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RESEARCH ARTICLE

AMELIORATING EFFECT OF DJULIS (FORMOSA RUBY®) SUPPLEMENTATION ON SKIN AGING: A DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

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ABSTRACT

Djulis (*Chenopodium formosanum*) is a native grain plant, and shows that it has anti-oxidant and anti-glycation. However, it was still unclear whether djulis extracts improve skin condition and anti-glycation. The trial enrolled 300 subjects, who were double-blind and randomly assigned (in a 1:1 ratio) to placebo or djulis. The subjects were informed to consume one powder packet daily for 8 weeks. Skin conditions and self-assessment questionnaires of the subjects were collected at week 0, week 4 and week 8 of the study. The results showed that taking djulis extract powder significantly increased lightness, collagen density, elasticity and hydration, and significantly decreased advanced glycation end-products (AGEs), wrinkle, trans-epidermal water loss (TEWL) compared to placebo group. Djulis can improve human skin and can be used as one of the skin health ingredients.

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INTRODUCTION

The skin, being the largest organ of the human body, serves as a direct reflection of overall health. In the realm of skincare, the pivotal role of anti-glycation is paramount (1). Anti-glycation represents a mechanism designed to counteract the detrimental impact of sugar molecules on skin tissues (2). Elevated levels of glucose in the body can lead to the formation of advanced glycation end-products (AGEs), substances that possess the potential to disrupt the structural integrity of collagen, thereby diminishing skin elasticity and promoting the formation of wrinkles (3). Collagen, as one of the primary structural proteins in the skin, plays a crucial role in maintaining skin elasticity and firmness (4).

With advancing age, the synthesis and quantity of collagen decrease, resulting in skin laxity and the emergence of wrinkles (5). Beyond the protective measures of anti-glycation and collagen preservation, additional skincare strategies encompass the utilization of products containing retinol, antioxidants, and other compounds, which facilitate cellular renewal, decelerating the aging process and attenuating wrinkle formation (6). Melanin, a biological pigment responsible for skin, hair, and eye color, primarily consists of the amino acid tyrosine (7). Skin whitening extends beyond altering skin tone, addressing the reduction of pigment deposition and discoloration (8). An integral step in the skin whitening process involves impeding tyrosinase, the enzyme responsible for melanin synthesis (9).

The maintenance of skin moisture is contingent upon the retention of water and prevention of water evaporation (10). The skin's natural protective barrier on the surface, comprised of lipids, establishes a shield inhibiting moisture loss (11). Thus, anti-glycation, collagen preservation, wrinkle attenuation, skin whitening, and moisture retention collectively form a comprehensive strategy for maintaining skin health. Indigenous to Taiwan, *C. formosanum* Koidz. (commonly known as djulis) plays a dual role as both a cereal crop and a crucial component in wine brewing. Termed "Hung Li" or the "ruby of cereals" due to its vivid red color attributed to nitrogenous pigments, this grain has its roots in the cultivation practices of Taiwan's aboriginal peoples (12). Djulis stands out for its nutritional richness, encompassing a diverse spectrum of essential components such as starch, protein with essential amino acids, and dietary fiber (13). Recognized as a comprehensive and nutritious whole-grain food, djulis is particularly noteworthy as a source of essential nutrients for individuals adhering to vegetarian diets (14). Beyond its nutritional content, djulis serves as a reservoir of beneficial phytochemicals, including flavonoids, phenolic acids, betanins, and other plant secondary metabolites (15). This unique composition contributes to djulis' notable antioxidant and anti-inflammatory properties, further enhancing its appeal as a health-promoting dietary choice (16). In a previous study, it was found that taking djulis drink for 8 weeks can protect the skin against oxidative stress-induced damage, delay skin aging and improve skin conditions (17). In order to improve the credibility and clinical applicability of previous studies, this study scale was expanded to 300 subjects compared with the previous 30 subjects' trial, it can help to understand the efficacy of djulis on the skin more deeply. This study was explored whether the skin can be improved after consuming the Formosa Ruby® djulis extract powder. This study evaluated the clinical benefits of an 8-week supplementation of a collagen beverage on skin appearance and blood biochemistry.

MATERIALS AND METHODS

Clinical trial design: The study was registered in clinicaltrials.gov (No. NCT05591352), was performed under a protocol approved by the Antai Medical Care Cooperation Antai-Tian-Sheng memorial Hospital Institutional Review Board (Approval Number: TSMH-IRB 22-043-B), and was conducted according to the code of ethics on human experimentation established by the Declaration of Helsinki (1964) and its amendments. Written informed consent was obtained from all participants after a full explanation of the study. A double-blinded, placebo controlled, randomized study was conducted. The subjects were randomly assigned to two groups with 150 subjects in each group. The subjects were informed to consume one powder packet daily for 8 weeks. Before measurements, subjects were instructed to wash and wipe their face, and acclimatize for at least 30 min to the standardized laboratory conditions (room temperature 25°C, RH 55 ± 5%). Skin conditions and self-assessment questionnaires of the subjects were collected at week 0, week 4 and week 8 of the study. The fasting blood samples were collected at week 0 and week 8 of the study, and examined AGE, blood urea nitrogen (BUN), creatinine (CRE), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT). Inclusion criteria: Healthy adults aged above 20 years old. The exclusion criteria included: i) skin disease, liver cirrhosis, or chronic renal failure; ii) allergy to cosmetics, drugs, or foods; iii) pregnant and breastfeeding; iv) taking chronic drugs; v) people who had any cosmetic procedures (intense pulse light, medical peelings, or laser therapy) before 4 weeks of the study.

Supplement formulation: The djulis powder contains Formosa Ruby® djulis extract powder (300 mg), sucralose, tricalcium phosphate, isomalt (hydrogenated palatinose), citric acid. The placebo powder contains sucralose, tricalcium phosphate, isomalt (hydrogenated palatinose), citric acid. Subjects were required to consume one powder packet daily for 8 weeks. The placebo and experimental product were packaged in the same appearance, shape, and size. Neither the subject nor the operator will know the content group to be taken.

Clinical skin efficacy assessment: DermaLab® Series Skin Lab Combo was utilized to scan and analyze skin collagen density. The color scale indicates collagen density; white reflects the highest collagen density, and black reflect the lowest. Cutometer® dual MPA580 was utilized to measure skin elasticity, and the higher the relative value, the more significant the improvement. Corneometer® CM825 was utilized to measure skin moisture content, and the higher the relative value, the more significant the improvement. Chroma Meter MM500 was utilized to measure skin lightness, and the higher the relative value, the whiter the skin tone. Mexameter® MX18 was utilized to measure skin melanin index, and the lower the relative value, the more significant the improvement. VISIA Complexion Analysis System was utilized to measure skin texture, wrinkle, pores. The VISIA System ensured consistent positioning of each subject's head with a configurable head support. The photographic images were captured with standard and ultraviolet light at 0-degree head positioning. The results were presented as the mean value and the relative percentage (%) to the baseline.

Statistical analysis: The comparison of measurement results for skin parameters among groups and between groups was analyzed by student's *t*-test through GraphPad Prism, as $p < 0.05$ was considered statistical significance.

RESULTS

Djulis had anti-glycation effect: Table 1 showed the basic information of the subjects. The male to female ratio was similar between the two groups, and the mean age was also similar. Table 2 showed the liver and kidney function of the subjects at weeks 0 and 8 during the trial. No significant differences in the functional indicators of liver (GOT, GPT), kidney (CRE, BUN) after the djulis powder administration. This suggested that parameters evaluated for liver and kidney indicators show no side effects of djulis powder. In addition, taking djulis powder for 8 weeks can significantly reduce the AGEs 30.8% compared to week 0, and reduce AGEs 40% compared to placebo group (Fig. 1A). The above results showed that djulis had anti-glycation effect.

Table 1. Basic information of subjects

Items	Placebo group (n = 150)	Djulis group (n = 150)
Sex (Male)	21	29
Sex (Female)	129	121
Age (years)	48.3	46.2

Table 2. Subjects' blood biochemical values (*n* = 300)

Items	Group	week 0	week 8
AGEs	Placebo group	31.82 ± 15.91	27.40 ± 12.36***
	Djulis group	23.68 ± 13.33	16.42 ± 6.90***, ###
BUN	Placebo group	13.73 ± 3.52	13.86 ± 3.31
	Djulis group	13.36 ± 3.44	13.48 ± 3.32
CRE	Placebo group	0.71 ± 0.14	0.72 ± 0.15
	Djulis group	0.71 ± 0.15	0.71 ± 0.15
GOT	Placebo group	19.40 ± 5.61	19.43 ± 15.47
	Djulis group	18.34 ± 5.63	18.38 ± 5.95
GPT	Placebo group	17.70 ± 7.97	19.38 ± 23.25
	Djulis group	17.05 ± 7.60	18.13 ± 8.53

The data are presented as the mean ± standard deviation. AGEs : Advanced glycation end products. BUN: Blood urea nitrogen. CRE: Creatinine. GOT: Glutamic oxaloacetic transaminase. GPT: Glutamic pyruvic transaminase. *** Significant ($p < 0.001$) differences from week 0. ### Significant ($p < 0.001$) differences from placebo group.

Djulis increased lightness, collagen density, elasticity and hydration: The next step was to analyze whether djulis powder can improve skin condition. Taking djulis powder for 8 weeks can significantly increase skin lightness, collagen density, elasticity and hydration compared to week 0, and was also significantly better than the placebo group (Fig. 1B-1E). The above results showed that djulis had the potential to increase lightness, collagen density, elasticity and hydration.

Djulis decreased wrinkle, TEWL and improved somatosensory: Taking djulis powder for 8 weeks can significantly decrease skin wrinkle, TEWL compared to week 0, and the anti-wrinkle effect and water-locking effect was significantly better than placebo group (Fig. 2). The above results showed that djulis had the potential to decrease wrinkle and TEWL. Finally, somatosensory questionnaire results showed that taking djulis powder for 8 weeks, subjects felt improvement in skin conditions such as dryness, flakiness, and sallow skin tone (Fig. 3).

DISCUSSION

This study suggested that djulis (Formosa Ruby®) can increase lightness, collagen density, elasticity and hydration and decrease AGEs, wrinkle, TEWL in 300 subjects' clinical cases. In our previous study (n = 30), djulis had been found to increase superoxide dismutase (SOD) and catalase, and improve lightness, elasticity, crow's feet, texture, wrinkles, pores, and collagen density compared to baseline (17).

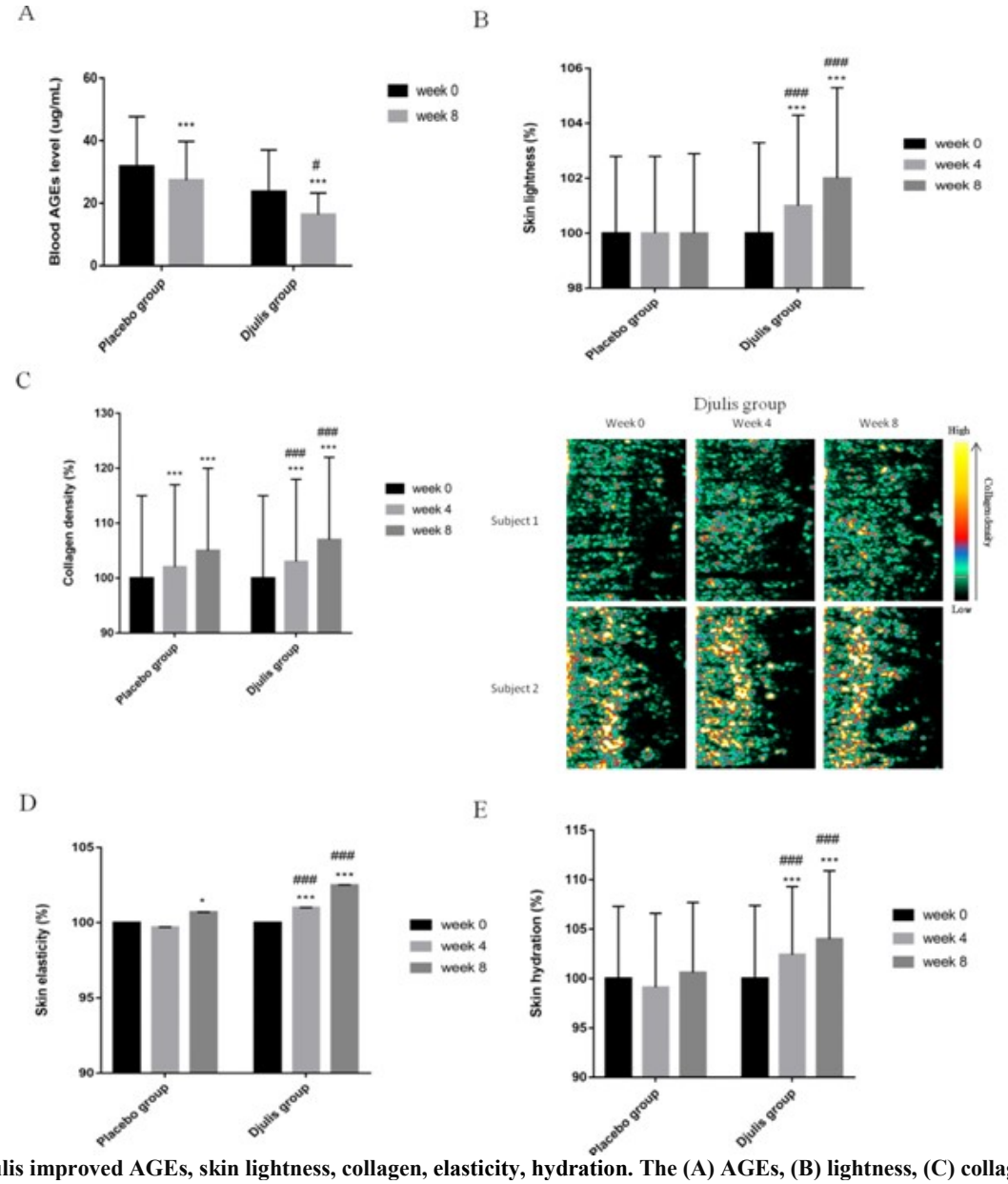

Figure 1. Djulis improved AGEs, skin lightness, collagen, elasticity, hydration. The (A) AGEs, (B) lightness, (C) collagen, (D) elasticity (E) hydration (n = 150; mean value ± SD) *, compared with baseline (week 0) (*, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$). #, compared with placebo group (#, $p < 0.05$, ##, $p < 0.01$, ###, $p < 0.001$)

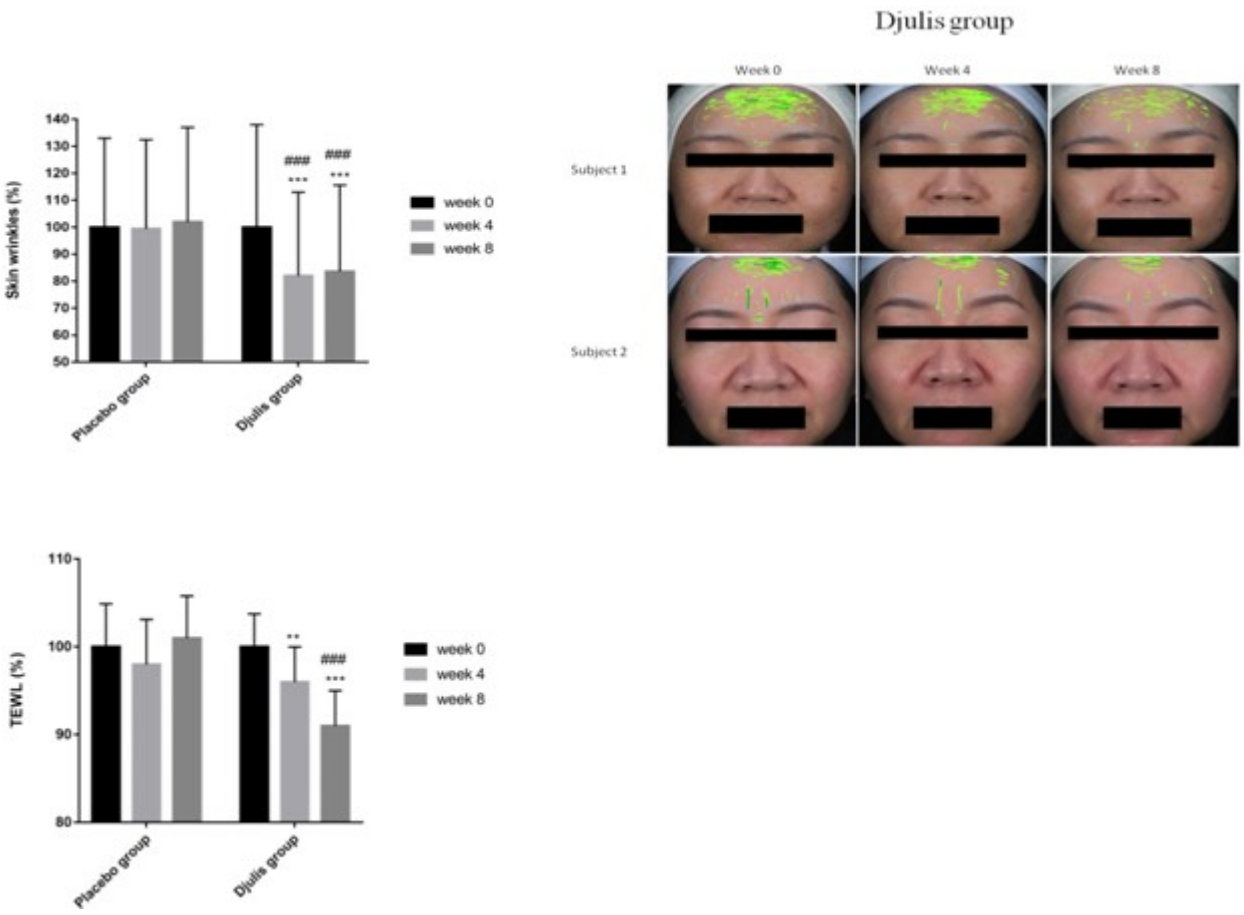

Figure 2. Djulis decreased wrinkles and TEWL. The (A) wrinkles, (B) TEWL (n = 150; mean value ± SD) *, compared with baseline (week 0) (*, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$). #, compared with placebo group (#, $p < 0.05$, ##, $p < 0.01$, ###, $p < 0.001$)

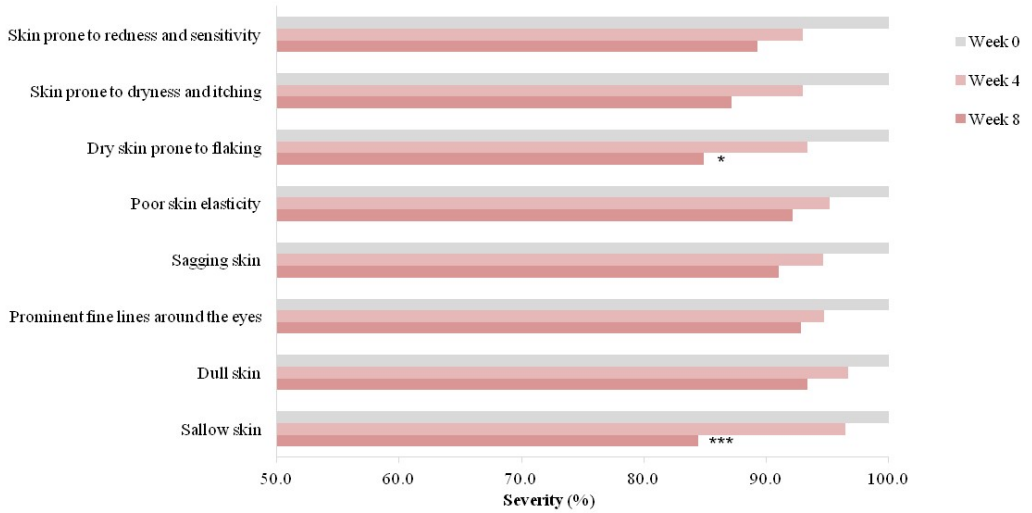

Figure 3. Djulis improved skin conditions by somatosensory questionnaire (n = 150; mean value ± SD) *, compared with baseline (week 0) (*, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$). #, compared with placebo group (#, $p < 0.05$, ##, $p < 0.01$, ###, $p < 0.001$).

In recent years, the development of natural products or materials with antioxidant and anti-glycation properties for improving skin aging has been ongoing. Several research studies focusing on active ingredients derived from djulis (*C. formosanum*) have elucidated the potent bioactive properties of polyphenols(18). These compounds have been demonstrated to exhibit robust free radical scavenging capabilities, thereby conferring antioxidant benefits (19). Additionally, polyphenols have shown efficacy in reducing inflammation and providing resistance against ultraviolet radiation, suggesting their potential role in mitigating oxidative stress and UV-induced damage to the skin (20). Rutin, another noteworthy component identified in djulis, has been found to play a crucial role in inhibiting the formation of AGEs during collagen synthesis (21). This inhibition of AGEs holds significance in the context of preserving skin elasticity and preventing age-related deterioration of collagen structures (3). The multifaceted bioactivity of rutin contributes to its potential as a valuable component in skincare formulations (22). Our prior investigations into compound profiling revealed the presence of 20-hydroxyecdysone in djulis (23). This bioactive compound, belonging to the phytoecdysteroid class, is

commonly encountered in djulis (23). Notably, 20-hydroxyecdysone, when isolated from *C. quinoa* seeds, has exhibited remarkable inhibitory activity against collagenase, indicating its potential role in preserving collagen integrity (24). Additionally, it has demonstrated strong free radical scavenging activity against DPPH free radicals and a potent ability to chelate iron ions (25). These findings underscore the diverse therapeutic properties of 20-hydroxyecdysone, rendering it a promising candidate for skincare applications. The inherent advantage of botanical extracts lies in their intricate composition, which often leads to a synergistic effect among various compounds, thereby enhancing overall efficacy (26). An intrinsic factor in skin aging is the gradual accumulation of AGEs. The receptor for AGEs (RAGE) is highly expressed in skin keratinocytes and fibroblasts through interaction with AGEs (27). Activation of RAGE reduces type I collagen synthesis and matrix production in fibroblasts (28). Consistent with previous studies, djulis reduced UV-induced intracellular reactive oxygen species (ROS) generation and initiated the antioxidant defense system by activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) signaling pathway in human skin fibroblasts (27). Djulis modulated mitogen-activated protein kinase (MAPK) and transformed growth factor-beta (TGF-β) signaling pathways to alleviate oxidative stress-induced skin aging (27). In a clinical trial of 300 subjects, djulis was also found to have anti-glycation effects and increased lightness, collagen density, elasticity and hydration. This synergism allows for the integration of multiple activities, contributing to a more comprehensive and potent skincare solution. The complexity of plant-derived compounds offers a holistic approach to skincare, addressing various aspects such as antioxidant protection, anti-inflammatory effects, and collagen preservation (29). Moreover, plant extracts hold significant promise in the realm of skincare due to their perceived natural origin, contributing to consumer appeal and the perception of safety (30). The abundance and sustainability of botanical resources further add to their attractiveness as ingredients in skincare formulations. As the demand for natural and sustainable products continues to rise, botanical extracts, with their multifaceted benefits and holistic approach to skincare, are poised to play a pivotal role in shaping the future of skincare formulations.

Conflicts of Interest: All authors declare no conflict of interest.

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