



## Hydrolyzed Collagen Combined With Djulis and Green Caviar Improve Skin Condition: A Randomized, Placebo-Controlled Trial

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### Abstract

Aging is a natural process that will cause physiological changes in organs. The effects of djulis and green caviar in skincare are currently unclear. This study combined hydrolyzed collagen with djulis and green caviar to develop new functional formulas that improve skin parameters. Fifty subjects were randomly assigned and divided into a placebo group (n=25) and a collagen drink group (n=25), and gave 50 ml of collagen of a collagen drink or placebo drink daily for 28 days, and we examined skin moisture, elasticity, gloss, spot, wrinkle, roughness, smoothness, pore, collagen and erythema. We find that intake of collagen drinks group improved skin parameters at 14 days and 28 days compared with baseline (0 day). The collagen drinks group improved skin parameters at 28 days compared with the placebo group. This clinical study proved the combination of collagen with djulis and green caviar for the substantial improvements in moisture, elasticity, gloss, spot, wrinkle, roughness, smoothness, pore, collagen, and erythema in the skin.



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### Keywords

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### Introduction


Collagen types I and III are the most abundant collagen in the skin. The synthesis and degradation of collagen is related to skin aging.<sup>1</sup> It can also improve skin condition by supplementing collagen supplements. Hydrolyzed collagen is composed of small peptides with a low molecular weight of 3-6 KDa, rich in amino acids, such as glycine and proline,

and accumulate in cartilage or skin after digestion, helping to maintain stability or regeneration.<sup>2</sup> Fish hydrolyzed collagen peptide is smaller than other collagen peptides, so it is easier to be absorbed by the human body.<sup>3</sup> Studies had shown that fish collagen peptide increased the production of hyaluronic acid (HA), and stimulated the synthesis of extracellular matrix (ECM) molecules.<sup>4</sup> Collagen

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peptide had increased wound healing ability in mice models.<sup>5</sup> In recent years, there had been a tendency to extract collagen or enzyme hydrolysates from aquatic products, such as jellyfish, squid, various fish skins, and waste viscera, fish bones, and fish scales.<sup>6</sup> The study showed that fish collagen peptide had better antioxidant capacity, photo-protection, immune regulation properties, and improved skin aging,<sup>7</sup> so often used as a functional food or dietary supplement. Therefore, novel and effective anti-aging ingredients for skincare have drawn a lot of attention.

In recent years, many grain-containing products have been used for multiple purposes, including cosmetics and food. Red djulis is a cereal plant in Taiwan. The whole plant is colorful, and is traditionally called "the ruby of grains" because of its bright red grain color and biologically active ingredients.<sup>8</sup> Djulis is particularly rich in lysine, which increases calcium absorption to help build collagen,<sup>9</sup> and had been reported that red djulis extracts (*Chenopodium formosanum*) can induce accumulation of betacyanins and flavonoids in keratinocyte for protection against UV-induced damage.<sup>10</sup> Red djulis can effectively prevent glycation of proteins which may lead to skin aging and several chronic diseases.<sup>11</sup> Thus, djulis extracts may act as an active ingredient for skincare products. Previous toxicity study also performed the safety of red djulis administration, and results performed all in the normal range in behavior, organ/tissue weight, histological stain, and blood biochemistry of rats.<sup>12</sup> Aside from djulis extract, the green caviar (*Caulerpa lentillifera*), also has anti-aging effect. Marine organisms such as green caviar is a rich source of natural bioactive compounds such as phenolics and flavonoids.<sup>13</sup> Studies have shown that green caviar with a strong antioxidant capacity to protect seaweeds against ROS.<sup>14</sup> There is the high content of amino acids (threonine, valine, aspartic acid, glutamic acid), like collagen, which can increase skin elasticity, strengthen the skin immune system, and maintain skin elasticity.<sup>15</sup> Several studies had reported on the antioxidant and antibacterial effects of green caviar.<sup>16</sup> However, the efficacy of green caviar in skincare products was still unclear. In our previous study, collagen drinks including fish collagen and djulis can improve skin and achieve anti-aging.<sup>17</sup> In this study, we additionally add green caviar extracts to the collagen drink to explore the

anti-aging effect. Here, we used collagen drinks combined fish collagen with djulis, and green caviar to examine whether can improve skin condition. The key findings of this study provided important insight into the anti-skin aging potentials of fish collagen, djulis, and green caviar to be used as novel sources of anti-aging ingredients for skincare.

## Materials and Methods

### Experimental Design

This study, based on a clinical trial of subjects, and examined the digitalization results to sum up the product efficacy by non-invasive detection method. A total of fifty subjects were recruited, they were divided into two groups, one was the placebo group (n = 25), another was the collagen drinks group (n = 25). All subjects had completed the study without withdrawal. Then, subjects drank 50 ml every night for 14, 28 days, and observed the cheek of skin condition after supplementation. This trial period was from May 2020 to June 2020. No cosmetics were used in the test area on the day of the examination. On the day of examination. Clean the test area with clean water, sit quietly for 30 minutes in a constant temperature and humidity environment, then analysis. Subjects should not use any skincare product which has similar efficacy to collagen drinks.

### Subjects Recruitment

Follow the world medical association declaration of Helsinki, our experimental design was approved by ethics and medical criterion. The study was approved by the Ethics Committee of the Ministry of Health and Beauty Products of China (IRB No. EWISH-20190917-01), and the protocol was registered with the ClinicalTrials.gov (NCT04709588). All the subjects were volunteers and signed informed consent before the clinical trial. We recruited subjects with dry and rough skin, large pores, dark yellow complexion, and sagging skin (n = 50, average age 53 years, 44 females and 6 males), and then record the current skin condition of the subjects (before use). The exclusion criteria included: i) skin disorders; ii) liver diseases; iii) kidney diseases; iv) allergy to cosmetics, drugs, or foods; v) pregnant and lactating women; vi) people who had any cosmetic procedures before 4 weeks of the study; vii) area of facial spot over 3 cm<sup>2</sup>; viii) vegan; and, ix) people who took collagen supplements in the past 3 months.

### Supplement Formulation

Refer to our previous study,<sup>17</sup> collagen drink of the main ingredient: 12% fish collagen (extracted from *Pangasianodon hypophthalmus*), 8% apple juice, 2% djulis extract (*Chenopodium formosanum*), 1% green caviar (*Caulerpa lentillifera*), water ; Placebo drink of the main ingredient: 8% apple juice, water.

### Skin Moisture Measurement

Corneometer CM825 was used to measure the moisture. The degree of improvement in skin moisture is positively correlated with the increase of measurement value.

### Skin Elasticity Measurement

Cutometer dual MPA580 was used to measure the elasticity. The degree of improvement in skin elasticity is positively correlated with the increase of measurement value.

### Skin Gloss Measurement

Probe system GL2000 & MPA10 was used to measure the gloss. The degree of improvement in skin gloss is positively correlated with the increase of measurement value.

### Skin Spot Measurement

VISIA® Complexion Analysis (Canfield Scientific) was employed to measure the skin spots of full face. The blue dots in the software indicate the spots. The degree of improvement in skin spots is inversely correlated with the numbers of blue dots.

### Skin Pore Measurement

VISIA® Complexion Analysis was employed to measure the skin pores of full face. The purple dots in the software indicate the pores. The degree of improvement in skin pores is inversely correlated with the numbers of purple dots.

### Skin Erythema Measurement

VISIA® Complexion Analysis was employed to measure the skin erythema of full face. The degree of improvement in skin erythema is inversely correlated with the numbers of red dots.

### Skin Wrinkles Measurement

VISIA® Complexion Analysis (Canfield Scientific) was employed to measure the skin wrinkles of full face. Wrinkles are characterized by the long and narrow shape areas; the green lines in the software

reflect the presence and depth of wrinkles. The degree of improvement in skin wrinkles is positively correlated with the measured value.

### Skin Smoothness and Roughness Measurement

VISIOSCAN-VC98 was used to measure the smoothness and roughness. Visioscan VC 98 is a special UVA-light video camera with high resolution for the direct study of skin parameters. The image output shows the skin smoothness and roughness. The camera was connected to a computer via a digitalization unit.

### Skin Collagen Content

DermaLab® Series SkinLab Combo (Cortex) was employed to skin collagen content of upper cheek. The instrument uses ultrasound to analyze the collagen density of upper cheek.

### Statistical Analysis

The comparison of measurement results for skin parameters among groups and between groups was analyzed by one-way repeated measurement ANOVA and one-way ANOVA, respectively, followed by Tukey's post hoc test through GraphPad Prism, as  $P < .05$  was considered statistical significance.

**Table 1: Subject profile.**  
(n = 50; mean value ± S.D.)

	Collagen formula	Placebo drink
Age (year)	50 ± 2.0	57.2 ± 1.0
No. subjects	25	25

### Results

#### Skin Moisture and Elasticity

Table 1 showed that subject profile. Randomly divided into two groups, one group was placebo group (n = 25), another was the collagen drinks group (n = 25). Moisture content was significant increased at 14 and 28 days compared with before use, and collagen drinks group significant increased by 27.54% at 28 days compared with the placebo group (Table 2). Besides, we find that elasticity was significant increased at 14 and 28 days compared with before use, and collagen drinks group significant increased by 8.53% and 11.14% at 14, 28 days compared with the placebo group (Table 2). These results suggested that a combination of fish collagen,

djulis, and green caviar can increase moisture and elasticity of the skin.

**Skin Gloss and Spot Area**

Skin gloss was significant increased at 14, 28 days compared with before use, and collagen drinks group significant increased by 26.14% at 28 days compared with the placebo group (Table 2). And we find that the

spot area was significant decreased at 14, 28 days compared with before use, and compared with the placebo group, the collagen drinks group significant decreased by 10.64% and 12.42% at 14, 28 days respectively (Table 2). Figure 1 showed that skin images included gloss. These results suggested that fish collagen, djulis, and green caviar can increase skin gloss, and decrease spot area.

**Table 2: Improvement of skin moisture, elasticity, gloss, spot area, wrinkles for collagen (n= 25) and placebo drinks (n = 25)**

Item	Group	Day	Mean value ± SD	Statistical significance	
				Corresponding to the baseline	Corresponding to placebo
Moisture	Collagen	0	35.3 ± 1.2		ns
		14	44.0 ± 1.1	***	###
		28	56.0 ± 1.8	***	###
	Placebo	0	33.8 ± 1.5		
		14	42.2 ± 2.1	***	
		28	44.4 ± 1.5	***	
Elasticity	Collagen	0	0.5 ± 0.01		###
		14	0.5 ± 0.02	***	###
		28	0.6 ± 0.01	***	
	Placebo	0	0.5 ± 0.01		
		14	0.5 ± 0.01	ns	
		28	0.5 ± 0.01	ns	
Skin gloss	Collagen	0	3.3 ± 0.1		ns
		14	3.9 ± 0.1	***	###
		28	4.5 ± 0.2	***	
	Placebo	0	2.9 ± 0.1		
		14	3.6 ± 0.2	ns	
		28	3.0 ± 0.1	ns	
Spot area	Collagen	0	226.0 ± 2.8		###
		14	202.2 ± 2.4	***	###
		28	190.1 ± 3.1	***	
	Placebo	0	215.2 ± 2.4		
		14	215.4 ± 1.9	ns	
		28	207.7 ± 1.8	***	
Wrinkles	Collagen	0	68.6 ± 5.8		###
		14	57.5 ± 3.6	***	###
		28	56.4 ± 2.1	***	
	Placebo	0	62.2 ± 2.8		
		14	62.8 ± 2.3	ns	
		28	63.6 ± 2.8	ns	

ns, no significant difference.

\*\*\* P < .001 as significant difference corresponds to the baseline

###P < .001 as significant difference corresponds to placebo group

**Eye Wrinkles and Skin Pore**

Further, eye wrinkles were significant decreased at 14, 28 days compared with before use, and compared with the placebo group, the collagen drinks group significant decreased by 17.06% and 19.92% at 14, 28 days respectively (Table 2). Then,

we find that pore area was significant decreased at 14, 28 days compared with before use (Table 3). Figure 1 showed that skin images included wrinkles and pore area, suggesting a combination of fish collagen, djulis, and green caviar can decrease eye wrinkles and pore area of the skin.

**Table 3: Improvement of skin pore area, smoothness, roughness, collagen, erythema for collagen (n= 25) and placebo drinks (n = 25)**

Item	Group	Day	Mean value ± SD	Statistical significance	
				Corresponding to the baseline	Corresponding to placebo
Pore area	Collagen	0	1.7 ± 0.03		ns
		14	1.5 ± 0.03	***	ns
		28	1.4 ± 0.05	***	
	Placebo	0	1.5 ± 0.04		
		14	1.5 ± 0.03	ns	
		28	1.4 ± 0.04	ns	
Smoothness	Collagen	0	232.3 ± 11.8		###
		14	218.5 ± 9.8	***	###
		28	208.0 ± 8.5	***	
	Placebo	0	233.9 ± 8.4		
		14	236.2 ± 8.2	ns	
		28	244.6 ± 7.9	ns	
Roughness	Collagen	0	4.3 ± 0.2		###
		14	3.5 ± 0.1	***	###
		28	3.0 ± 0.1	***	
	Placebo	0	4.0 ± 0.2		
		14	4.2 ± 0.2	ns	
		28	4.1 ± 0.3	ns	
Collagen	Collagen	0	124.8 ± 2.0		ns
		14	126.0 ± 2.0	***	ns
		28	127.1 ± 2.1	***	
	Placebo	0	130.0 ± 2.2		
		14	129.0 ± 2.2	***	
		28	128.1 ± 2.3	***	
Erythema	Collagen	0	360.9 ± 13.3		###
		14	349.9 ± 13.4	***	###
		28	302.4 ± 12.3	***	
	Placebo	0	341.1 ± 16.8		
		14	371.3 ± 13.5	***	
		28	365.7 ± 13.0	ns	

ns, no significant difference.

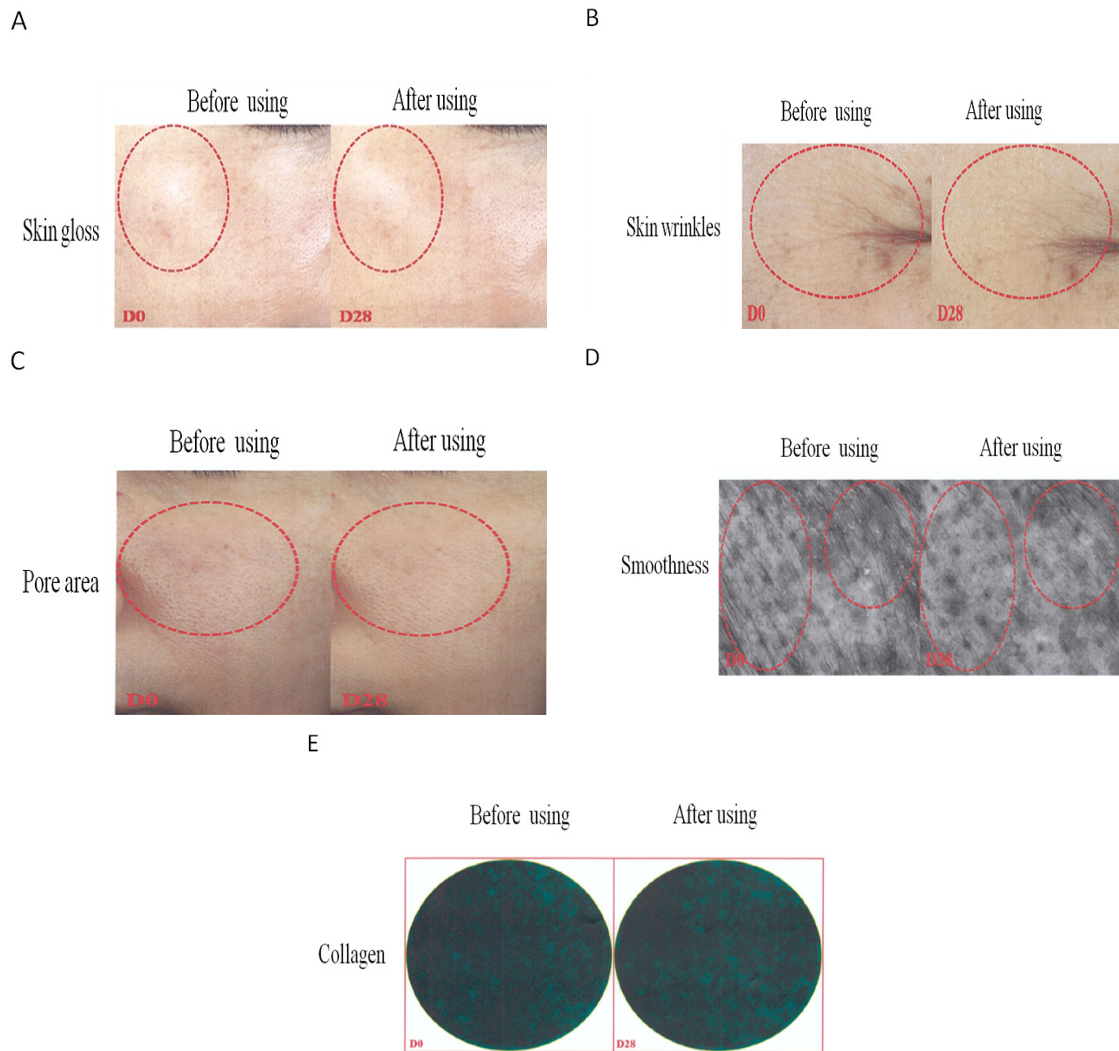
\*\*\* P < .001 as significant difference corresponds to the baseline

###P < .001 as significant difference corresponds to placebo group

**Skin Smoothness and Roughness**

The smaller the skin smoothness value was the smoother the skin. Conversely, the larger the skin roughness value was the rougher the skin. We find that smoothness value was significant decreased at 14, 28 days compared with before use, and compared with the placebo group, the collagen drinks group significant decreased by 6.92% and 14.98% at 14, 28 days respectively (Table 3). Figure 1 showed that skin images included

smoothness. And we find that skin roughness value was significant decreased at 14, 28 days compared with before use, and compared with the placebo group, the collagen drinks group decreased by 21.61% and 30.79% at 14, 28 days respectively (Table 3), suggesting a combination of fish collagen, djulis, and green caviar can increase skin smoothness and decrease the roughness of the skin.



**Fig. 1: Combined fish collagen with djulis, and green caviar improved skin gloss, wrinkles, pore area, smoothness and collagen. After drinking collagen drink for 28 days, the subjects were examined (A) skin gloss by probe system GL2000 & MPA10, (B,C) wrinkles, pore area by VISIA® Complexion Analysis, (D) smoothness by Visioscan VC 98, (E) collagen by DermaLab Series SkinLab Combo. Sample size = 50**

### **Skin Collagen and Erythema**

Skin collagen was significantly increased at 14, 28 days compared with before use, and compared with the placebo group (Table 3). Figure 1 showed that skin images included collagen. Also, we find that erythema was significantly decreased at 14, 28 days compared with before use, and compared with the placebo group, the collagen drinks group significantly decreased by 11.88% and 23.4% at 14, 28 days respectively (Table 3), suggesting a combination of fish collagen, djalulis, and green caviar can increase collagen and decrease erythema of the skin.

### **Discussion**

This clinical study was the first to use collagen, djalulis and green caviar, and improved skin moisture, elasticity, gloss, spot, wrinkle, roughness, smoothness, pore, collagen, and erythema. Other clinical studies showed that collagen supplements were considered effective cosmeceutical substances, which can improve skin health.<sup>18</sup> In our previous study, using fish collagen combined with djalulis can improve skin condition.<sup>19</sup> Oral supplements of the hydrolyzed collagen peptides were small molecules that were easily absorbed by the intestine and transferred to the skin. Lysine treatment of fibroblasts can stimulate collagen production and reduce melanocyte pigmentation.<sup>4</sup> Djalulis had inhibited the MMP-1 and ROS expression, thereby having anti-UV effects and promoting collagen synthesis.<sup>20</sup> The phenolic compounds and some UV-absorbing substances such as phlorotannins and mycosporine-like amino acids were mentioned as antioxidant substances in green caviar,<sup>21</sup> and enhanced fibroblasts proliferative and collagen synthesis. Our collagen drinks can increase moisture, elasticity, gloss and decrease spot area. Recently, some studies indicated female subjects aged 35 to 55 years into hydrolyzed collagen or placebo groups for 8 weeks, and skin moisture and elasticity were significantly improved,<sup>22</sup> other indicated that the subjects taking the hydrolyzed collagen with plant extracts had a significant increase in skin elasticity.<sup>23</sup> In skin gloss and spot area, oral collagen peptide supplements can significantly increase skin gloss and hydration after 4 weeks of ingestion, and increased collagen density.<sup>24</sup> Daily supplementation of collagen with vitamin C can improve skin gloss.<sup>25</sup>

In wrinkles and skin pore, oral bio-collagen peptide can improve skin wrinkles.<sup>26</sup> Intake of the rosehip extracts showed significant improved aging-induced skin wrinkles and pore area.<sup>27</sup> In skin smoothness, roughness and erythema, the addition of collagen with linseed oil reduced skin roughness and erythema, and increased smoothness.<sup>28</sup> Consistent with our results, our collagen drinks can increase skin smoothness, and decrease wrinkles, roughness, erythema, pore area. Dehydration can cause wrinkles and loss of elastin in the skin.<sup>29</sup> Therefore, improving skin hydration can reduce wrinkles, pores, roughness, as well as restored skin moisture, elasticity.<sup>30</sup> Our collagen drink can increase collagen synthesis, it may also be related to promoting the synthesis of hyaluronic acid.<sup>31</sup> Although the mechanism had not been explored in this study, we speculated that the biochemical mechanisms of collagen synthesis of djalulis 9 and green caviar,<sup>14</sup> which promoted amino acids to form collagen and elastin fibers,<sup>32, 33</sup> and activated collagen oligopeptides to act as ligands, bind to the receptors on the fibroblasts, and stimulated the production of new collagen and hyaluronic acid.<sup>34</sup> However, this still needed more experiments to clarify and confirm. Besides, the placebo group only had apple juice, and apple juice was also rich in antioxidants, it can improve the skin condition in the placebo group. Our collagen drinks combined with djalulis and green caviar can significantly improve the skin condition at 14, 28 days, and the ingredients contained were all-natural antioxidant ingredients, which were better than the current collagen drinks on the market.

### **Conclusion**

This clinical study was first demonstrated the combined fish collagen with djalulis, and green caviar for the substantial improvements in moisture, elasticity, gloss, spot, wrinkle, roughness, smoothness, pore, collagen, and erythema in the skin. Therefore, fish collagen, djalulis, and green caviar can be used as novel sources of anti-aging ingredients for skincare in the future.

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**Conflict of interest**

The authors declare no conflict of interest

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