J Ginseng Res 40 (2016) 260–268

Contents lists available at ScienceDirect

Journal of Ginseng Research

journal homepage: http://www.ginsengres.org

Research article

A single-center, randomized, double-blind, placebo-controlled study on the efficacy and safety of "enzyme-treated red ginseng powder complex (BG11001)" for antiwrinkle and proelasticity in individuals with healthy skin

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ARTICLE INFO

Article history:
Received 11 February 2015
Received in Revised form
3 July 2015
Accepted 23 August 2015
Available online 31 August 2015

Keywords:
elasticity
enzyme-treated red ginseng
human skin
Panax ginseng
wrinkle

ABSTRACT

Background: During the aging process, skin shows visible changes, characterized by a loss of elasticity and the appearance of wrinkles due to reduced collagen production and decreased elasticity of elastin fibers. *Panax ginseng* Meyer has been used as a traditional medicine for various diseases due to its wide range of biological activities including skin protective effects. Ginsenosides are the main components responsible for the biological activities of ginseng. However, the protective activities of an enzymatic preparation of red ginseng against human skin aging have not been investigated.
Methods: The efficacy of an enzyme-treated powder complex of red ginseng (BG11001) in preventing human skin aging was evaluated by oral administration to 78 randomized individuals. All patients were requested to take three daily capsules containing either 750 mg of BG11001 or a placebo vehicle for 24 wk; at the end of the testing period, skin roughness, elasticity, and skin water content were measured.
Results: BG11001 significantly reduced the average roughness of eye wrinkles and the Global Photo Damage Score compared with the placebo, although there were no significant differences in arithmetic roughness average between the groups. In addition, gross elasticity and net elasticity values increased, and transepidermal water loss level decreased, indicating improved skin elasticity and moisture content.
Conclusion: In conclusion, enzyme-treated red ginseng extract significantly improved eye wrinkle roughness, skin elasticity, and moisture content. Moreover, enzyme-treated red ginseng extract would be useful substance as a bio-health skin care product.

1. Introduction

Aging is a dynamic and highly complex process defined by multiple physiological changes over time. All bodily systems are subject to the aging process and the integumentary system is not an exception. The human skin covers the whole outer body, which makes the skin the largest organ of the integumentary system. The skin has multiple layers of ectodermal tissue and guards the underlying muscles, bones, ligaments, and internal organs. During the process of aging, the skin changes show the most visible signs characterized by decreased elasticity, increased roughness, uneven skin tone with dark spots, and the formation of wrinkles [1]. Wrinkles on the face are the most dominantly recognized signs of skin aging [2]. Over time, the epidermis becomes thinner, even though the number of cell layers remains unchanged. Not only does the dermal layer thin, but also less collagen is produced, and the

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p1226-8453 e2093-4947/$ – see front matter
http://dx.doi.org/10.1016/j.jgr.2015.08.006

changes in the connective tissue reduce the skin's strength and elasticity [3,4]. These changes in the structure of the skin cause the skin to wrinkle and slacken. Facial skin sites like the corners of the eyes are especially susceptible to wrinkle formation, which is also popularly known as "crow's feet".

The maintenance of younger-looking skin is constantly desired by a large proportion of the world's population. Therefore, many institutes and cosmetic and pharmaceutical companies have been trying to develop functional cosmetic materials from natural substances such as herbs, roots, essential oils, and flowers. *Panax ginseng* has a history of medical use for over 5,000 yr. *Panax* derived from Greek word "*Panakos*" presents *Pan*—meaning "all" and akos meaning "cure". Ginseng is said to mean "wonder of the world." Like the literal meaning of its name, *Panax ginseng* Meyer has been used as a traditional medicine for various diseases with wide range of biological activities, including anti-inflammatory [5], antioxidant [6], antitumor [7], and antistress effects [8]. In recent studies, researchers investigated the protective effects of *Panax ginseng*, against the UVB-irradiation on epidermal keratinocytes and dermal fibroblasts. They found that ginseng recovered the UVB-induced decrease in antiapoptotic gene expression in the human keratinocytes and dermal fibroblast, indicating that ginseng can protect cells from apoptosis caused by strong UVB radiation [9]. Another study showed that ginseng extract induced type I collagen production in human dermal fibroblast cells by activation of Smad signaling, suggesting ginseng as a potential candidate as a wrinkle-reducing agent by topical application [10].

Ginsenosides are the pharmacologically active components and are responsible for the biological functions in ginseng. Among more than 50 isolated ginsenosides, major ones (Rb1, Rb2 , Rc, Rd, Re, Rg1, and Rf) constitute more than 80% of the total ginsenosides and the minor ginsenosides (F1, F2, Rg3, Rh1, Rh2 compound Y, compound Mc, and compound K) are present at low concentrations in ginseng [11]. Many studies show that the minor ginsenosides have pharmacologically active than major ones because absorption of major ginsenosides by the gastrointestinal tract is quite poor [12]. As a result, the minor ginsenosides have been demonstrated to be pharmaceutically active and excellent potential drug candidates [13]. However, hydrolysis of sugar moieties to convert major ginsenosides to minor forms by digestive enzymes in gastrointestinal tract are quite low even though the minor ginsenosides are more easily absorbed into the bloodstream [12]. Since it is possible to transform into minor ginsenosides by enzyme treatment, enzyme-treated red ginseng has been shown to have strong antiwrinkle activity and reduced toxicity in *in vitro* and animal studies [14]. Also, our previous studies demonstrated that enzyme-treated ginseng protected UVB-induced skin damage through the regulation of procollagen type I and matrix metalloproteinase (MMP)-1 expression in hairless mice [15,16]. However, the protective activity of the enzymatic preparation of red ginseng against human skin aging has not been investigated. In this study, we investigated whether enzyme-treated powder complex of red ginseng (BG11001) prevents human skin aging by reducing skin wrinkles and enhancing elasticity.

2. Materials and methods

2.1. Preparation of enzyme-treated powder complex of red ginseng (BG11001)

Enzyme-treated extract of red ginseng was prepared following a patented protocol [Korea patent no. 10-2011-0091287 (in private), in press] [15]. Red ginseng powder with 10 times volume of distilled water was mixed for 2 h using a homo-mixer and then enzyme treated for 24 h at 55°C. Enzyme-treated red ginseng was heated up to 90°C, cooled down to 10–15°C, and then centrifuged. Supernatant was concentrated, added 10 times volume of 50% ethanol, and extracted for 40 min at 85°C. Finally, the same amount of malt dextrin was added, spray dried and used as raw material of BG11001.

For thin layer chromatography analysis of the ginsenoside compositions, the total ginsenosides were spotted together with the standard 20(S)-protopanaxdiol (PPD) or 20(S)-protopanaxtriol samples on thin layer chromatography plate (silica gel 60 F254, Merck) containing $CHCl_3$-MeOH-H_2O (65:35:10, v/v), thereafter stained by spraying with 30% H_2SO^4, followed by heating at 105°C.

2.2. Study design

This study was designed as a randomized, double-blind study to assess the effects of 250 mg of oral BG11001 given thrice a day for 24 wk of the trial period in patients with cutaneous photoaging. The compositions of the BG11001 and placebo tablets are shown in Table 1.

2.3. Global photodamage score

Patients' periorbital wrinkles were evaluated based on a global photodamage score (0, none; 1, none/mild; 2, mild; 3, mild/moderate; 4, moderate; 5, moderate/severe; 6, severe; 7, very severe) at Wk 0 (baseline). If the investigators' evaluations differed, low-grade efficacy and high-grade adverse effect were selected. The patients' periorbital wrinkles were classified into eight grades.

2.4. Participants

Ninety-eight healthy Asian women, aged between 40 and 60 yr, clinically diagnosed with a global photodamage score of 2–6 according to the Jung score of photoaging of facial skin were recruited and included in this study after written informed consent. Those who experienced any esthetic procedure like peeling, laser, intense pulsed light, dermabrasive therapies, or have used any antiaging cream or nutritional supplement within the past 3 mo could not participate in the study. Participants were requested not to expose themselves to sunlight during the trial. They were also requested not to use lotions, creams, or other products on the face and forearms. Participants agreed to follow these instructions during the

Table 1
Compositions of the BG11001 and placebo tablets

Ingredient	Tablet (mg)	Percentage (%)
BG11001 tablet		
BG11001	250	41.7
Microcrystalline cellulose	88.4	14.7
Dextrin	150	25
Maltitol syrup powder	96	16
Magnesium stearate	9	1.5
Silicon dioxide	3	0.5
HPMC	3.3	0.55
Glycerol fatty acid ester	0.3	0.05
Total	600	100
Placebo tablet		
Microcrystalline cellulose	210	35
Lactose powder	331.5	55.25
Caramel coloring	1.32	0.22
Gardenia yellow pigment	0.78	0.13
Maltitol syrup powder	43.5	7.25
Magnesium stearate	9.3	1.55
HPMC	3.3	0.55
Glycerol fatty acid ester	0.3	0.05
Total	600	100

HPMC, hydroxypropylmethylcellulose.