reasons unrelated to the study design or product supplementation. A total of 50 participants were allocated the placebo treatment whereas 51 participants received the verum treatment with MDH Nu sd supplementation. The nutritional supplement was well-tolerated by all participants in the study, with no adverse effects reported during the observation period. Further, no adverse effects were reported regarding skin compatibility and all volunteers showed general acceptance after the treatment with either product.

3.4 Moldavian Dragonhead Supplementation Improves Skin Hydration

Water plays a crucial role in the structural integrity of collagen [50]. As such, the observed *in vitro* effects on collagen synthesis may translate to clinical benefits, particularly in terms of skin hydration. We hypothesized that increased collagen levels in the skin may lead to increased hydration, given collagen's capacity to bind water molecules [51]. Compared to baseline (D0), supplementation with DracoBelle™ Nu sd significantly increased hydration levels by 16.4, 53.6 and 71.1 % after 28, 56 and 84 days, respectively (Figure 3a). The hydration increase was further significant compared to the placebo-treated group at the respective time points. This was also evident in the hydration maps evaluated to track the global hydration changes. Over the period of 84 days, a steady increase in hydration (corresponding to a darker blue signal in the hydration maps, with red being dry areas) was observed (Figure 3b).

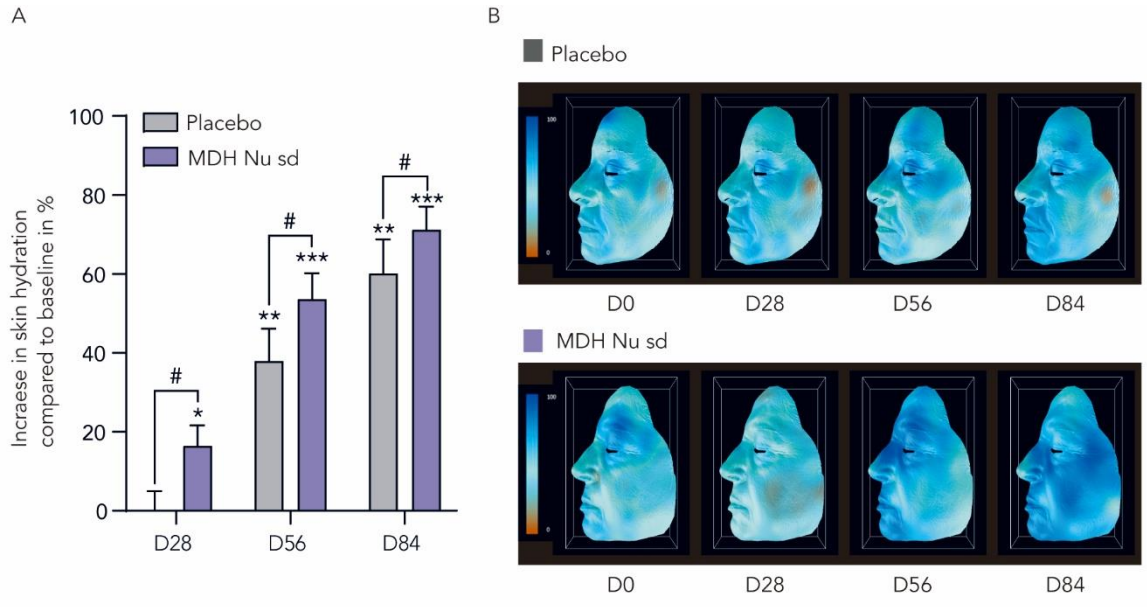

Figure 3 Effects of Moldavian dragonhead supplementation on skin hydration. (a) Skin hydration changes after 28, 56 and 84 days of MDH Nu sd supplementation, compared to placebo and baseline controls. (b) Skin hydration maps generated for each timepoint (D0, D28, D56 and D84). Dark blue indicates increased hydration, and white to red indicates less hydrated areas of the skin. Mean ± SEM (n = 50 for placebo, n = 51 for MDH Nu sd group), Students t-test and Wilcoxon signed-rank test, *p < 0.05, **p < 0.01, ***p < 0.001 compared to baseline, #p < 0.05 compared to placebo.

3.5 Moldavian Dragonhead Extract Increases Dermis Thickness

Enhanced collagen synthesis can lead to a denser dermal layer, thereby increasing overall skin thickness. To investigate this, changes in epidermis, dermis and full skin thickness were evaluated via ultrasound analysis. After 84 days of nutritional supplementation of MDH Nu sd significantly increased the skin thickness compared to baseline (Figure 4). When investigating this further and looking at the individual skin layers, it was evident that the increase in skin thickness resulted from modifications in the dermis. Whilst the epidermal thickness mainly remained unchanged after 84 days, the overall thickness of the dermis was significantly increased by 8.7 %. Due to the localization of collagen predominantly to the dermal layer, these results further consolidate the collagen-boosting effects of MDH Nu sd supplementation.

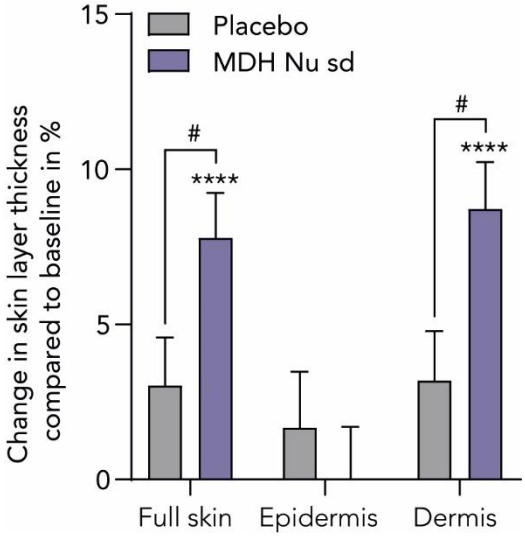

Figure 4 Increased skin and dermis thickness after 84 days. Changes in full skin, epidermis and dermis thickness as measured by ultrasound after 84 days of MDH Nu sd supplementation. Mean ± SEM (n = 50 for placebo, n = 51 for MDH Nu sd group), Students t-test and Wilcoxon signed-rank test, ****p < 0.0001 compared to baseline, #p < 0.05 compared to placebo.

4. Discussion

In this study, the effects of Moldavian dragonhead extract on skin aging are primarily examined, with a focus on its ability to enhance collagen production and improve skin hydration and thickness. From a mechanistic standpoint, the Moldavian dragonhead extract stimulated the expression of key collagen genes, including COL16A1, COL3A1, and COL6A1, as well as biglycan (BGN) and matrix metalloproteinase MMP-14. This provides valuable insights into its mode of action. Reduced COL3A1 levels have been observed in a model of extrinsic skin aging where dermal fibroblasts are irradiated with UV-B [52]. COL16A1 helps maintain the structural integrity of the dermal ECM, which is crucial for skin elasticity and resilience [23]. Its decline during aging may further contribute to the fragmentation and disorganization of collagen fibers [53], reduced dermal thickness and wrinkle formation [54] highlighting its importance in maintaining youthful skin. BGN is involved in collagen fibril assembly and organization [25]. Knockdown of biglycan in mice was shown to alter collagen structure, affecting tendon mechanical properties and wound healing [55, 56]. Additionally,

decreased BGN levels in the aging skin suggest its loss could compromise skin resilience and elasticity [57, 58]. Therefore, the upregulation of these genes indicates that Moldavian dragonhead extract can positively influence the skin's collagen framework, enhancing its overall quality and organization.

These results are consistent with previously observed collagen-boosting effects of the Moldavian dragonhead extract. In *C. elegans*, expression of collagen levels decreases with age [42], and intriguingly, the extract treatment demonstrated a stimulating effect, preserving a youthful collagen expression [27]. Furthermore, the extract activated the longevity pathway AMPK-FOXO1 in C2C12 myoblast cells [27]. As such, FOXO proteins have been emerging as pro-longevity factors in several species and pathways (reviewed in [59]), including the maintenance of skin health [60]. The ability of the Moldavian dragonhead extract to activate such pathways while boosting the expression of multiple collagen subtypes suggests a holistic approach to improving the skin's dermal network. This stimulation and reorganization can, in turn, lead to enhanced skin hydration and density, as was observed in the present study and the previously performed open-label pilot trial [27]. Similar stimulating effects on collagen have been observed for various botanical extracts, apple-derived exosomes [61], red seaweed [62], cinnamon [63], passion fruit seed [64], and Panax ginseng [65], among others. These studies highlight the considerable potential of plant-derived extracts in skin anti-aging, offering natural alternatives for health-conscious consumers.

It cannot be excluded that various compound classes contribute to the demonstrated activities, but most probably, the significant flavonoid-glucuronides of Moldavian dragonhead, particularly luteolin-glucuronide and apigenin-glucuronide [45], contribute to the demonstrated collagen-boosting and anti-aging effects. They show chemical similarity to the flavonoid-glucuronides, namely baicalin and scutellarin, present in Baikal skullcap (*Scutellaria baicalensis* Georgi) extracts. Skullcap extracts, baicalin, and scutellarin, which are common dietary supplement ingredients, have been frequently investigated for their skin anti-aging effects. Scutellarin and baicalin have demonstrated promising biological activities that can improve skin health, including protection against UV irradiation [66, 67], inhibition of inflammation [68], and stimulation of skin repair [69]. Scutellaria, a genus taxonomically related to Moldavian dragonhead, has been extensively studied and shown to possess antioxidant, anti-inflammatory, and antimicrobial properties, attributes that are highly desirable in skincare applications [70]. Furthermore, flavonoids, in general, have been linked to the modulation of collagen production [71, 72]. The wide range of pharmacological activities exhibited by flavonoids, including their potential to influence collagen synthesis, suggest that the presence of flavonoid-glucuronides in Moldavian dragonhead could contribute to the extract's collagen-boosting effects. Recently, flavone glucuronides isolated from *Potentilla chinensis* were found to inhibit ROS generation and MMP-1 secretion in TNF-α exposed human dermal fibroblasts [73]. Furthermore, hesperitin glucuronide protected human dermal fibroblasts from UV-A-induced cell death [74]. These protective effects against photo-aging may also contribute to the observed collagen-boosting benefits.

In summary, the natural Moldavian dragonhead extract targets a range of age-related skin concerns, including collagen degradation, dermal thinning, and impaired skin hydration. The thinning of the aging skin, particularly the dermis, can have significant impacts on the elderly population [4, 75]. The decreased production and organization of key dermal components like collagen and proteoglycans leads to a loss of firmness, elasticity, and barrier function [76]. Consequently, the thinning dermal layer becomes more vulnerable to environmental stressors,

impairing its ability to heal and regenerate and contributing to visible signs of aging [77, 78]. Anti-aging skin interventions, such as dietary supplements that support these dermal components, can help counteract these age-related changes. For future research and to confirm the flavonoid glucuronide activity on skin health and collagen production, it would be advantageous to conduct more extensive clinical studies of the effect of highly pure flavonoid-glucuronides derived from the Moldavian dragonhead.

5. Conclusion

The rejuvenating effects of Moldavian dragonhead extract, including increased dermal thickness and improved skin moisture, are auspicious and have significant implications for dermatology and cosmetic science. By addressing skin aging “from within”, dietary supplementation with this natural compound may offer an effective and safe alternative to more invasive interventions. As consumer demand for natural, plant-based cosmetic and nutraceutical solutions continues to rise, Moldavian dragonhead extract could become a valuable supplement for maintaining healthier, more youthful-looking skin. By enhancing the skin's structural integrity and resilience, these interventions can improve overall skin health and appearance, with notable benefits for the aging population.

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Author Contributions

JB, EB, FW and TG designed research; JB and EB conducted research; JB, EB and TG analyzed data and performed statistical analysis; and JB and TG wrote the paper. JB had primary responsibility for final content. All authors read and approved the final manuscript.

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Competing Interests

JB, EB, FW and TG are employed by Mibelle Biochemistry/Mibelle Group. The authors have no conflict of interest to declare.

Data Availability Statement

Data described in the manuscript, code book, and analytic code will be made available upon request pending.

Additional Materials

The following additional materials are uploaded at the page of this paper.

1. Analytical Report.
2. Table S1: Nutrition Declaration.

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