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Collagen formula with Chinese herbal medicine can improve skin condition and reduce inflammation: a double-blind, randomized, placebo-controlled trial

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Abstract

Purpose – Population aging was a global trend, and the most obvious thing after aging was the change in skin appearance. Therefore, the active ingredients that delay skin aging were particularly noticed. Past studies had pointed out that Chinese herbal extracts can improve skin elasticity, reduce wrinkles and melanin precipitation. The purpose of this paper is to explore whether combining hydrolyzed collagen with Chinese herbal extracts can improve skin conditions and achieve anti-inflammatory effects.

Design/methodology/approach – Fifty subjects were randomly divided into collagen or placebo groups, and one bottle of collagen or placebo drink was used every day for four weeks, after which skin and inflammatory factors were tested.

Findings – In comparison with the baseline results, the skin parameters were improving after four-week intervention. In addition, the IL-6, IL-8, TNF-a were significantly decreased and tissue inhibitor matrix metalloproteinase 1 (TIMP-1) was increased after four-week hydrolyzed collagen intervention.

Originality/value – This study showed that hydrolyzed collagen combined with Chinese herbal extracts can improve the condition of the skin, and can also reduce inflammatory associated factors, thereby achieving anti-aging effects.

Keywords Chinese herbal extracts, Hydrolyzed collagen, Skin aging

Paper type Research paper

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Introduction

Skin conditions often reflected the aging process of the entity through the appearance of the thickened epidermis, sagging, wrinkles, roughness, dullness and spots (Ganceviciene *et al.*, 2012). The cause of skin aging was primarily affected by intrinsic (e.g. free radicals) and extrinsic factors (e.g. UV irradiation, pollutants, cigarette smoking) (Poljsak *et al.*, 2012). Especially, photoaging usually took the main responsibility for the progression of skin aging in most cases apart from chronological aging (Pandel *et al.*, 2013). Collagen was the most abundant component in the extracellular matrix. It can maintain the skin structure and make its multiple functions play a role in determining the physiology of the skin. The degradation of collagen and the reduction of elastin and glycosaminoglycans were factors that cause aging (El-Domyati *et al.*, 2002). Hydrolyzed collagen had functional peptides (biopeptides), can produce short-chain amino acids and had a wide range of physiological activities (Avila Rodriguez *et al.*, 2018). Moreover, its small molecule protein structure was easy for the human body to absorb effectively, so it had not only been used in the research of physiology and medicine but also used for the development of food and health care.

In recent years, the health product market advocates nature, and it had become a trend to use natural plant substances as the source of health product ingredients. Studies had pointed out that Chinese herbal medicine can enhance skin elasticity, reduce skin keratosis, pigmentation and prevent sebum function loss (Lin *et al.*, 2018). Some studies showed that the snow lotus extract had free radical scavenging ability and can be used as an antioxidant (Yi *et al.*, 2010), and bird's nest extract can significantly enhance the production of collagen and the growth of fibroblasts (NIH-3T3) (Zeng and Lai, 2019). In addition, bird's nest had a good moisturizing effect and improvement owing to the mucilage rich in fucose and various phenolic compounds, as a natural moisturizer, anti-aging and wound repair (Matsukawa *et al.*, 2011). Lotus seed extract can increase total phenol content and antioxidant capacity and can also delay the aging of nematodes (Zhu *et al.*, 2017; Li *et al.*, 2019). Therefore, the use of these natural products with nutritional curative effects and few side effects as the basis for research and development of health products was sufficient to prove the superior nature of Chinese herbal medicine. However, there were few clinical studies on the improvement of skin aging with Chinese herbal extracts. In this study, we used a collagen drink made of Chinese herbal medicine, which contained extracts of snow lotus, bird's nest and lotus seeds to explore whether it can improve skin brightness, hydration, wrinkles, elasticity and collagen content and analyze the inflammatory factors in the blood.

Materials and methods

Clinical design

This clinical research was approved by the ethics committee of the Antai Medical Care Corporation Antai Tian-Sheng Memorial Hospital (IRB No. 20–003-B), and the study protocol was registered with the ClinicalTrials.gov (NCT04266405). All methods were performed following the Declaration of Helsinki and the International Conference on Harmonization (ICH) guidelines on Good Clinical Practice (GCP). 50 adult volunteers (over 20 years old) were recruited in this trial between February 2020 and April 2020 and informed consent was obtained from all subjects before the study. The study was performed at the Department of Cosmetic Science and Institute of Cosmetic Science, Chia Nan University of Pharmacy and Science, Taiwan. Eligible 50 subjects were allocated to the experimental (collagen formula) and control (placebo) groups by block randomization. Each subject was informed to consume one bottle of a 50 mL of collagen drink or a placebo drink daily for four weeks and was not allowed to take any other collagen supplement during the

intervention period. Individuals over 20 years old could participant in this study. The exclusion criteria included:

- skin disorders;
- liver diseases;
- kidney diseases;
- allergy to cosmetics, drugs or foods;
- pregnant and lactating women;
- people who had any cosmetic procedures (intense pulse light, medical peelings, or laser therapy) before 4 weeks of the study;
- area of facial spot over 3 cm^2;
- vegan; and
- people who took collagen supplements in the past three months.

Collagen formula

Collagen formula contains: 5% fish collagen, 5% lotus seed extract, 4% bird's nest, 2% snow lotus extract, 70% water, 4% pectin, 1% citric acid, 8% corn syrup, 1% sucralose). Placebo drink (ingredients: 86% water, 4% pectin, 1% citric acid, 8% corn syrup, 1% sucralose). Each subject was required to undergo skin condition checks at zero, two and four weeks, and blood was drawn at zero and four weeks to analyze inflammatory factors.

Skin measurement

Chroma Meter MM500 (Mino lta, Japan) was used to measure the skin brightness of upper check; L value (in the range of 1–100) defined by International Commission on Illumination indicates the change of skin brightness. Corneometer CM825 (CK, Germany) was employed to analyze the skin hydration of upper check based on the skin conductance response. Cutometer MPA580 (CK, Germany) was used to measure skin elasticity of upper check by suction method; the instrument creates negative pressure to deform skin and the mechanical property of the skin was analyzed. VISIA Complexion Analysis (Canfield Scientific, USA) was used to obtain the values of skin wrinkles, textures and pores. DermaLab Series SkinLab Combo (Cortex, Denmark) was used to indicate the collagen density of the upper check. Tewameter TM210 (Courage and Khazaka, Cologne, Germany) was used to measure transepidermal water loss (TWEL) (Goldsberry *et al.*, 2014).

Inflammatory factor detection

The measurement of IL-6, IL-8, TNF-α and TIMP-1 in blood was based on the Enzyme-linked immunosorbent assay (ELISA). The ELISA kits were obtained from Cloud-Clone Corp. (US). All experimental procedures were following the recommended protocols provided by the company. The values of the coefficient of determination were over 0.98 (Lequin, 2005).

Statistical analysis

The experimental data analysis were first calculated by the normal distribution and then calculated by the paired *t*-test check; the non-normal distribution was calculated by the Wilcoxon signed-rank test. $p < 0.05$ was considered statistical significance.

Results and discussion

Collagen formula with Chinese herbal medicine improved skin condition

Table 1 showed the average age and gender of the subjects in this trial. The average age of recruiting volunteers in the placebo group and the collagen formula group was similar, and all subjects were healthy women. The subjects were tested on their skin after drinking the collagen drink daily for four weeks. Table 2 showed that after four weeks of drinking, the collagen formula with Chinese herbal medicine can significantly improve the subjects' skin brightness, hydration, wrinkles, elasticity and collagen content. The mean levels of skin brightness, hydration, transepidermal water loss (TWEL), wrinkles, textures, pores, elasticity and collagen content were improved by 2%, 7.3%, 7.3%, 15%, 5.2%, 1.8%, 4.3%,

Group	Collagen formula	Placebo drink
Age (years)	47.3 ± 8.7	44.8 ± 11.7
Female number	25	25

Notes: Sample size = 25; mean value ± S.D.

Table 1. Subject profile

		Collagen formula (n = 25)			Placebo drink (n = 25)		
Item	Week	Mean value ± SD	Improvement (%)	P value	Mean value ± SD	Improvement (%)	P value
Brightness	0	58.3 (3.0)			58.3 (3.6)		
	2	58.8 (3.1)	1	$< 0.001^{a}$*, 0.78^{b}	58.6 (3.6)	0	0.07
	4	59.5 (3.0)	2	$< 0.001^{a}$*, 0.30^{b}	58.6 (3.4)	0	0.1
Hydration	0	36.7 (7.0)			36.4 (6.2)		
	2	39.1 (5.6)	6.5	0.031^{a}*, 0.25^{b}	36.8 (7.6)	1.1	0.71
	4	39.4 (6.7)	7.3	0.004^{a}*, 0.24^{b}	37.1 (7.8)	1.9	0.51
TWEL	0	16.4 (6.6)			19.2 (6.4)		
	2	15.8 (7.0)	3.6	0.08^{a}, 0.004^{b}	19.2 (7.9)	0	0.99
	4	15.2 (7.0)	7.3	0.02^{a}*, 0.008^{b}	18.8 (7.6)	2	0.55
Wrinkle	0	28 (15.5)			24.6 (13.4)		
	2	26.8 (15.4)	4.2	0.25^{a}, 0.60^{b}	24.6 (12.9)	0	0.97
	4	23.8 (15.5)	15	0.044^{a}*, 0.94^{b}	24.8 (13.2)	0.8	0.92
Texture	0	499.6 (342.9)			491.5 (461.9)		
	2	469.2 (328.9)	6	0.94^{a}, 0.77^{b}	495.5 (416.3)	0.8	0.87
	4	473.5 (326.4)	5.2	0.67^{a}, 0.77^{b}	490.1 (455.2)	0.2	0.96
Pore	0	708.3 (262.1)			843.4 (443.1)		
	2	702.4 (262.0)	0.8	0.79^{a}, 0.10^{b}	856.1 (400.4)	1.5	0.69
	4	695 (281.7)	1.8	0.44^{a}, 0.15^{b}	841.8 (415.1)	0.2	0.4
Elasticity (R5)	0	0.231 (0.03)			0.239 (0.013)		
	2	0.239 (0.024)	3.4	0.001^{a}*, 0.58^{b}	0.239 (0.013)	0	0.77
	4	0.241 (0.019)	4.3	0.001^{a}*, 0.28^{b}	0.240 (0.014)	0.3	0.58
Collagen content	0	31.9 (10)			33.7 (16.2)		
	2	34.1 (10.4)	6.8	$< 0.001^{a}$*, 0.92^{b}	33.7 (16.2)	0	0.96
	4	37.1 (10.5)	16.3	$< 0.001^{a}$*, 0.48^{b}	34 (16.6)	1.1	0.62

Notes: [a]Compared the baseline (week 0) and the week 2 or week 4. [b]Compared the collagen formula and the placebo group. *Significantly different, $p < 0.05$. Sample size = 25; mean value ± S.D. Statistical analyses were conducted paired t-test check or wilcoxon signed-rank test

Table 2. Skin measurement after taking collagen formula

16.3%, respectively, and p value was 0.0005, 0.004, 0.02, 0.044, 0.67, 0.44, 0.001, 0.0005, respectively, in comparison with the baseline results. Figure 1 showed that skin images included wrinkles, textures, pores and collagen content. In recent years, with the increasingly close relationship between the cosmetics industry and the medical and health industry, functional medicated cosmetics had gradually increased (Avila Rodriguez *et al.*, 2018). They had a good effect on protecting people's skin health and preventing skin diseases and provided auxiliary measures for clinical treatment. Therefore, there were more and more reports on the use of Chinese herbal extracts to add skincare products (Wang *et al.*, 2018). Studies had shown that the use of ultraviolet radiation will cause obvious damage to the skin of mice and collagen degradation, mast cells and neutrophils infiltrate the skin, leading to inflammation (Cho *et al.*, 2017; Mahmood and Akhtar, 2012). However, once the use of lotus seed extracts can significantly reverse these conditions. In addition, myricetin, gallic acid, astragalin, myricetin-3-O-glucoside and myricetin in lotus extracts were the main active compounds, which can be used as topical treatment materials against skin damage (Varela-Rodriguez *et al.*, 2020). Long-term intake of lotus seed tea had been shown to prevent skin moisture loss, reduce the formation of abnormal keratinocytes and help inhibit protein oxidation (Kim and Moon, 2015). Bird's nest was rich in glycoproteins and minerals; pharmacological studies had revealed that bird's nest was beneficial for enhancement of immune system and skin cell renewal and reduction of the expression of TNF-α (Careena *et al.*, 2018). Moreover, the epidermal growth factor (EGF) in bird's nest extracts interacted with collagen, hyaluronic acid and elastin to promote metabolism and repair skin damage (Kong *et al.*, 2016), as well as, colony-stimulating factor (CSF) in bird's nest extract can

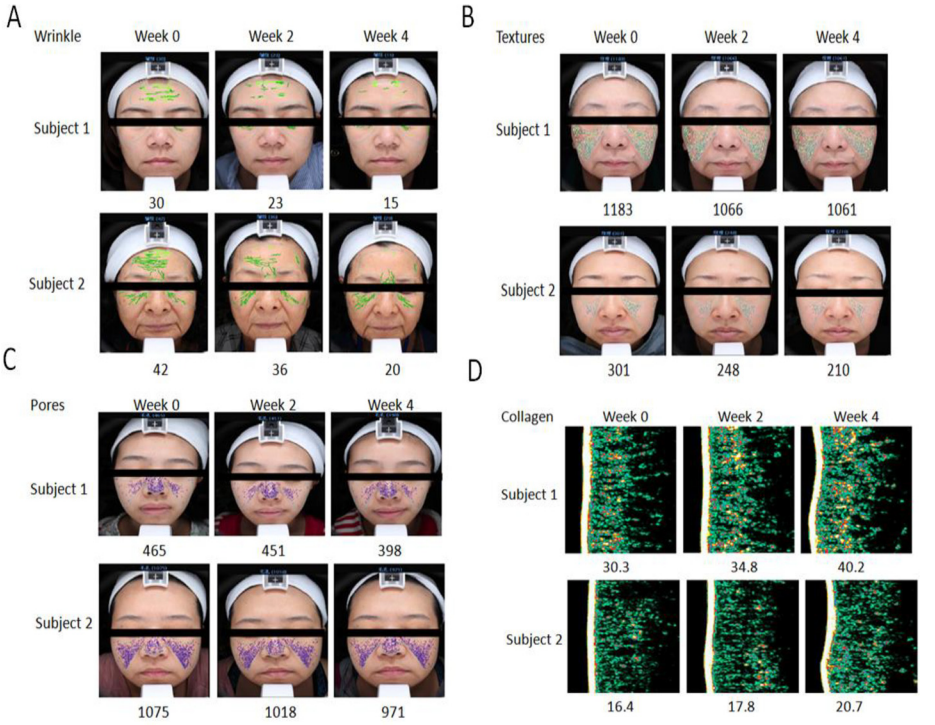

Figure 1.
Collagen formula with Chinese herbal medicine improved wrinkles, textures, pores and collagen. After drinking collagen formula for four weeks, the subjects were examined (A) skin wrinkle, (B) texture, (C) pore by VISIA complexion analysis and collagen density by DermaLab Series SkinLab Combo (Sample size = 25)

promote the proliferation and differentiation of hematopoietic stem cells, providing skin cell reorganization and regeneration (Roh *et al.*, 2012). Some studies also showed that snow lotus extracts can improve the oxidative damage of HaCaT cells after UVB radiation, thereby reducing the photoaging damage of the skin (Gong *et al.*, 2019). Rutin and Hispidulin were flavonoids of the flavonol type that are found plenty in snow lotus extract, which had been reported to have anti-inflammation, anti-oxidation and anticancer activity (Gong *et al.*, 2019). The flavonoids may exert anti-inflammatory effects *in vitro* in LPS stimulated RAW 264.7 macrophages through inhibition of NF-kB signal pathway activation (Hou *et al.*, 2018). Snow lotus extracts were rich in flavonoids, which can inhibit melanin deposition in human melanocytes (Promden *et al.*, 2018). Consistent with our results, combining these Chinese herbal extracts can improve skin conditions. Chinese herbal extracts combined with hydrolyzed fish collagen can promote the secretion of collagen, elastin, hyaluronic acid and the synthesis of ceramide and glucosylceramide in fibroblasts (Sommerfeld, 2007).

Collagen formula with Chinese herbal medicine regulated inflammatory cytokines. After taking the collagen drink for four weeks, the subject had a blood draw to analyze the inflammation in the body. IL-6, IL-8 and TNF-α were pro-inflammatory cytokines and were related to skin aging. TIMP Metallopeptidase Inhibitor 1(TIMP-1) was an enzyme in the process of collagen metabolism, which can inhibit matrix metalloproteinases and prevent collagen degradation. Table 3 showed the subjects after drinking for four weeks, the collagen formula with Chinese herbal medicine can significantly decrease IL-6, IL-8 and TNF-α, by 16% (p-value, 0.02), 49% (0.006) and 16% (0.03), respectively, and TIMP-1 was significantly increased by 19% (0.02) compared with the baseline result. The collagen formula in this study can promote the production of extracellular matrix components, thereby improving skin conditions, which were all related to the regulation of inflammatory cytokines. An increase of oxidative stress caused by endogenous or exogenous stressors may prompt the expression of IL-6 and TNF-α, which further up-regulate MMP production and suppress collagen synthesis (Sirikaew *et al.*, 2019; Serra *et al.*, 2010). It had been confirmed that the level of IL-6 in plasma ws higher in elderly people than in younger ones (Puzianowska-Kuźnicka *et al.*, 2016). Moreover, IL-8 played an essential role in the modulation of UVB-induced inflammation in keratinocytes and fibroblasts (Kang *et al.*, 2007). Hence, the reduction of these cytokines was beneficial for delaying skin aging and managing skin inflammation. Premature and chronological aging was majorly subjected to the degradation of collagen and elastin under the influence of MMPs and elastase. High

Item	Collagen formula (n = 25) Week	Mean value ± SD	P value	Placebo drink (n = 25) Mean value ± SD	P value
IL-6	0	24 (3.0)		25 (3.0)	
	4	20 (2.0)	0.02[a]*	24 (2.0)	0.3
IL-8	0	453 (88.7)		347 (73.3)	
	4	228 (86.2)	0.006[a#]	279 (30.4)	0.2
TNF-α	0	24 (2.0)		23 (2.0)	
	4	21 (1.0)	0.03[a]*	22 (1.0)	0.5
TIMP-1	0	300 (15)		310 (19)	
	4	357 (20)	0.02[a]*	326 (25)	0.3

Notes: [a]Compared the baseline (week 0) and the week 2 or week 4. *Significantly different, $p < 0.05$. #Significantly different, $p < 0.01$. Sample size = 25; mean value ± S.D. Statistical analyses were conducted paired t-test check or wilcoxon signed-rank test. TIMP-1: Tissue inhibitor matrix metalloproteinase 1

Table 3. Collagen formula regulated IL-6, IL-8, TNF-α and TIMP-1

expression of TIMP-1 was allowed to mitigate the impact of skin photodamage in UVB-exposed rodents through stabilizing the ECM structure, preventing skin sagging and coarseness and lowering the expression of TNF-α (Pittayapruek *et al.*, 2016).

Conclusion

Combining different Chinese herbal extracts and fish collagen can improve skin conditions and had anti-inflammatory effects. We successfully unveiled that the positive correlation between the changes of skin aging-associated proinflammatory cytokines as well as TIMP-1 and improvement of skin parameters after four-week collagen formula intervention, albeit that further investigation may require for the meticulous connection. Last but not least, we introduced the extracts of skin-beneficial ingredients in TCM in addition to common fruit extracts into this study to substantially unveil the scientific benefits of real collagen supplementation in Asia.

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