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Original Article

Anti-aging Efficacy and Safety of Topical Application of Two Standardized Fenugreek Seed Extracts on Facial Skin in Women: Randomized, Double-Blind, Placebo-Controlled, Clinical Study

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ABSTRACT

Introduction: Fenugreek (*Trigonella foenum graecum L.*) is widely used in culinary and medicinal applications and has recently gained attention for its potential anti-aging properties. **Objectives**: This randomized, double-blind, placebo-controlled study evaluated the anti-aging efficacy and safety of topical application of flavonoid glycosides-based and eleutheroside-oligosaccharide-based standardized fenugreek seed extract creams, namely INDUS1520 and INDUS1530, respectively. **Methods**: Seventy-five healthy women aged between 35 and 55 years with mild to moderate facial wrinkles were randomly allocated to receive either INDUS1520, INDUS1530, or a Placebo cream for 60 days. Efficacy outcomes included skin luminescence, color, trans-epidermal water loss, moisture content, gloss, elasticity, firmness, wrinkle depth, surface roughness, and collagen distribution. Safety was assessed using a dermatological assessment and subject-reported intolerance questionnaire for adverse events. **Results**: INDUS1530 significantly improved skin hydration and wrinkle depth, while INDUS1520 significantly reduced trans-epidermal water loss compared with Placebo. Both creams showed a trend of decreased skin roughness and increased collagen distribution, although this difference was not statistically significant between the groups. All treatments, including Placebo, increased skin gloss. No adverse events or skin irritation were observed. **Conclusions**: Both fenugreek seed extract creams were well tolerated and demonstrated potential anti-aging benefits, with INDUS1530 showing more pronounced effects on skin hydration and wrinkle reduction. These findings support the use of standardized fenugreek seed extracts as safe and effective ingredients in anti-aging skin care products.

Keywords: Anti-aging, Fenugreek seed extract, Skin hydration, Skin elasticity

INTRODUCTION

Human skin is exposed to many environmental factors, such as air pollutants and radiation. Air pollution accelerates aging and induces inflammation, resulting in disorders, wrinkles, and pigmentation[1]. Solar ultraviolet (UV) radiation, particularly UVB, with wavelengths ranging from 290 to 320 nm, exerts many harmful effects on the skin, including the development of an impaired immune system, induction of photoaging[2], and oxidative stress to accelerate aging and skin cancer development[3].

Skin aging is characterized by decreased elasticity, variations in pigmentation, and alterations in the extracellular matrix (ECM). The production of reactive oxygen species increases, causing an imbalance in free radical levels, which results in fewer fibroblasts and keratinocytes, slower skin renewal and collagen production, more matrix metalloproteinases, fewer metalloproteinases inhibitors, breakdown of cell parts, DNA damage, and misfolded proteins.

To address age-related dermatological changes, researchers have investigated a range of interventions, including skincare products enriched with antioxidants and lifestyle modifications designed to decrease reactive oxygen species production and enhance skin health[4]. For centuries, natural remedies have been developed to address dermatological conditions and various skin disorders[5]. Recently, plant-derived natural medicines have gained popularity owing to their cost-effectiveness and sustained acceptance[6].

There is considerable evidence that various plant extracts containing a wide range of active phytoconstituents such as glycosides can be effectively utilized in skincare applications[7]. Although many plant extracts have demonstrated potential efficacy and have associated claims for natural anti-aging solutions, most have not been substantiated by clinical studies[8-9]. In addition, anti-aging solutions must be safe for skin-specific applications[10].

Fenugreek (Trigonella foenum graecum, family: Leguminosae) is widely used in culinary applications as a spice, lactation aid, and in traditional medicine, particularly for the management of diabetes [11]. Recently, fenugreek seeds have gained attention for their potential anti-aging properties[12]. The seeds are rich in compounds such as diosgenin, a type of phytoestrogen that might boost collagen production, which could help diminish the visibility of fine lines and wrinkles[13]. Some studies have suggested that the topical application of fenugreek might improve skin texture, firmness, overall appearance[14], elasticity, and hydration[15]. Fenugreek has been found to help reduce collagen breakdown and boost collagen production, suggesting that it may have anti-aging benefits. However, these benefits have not been

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confirmed by clinical evidence.

Fenugreek seeds are rich in fibers and an array of phytochemicals, including alkaloids, saponins, and flavonoid glycosides such as rutin, quercetin, vitexin, and isovitexin[16]. Research has demonstrated that flavonoid glycosides present in fenugreek exhibit significant in vitro antioxidant activity[17]. The flavonoid apigenin from fenugreek seeds has been reported to inhibit UVB-induced skin carcinogenesis in mice and apoptosis of human dermal fibroblasts[18-19]. A cream formulation containing fenugreek flavonoid glycosides exhibits antioxidant and anti-inflammatory properties[14].

Fenugreek galactomannan has shown potential in the cosmeceutical and nutraceutical industries[20]. Fenugreek galactomannan has the capacity to retain water molecules, which is attributed to the high concentration of hydroxyl groups present in its structure, and enhances skin hydration[20].

The *in vitro* anti-aging potential of flavonoid glycosides and eleutheroside-oligosaccharide-based standardized fenugreek seed extracts (INDUS1520 and INDUS1530, respectively) increased hyaluronic acid, collagen, and elastin levels in human dermal fibroblast cell lines[21]. Furthermore, INDUS1520 and INDUS1530 showed robust safety for topical application in a series of safety studies[22-23]. Although these preclinical results are encouraging, translating them to the human population to validate the anti-aging potential of INDUS1520 and INDUS1530 in clinical studies is required. Therefore, the present study aimed to evaluate the anti-aging efficacy and safety of the topical application of INDUS1520 and INDUS1530 in cream formulations.

MATERIALS AND METHODS

Study Design

This study employed a double-blind, parallel-group, placebo-controlled design to assess the safety and efficacy of INDUS1520, INDUS1530, and Placebo creams. The registered Independent Ethics Committee of C.L.A.I.M.S Pvt. Ltd, Mumbai, India approved the study protocol (approval number: CL/011/0417/STU). The study adhered to the principles of the Declaration of Helsinki and its amendments, the principles of Good Clinical Practice, and Schedule Y. The study commenced after registration with the Clinical Trial Registry of India (CTRI/2017/06/008809).

Population

This study included 75 healthy women aged 35–55 years old. The included randomized participants had skin phototypes III (light brown, sometimes burns, difficult to tan) and IV (moderately brown, rarely burns, tans with ease) according to the Fitzpatrick scale [24] and exhibited either mild (minor wrinkles and fewer lines) or moderate (fine-to-moderate depth wrinkles with an average number of lines) wrinkles in the crow's foot area. During screening, individuals were ineligible if they had skin disorders, were pregnant or breastfeeding, or had participated in another study. The participants were instructed to avoid additional skincare products and protect their faces from UV rays. All participants signed an informed consent form before participation.

The investigational products (IP)

The IPs were prepared using standardized fenugreek seed extracts, INDUS1520 and INDUS1530, provided by Indus Biotech, Ltd. (Pune, India). The total flavonoid glycoside content of INDUS1520 was 40.63%, with selected flavonoids from Group 1 (vitexin + isovitexin + vitexin 2-O-rhamnoside) was 25.13%, and that of Group 2 (vicenin 1 + vicenin 2 + vicenin 3 + schaftoside + isoschaftoside + orientin + iso-orientin) was 15.50%, analyzed as per the reported method [25]. INDUS1530 was found to have 41.05% of the total content of the markers eleutheroside and oligosaccharides (d-pinitol, raffinose, and stachyose), as previously reported [22].

The IPs were cream formulations containing 3% INDUS1520, 3% INDUS1530, and a matching placebo cream prepared at Orac Lifesciences Pvt. Ltd., Mumbai, India. The excipients used in the preparation of all three creams were propylene glycol (2%), ethylenediaminetetraacetic acid disodium salt (dihydrate) (0.1%), distilled water (q.s. to 100), cetostearyl alcohol (1%), light liquid paraffin (2%), Polyethylene glycol-40 hydrogenated castor oil (2%), zinc oxide (0.1%), titanium dioxide (0.05%), acrylamide sodium acrylate copolymer/paraffin liquid oil/trideceth-6 (2%), 1,3-dimethylol-5,5-dimethylhydantoin (0.6%), perfume (0.5%), and a 20% citric acid solution (as required). The pH values of INDUS1520, INDUS1530, and Placebo creams were 6.52, 6.49, and 6.46, respectively. These creams were packaged in opaque 100 g containers (polyethylene terephthalate jars, dimensions 5.5 x 3.5 cm), each containing approximately 65 ± 3 g of product. The containers were coded and randomized according to a computer-generated randomization list. Individual sealed opaque envelopes labelled with randomization codes were maintained at the study site.

The stability of the IPs was verified through in-house accelerated stability studies conducted over a six-month period in compliance with the international guidelines for stability testing, ICH Q1A(R2) guidelines[26]. All cream formulations retained their color, consistency, and pH range of 5–7 at 25°C. The IPs conformed to all predefined assay and microbial analysis standards at the six-month mark.

Procedure

To comply with the measurement protocols, all skin assessments were carried out at temperatures between 20 and 22°C, and the relative humidity was maintained at 40–60%. Participants were asked to wash their faces with water and were given at least 1 h to acclimate to room conditions before the measurements. To minimize inter-individual variability, all measurements for a single outcome were performed by a single person throughout the study. Given the significant changes in skin microtopography, these measurements were consistently obtained from the same location each time.

A study flowchart with participant numbers (enrollment, allotment, follow-up, and analysis) is presented according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines in Figure 1. At the start of the study on Day 0 (D0, baseline), the participants provided informed consent, and their eligibility was verified according to the inclusion and exclusion criteria, as well as their medical and medication histories. The baseline measurements were recorded. Participants were then given study diaries and randomly assigned to either INDUS1520, INDUS1530, or a Placebo cream. They were instructed to apply approximately 1 g of the designated product to their moistened face, gently massaging it for 30 s twice a day, once in the morning and once at night. This routine application was consistently followed for the next 60 days, with assessments planned for days 30 (D30) and 60 (D60).

Efficacy Outcome Measures

The efficacy outcomes of the study were skin luminescence and color, trans-epidermal water loss (TEWL), moisture content, skin gloss, skin elasticity and firmness, wrinkle depth (Rt), surface roughness (Ra) in the crow's feet region, and collagen distribution at baseline, D30, and D60.

Skin luminescence and color

Skin luminescence and color were quantitatively assessed using a spectrophotometer (Konica Minolta, Japan) by gentle direct placement onto the cheeks. Measurements were expressed according to the International Commission on Illumination (CIE) Lab* color space

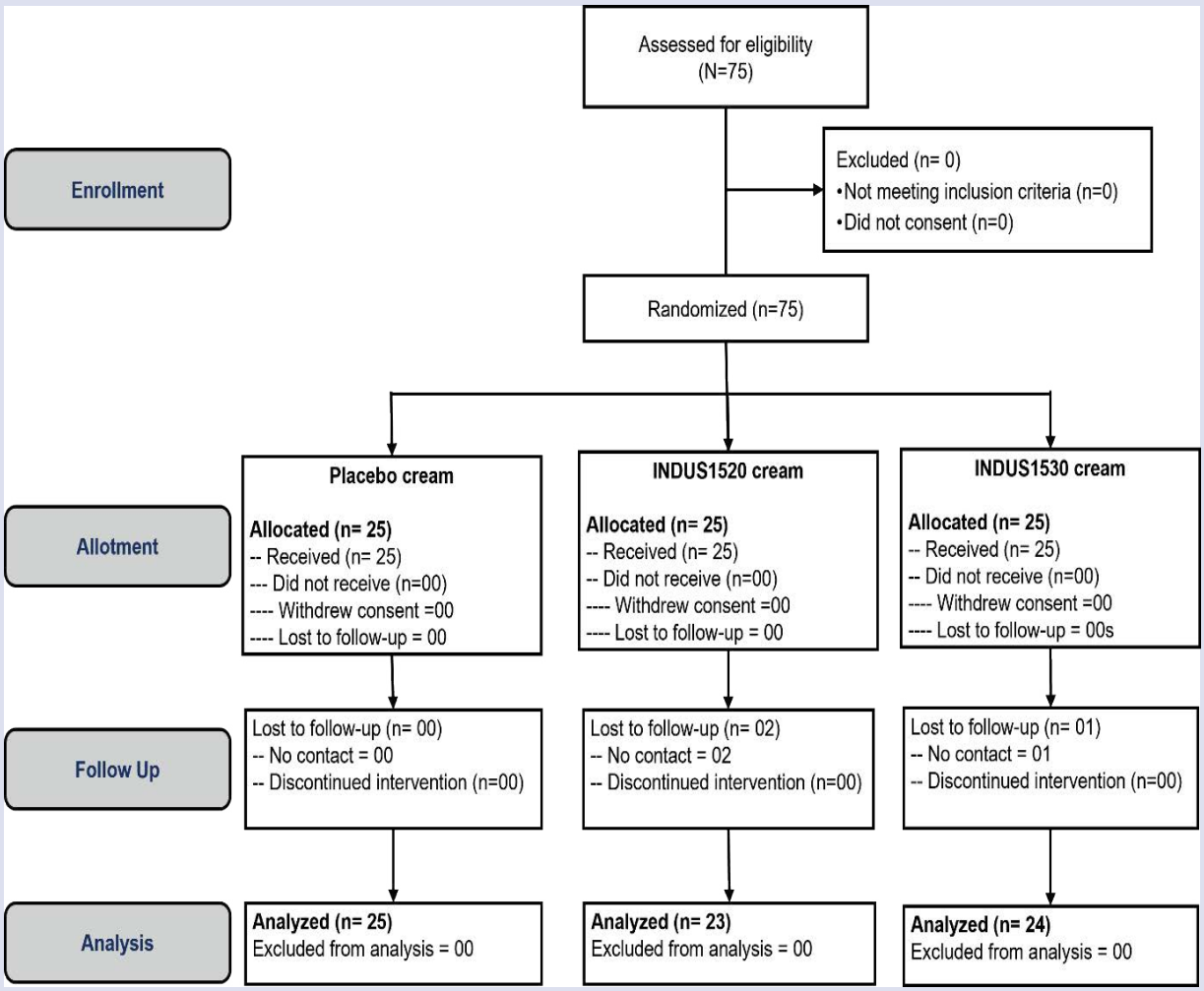

Figure 1. CONSORT Flowchart

standards. This system defines color based on three coordinates: L*, representing lightness (ranging from 0 for black to 100 for white); a*, indicating the green-to-red chromaticity axis (negative values for green, positive values for red), and b*, representing the blue–yellow chromaticity axis (negative values for blue, positive values for yellow)[27]. The individual typology angle (ITA) of skin color was calculated using the following formula: ITA = (arc tangent [(L*−50)/b*])(180/3.14159)[28]. An increase in L* values indicate an improvement in skin luminescence and brighter skin tone. Conversely, an increase in the ITA value was considered indicative of a decrease in skin pigmentation, suggesting a lighter skin complexion.

TEWL

At each visit, the TEWL, an important measure of skin barrier health, was assessed using a vapometer. (Delfin Technologies, Kuopio, Finland)[29]. This instrument quantifies water vapor emission from the stratum corneum, thereby offering an objective assessment of the skin barrier function[30]. Measurements were conducted in triplicate, and each reading was obtained after the vapometer probe was stabilized for approximately 30 s. The TEWL value, expressed in g/m^2/h, was calculated using a device based on the increase in relative humidity within the vapor chamber. A reduction in TEWL indicates an enhancement in skin barrier properties, whereas a significant increase suggests damage to healthy skin and a compromised barrier function.

Moisture content

MoistureMeter D and MoistureMeter SC from Delfin Technologies (Finland) were used to assess moisture in the deeper layers (subcutis) and outermost epidermis (Superficial, stratum corneum), respectively, using the electrical capacitance technique[31]. For each measurement, the probes were gently applied to the designated facial areas, and readings were taken in triplicate to ensure accuracy and consistency. An increase in the recorded capacitance values from both devices indicated enhanced skin hydration, reflecting an improvement in the ability of the skin to retain moisture[32].

Skin gloss

Skin gloss was quantified using a portable skin glossmeter (Delfin Technologies, Kuopio, Finland), which specifically evaluates the specular reflection of light from the skin surface[29]. This method provides an objective assessment of skin smoothness and light-reflecting properties. During the operation, the laser light beam emitted by the device contacts the skin surface and is reflected at equal but opposite angles. The reflected light is then captured by a photodetector within the instrument, and the total intensity of the light beam is calculated as a "gloss value (GU)." Measurements were performed in triplicate on designated skin areas to ensure accuracy and consistency. Elevated GUs indicate an enhancement in skin gloss, reflecting the improved uniformity of the skin surface and increased light reflection.

Skin elasticity and firmness

The mechanical properties of the skin were quantitatively evaluated using a non-invasive cutometer (Courage + Khazaka Electronic GmbH, Cologne, Germany) and suction-based skin elasticity meter[33]. All measurements were performed on the cheeks. The Cutometer operates by applying a standardized negative pressure to the skin, drawing it into an aperture. An integrated optical system precisely measures the vertical deformation of the skin over time, generating a force-deformation curve. From these curves, key p-values were derived to characterize skin elasticity and firmness, as previously reported[15]. Firmness (R0) is defined as the immediate deformation of the skin, with values approaching zero indicating increased firmness. Elasticity (R7) was calculated as the ratio of immediate recovery to the maximum post-suction skin distension. An R7 value close to 1 (100%) signifies superior elasticity, reflecting the capacity of the skin for rapid and complete recoil after deformation.

Wrinkles and roughness around the crow's feet

In this study, silicon imprints were analyzed using the Antera 3D™ imaging system (Miravex Limited, Ireland), which provides high-resolution three-dimensional visualization of skin surface features[34]. The silicon imprint technique is a noninvasive method for assessing skin topography, particularly in areas prone to wrinkles, such as crow's feet, to capture skin texture, detailed wrinkles, pores, and surface roughness[35].

Two key metrics, average roughness (Ra) and average wrinkle depth (Rt) were calculated. The Ra is the mean deviation of the surface profile from a hypothetical surface and is an overall measure of skin texture irregularities. In contrast, Rt quantifies the maximum vertical distance between the highest peak and the lowest valley within the analyzed area, offering insight into the severity of wrinkles present. These objective measurements allow for a comprehensive assessment of skin conditions.

Collagen distribution

Collagen distribution was measured using a method called Spectrophotometric Intracutaneous Analysis (SIAscopy)[36], which is a modern, non-invasive imaging technique developed by Astron Clinica and MedX Health Corp. Australia to evaluate skin health and track changes over time. Detailed images of the internal structure of the skin were generated by projecting light onto the skin surface, reflecting the light patterns influenced by the composition and structure of the skin. A reduction in SIAscopy values signifies an enhancement in collagen distribution and positive changes in skin structure and health[36].

Subjective efficacy assessments

A comprehensive evaluation questionnaire, developed in-house, was administered during each follow-up visit to collect data on the products and their effectiveness. The degree of improvement in various facial and body skin conditions, including skin moisturization, wrinkles around the eyes and face, skin firmness, evenness of facial skin tone, visible facial glow, skin smoothness, and softness, was assessed.

Safety Outcome measures

Skin tolerance to the study products was evaluated by assessing the subjective responses of participants on D30 and D60 using two in-house developed "skin safety assessment questionnaires" named as (1) Dermatological and (2) Self-assessment. Dermatological skin safety questionnaires were filled with clinical assessments by dermatologists and observable cutaneous reactions, such as erythema, edema, cutaneous dryness, roughness, and other adverse reactions. These were graded on a 4-point scale: none (0), very slight (0.5), slight (1), moderate (2), and severe (3). Self-assessment skin safety questionnaires were filled out by the participants to capture subjective skin sensations, including pricking, tingling, itching, redness, and burning, each graded on a 3-point scale: slight (1), moderate (2), and severe (3). Throughout the study period, all adverse events (AEs) were meticulously monitored under the direct supervision of the study investigator and dermatologist, with comprehensive documentation maintained in each participant's diary.

Statistical Analysis

All statistical analyses were performed using SPSS version 10.0 (IBM Corp., Armonk, NY, USA). Data are presented as mean ± standard deviation. The Shapiro-Wilk test was used to evaluate the normality of the data. A significance level of $P < 0.05$ was set for all analyses.

Moisture content (facial skin/subcutis), R7, R0, Ra, and collagen content followed a normal distribution. Parametric tests were performed (Dunnett's Multiple Comparison Test for pairwise comparisons). Skin efficacy measures, L values*, ITA, TEWL, moisture content (stratum corneum), and skin gloss were discrete and analyzed using non-parametric tests (Wilcoxon signed-rank test). Absolute values were compared between the groups (vs. baseline) and between the groups (vs. Placebo), and changes from baseline at D30 and D60 were calculated and compared between groups (vs. Placebo).

The scores obtained from subjective assessments of efficacy were analyzed using chi-square tests, which evaluate the distribution of responses (disagree or neutral vs. agree) within and between groups.

RESULTS

The mean age of participants was 43.40 ± 4.90 years (Placebo), 44.83 ± 4.72 years (INDUS1520), and 43.58 ± 4.19 years (INDUS1530). None of the groups had significant differences in the average age, indicating the effectiveness of randomization with respect to age.

Seventy-two out of the 75 randomized participants completed the study, with three dropouts (two from INDUS1520 and one from INDUS1530). The effects of treatment on the efficacy outcome measures are shown in Table 1.

Effects on Skin Luminescence and Color

At D60, there was a significant decrease in skin luminescence (L*) values in Placebo (1.89% $P < 0.001$) and INDUS1520 (2.25%, $P < 0.001$) but not in INDUS1530 within the groups (vs Baseline). Similarly, color (ITA) values in the Placebo (-16.1%, $P < 0.01$) and INDUS1520 [-20.1%, $P < 0.05$) groups, but not in the INDUS1530 group on D60. Except for these values, none of the absolute values or changes in values showed a significant difference between or within the groups at any visit.

Effects on TEWL

There was a significant decrease in absolute TEWL between the INDUS1520 (and Placebo) groups at D60 (15.19%, $P < 0.05$). Within the group comparison (vs. baseline), the absolute TEWL significantly increased in the INDUS1530 group (16.04%, $P < 0.001$). No other absolute or change in values showed a significant difference between or within groups at any visit.

Effects on Moisture Content

The mean moisture content (facial skin/subcutis) significantly increased in Placebo (5.1%, $P < 0.05$) at D60. A significant increase in INDUS1530 within the group on D30 (5.76%, $P < 0.05$) and D60 (6.2%, $P < 0.05$) indicated enhanced hydration. The mean moisture content (stratum corneum) values in the Placebo (19.10%, $P < 0.05$) and INDUS1530 (18.70%, $P < 0.05$) groups significantly increased at D30 but not at D60, indicating better hydration. No other absolute or change in values showed a significant difference between or within groups at any visit.

Table 1. Effects of treatment on efficacy outcome measures

Measure	Absolute/ Change	Day	Placebo	INDUS1520	INDUS1530
Skin luminescence (L*values)	Absolute	Baseline	55.54 ± 02.81	53.68 ± 02.48	55.02 ± 04.24
		D30	55.65 ± 02.91	53.63 ± 02.65	55.29 ± 04.32
		D60	54.49 ± 03.26$^{\#\#\#}$	52.47 ± 02.58$^{\#\#\#}$	54.41 ± 04.59
	Change	D30	00.11 ± 01.26	-00.05 ± 01.43	00.27 ± 01.36
		D60	-01.05 ± 01.19	-01.21 ± 01.41	-00.61 ± 01.54
Skin color (ITA value)	Absolute	Baseline	14.51 ± 07.10	10.40 ± 07.17	12.91 ± 11.79
		D30	14.95 ± 07.67	10.41 ± 07.71	13.67 ± 11.65
		D60	12.18 ± 08.81$^{\#\#}$	08.31 ± 08.96$^{\#}$	11.88 ± 13.43
	Change	D30	00.44 ± 03.15	00.07 ± 03.75	00.76 ± 02.80
		D60	-02.33 ± 03.27	-02.09 ± 04.53	-01.02 ± 03.99
TEWL (g/m²/h)	Absolute	Baseline	17.49 ± 03.70	15.65 ± 02.81	15.52 ± 04.14
		D30	17.94 ± 04.04	16.21 ± 03.47	16.52 ± 03.50
		D60	18.82 ± 04.15	15.96 ± 03.28*	18.01 ± 05.36$^{\#\#\#}$
	Change	D30	00.45 ± 03.89	00.56 ± 02.43	01.00 ± 02.62
		D60	01.33 ± 03.24	00.31 ± 03.37	02.49 ± 03.68
Moisture content (%) - facial skin/subcutis	Absolute	Baseline	30.94 ± 03.45	29.07 ± 04.98	30.19 ± 05.03
		D30	31.51 ± 03.48	29.96 ± 04.10	31.93 ± 03.62$^{\#}$
		D60	32.52 ± 03.28$^{\#}$	30.64 ± 03.03	32.06 ± 03.59$^{\#}$
	Change	D30	00.57 ± 03.52	00.88 ± 04.13	01.74 ± 04.20
		D60	01.58 ± 02.98	01.57 ± 03.55	01.87 ± 03.84
Moisture content (%)- stratum corneum	Absolute	Baseline	28.16 ± 11.84	26.19 ± 12.75	27.96 ± 15.78
		D30	33.54 ± 15.33$^{\#}$	26.00 ± 12.85	33.19 ± 18.05$^{\#}$
		D60	32.02 ± 15.88	25.76 ± 15.24	29.41 ± 14.25
	Change	D30	05.38 ± 13.28	-00.19 ± 07.12	04.64 ± 09.79
		D60	03.86 ± 11.50	-00.43 ± 09.47	02.55 ± 10.43
Skin gloss (GU)	Absolute	Baseline	40.62 ± 07.05	41.35 ± 06.98	42.60 ± 08.13
		D30	45.18 ± 04.93$^{\#\#}$	45.39 ± 04.36$^{\#\#}$	46.94 ± 06.09$^{\#\#}$
		D60	46.57 ± 05.46$^{\#\#\#}$	42.22 ± 04.92*	46.51 ± 05.39$^{\#\#}$
	Change	D30	04.55 ± 06.94	04.04 ± 03.96	04.35 ± 06.50
		D60	05.94 ± 08.50	00.87 ± 08.60	03.91 ± 08.12
Skin firmness (R0) (Arbitrary Unit)	Absolute	Baseline	0.32 ± 0.05	0.34 ± 0.04	0.34 ± 0.05
		D30	0.37 ± 0.05$^{\#\#\#}$	0.36 ± 0.06	0.36 ± 0.06
		D60	0.33 ± 0.06	0.33 ± 0.05	0.35 ± 0.07
	Change	D30	0.05 ± 0.03	0.02 ± 0.04	0.02 ± 0.05
		D60	0.01 ± 0.04	-0.01 ± 0.03	0.00 ± 0.06
Skin elasticity (R7) (Arbitrary Unit)	Absolute	Baseline	0.29 ± 0.04	0.28 ± 0.05	0.27 ± 0.05
		D30	0.29 ± 0.05	0.30 ± 0.05$^{\#\#}$	0.29 ± 0.06
		D60	0.33 ± 0.04$^{\#\#\#}$	0.32 ± 0.05$^{\#\#\#}$	0.29 ± 0.06**
	Change	D30	0.01 ± 0.03	0.02 ± 0.02	0.01 ± 0.04
		D60	0.04 ± 0.04	0.04 ± 0.03	0.01 ± 0.04
Skin surface roughness (Ra) (Arbitrary Unit)	Absolute	Baseline	13.71 ± 02.17	14.91 ± 02.53	13.87 ± 03.30
		D30	13.72 ± 02.35	13.87 ± 03.16	13.10 ± 02.70
		D60	14.09 ± 02.98	14.31 ± 03.02	13.79 ± 02.95
	Change	D30	00.01 ± 02.78	-01.04 ± 01.75	-00.76 ± 02.85
		D60	00.38 ± 02.90	-00.60 ± 01.83	-00.08 ± 02.43
Depth of most profound wrinkle in crow's feet area (Rt)	Absolute	Baseline	0.10 ± 0.03	0.11 ± 0.03	0.12 ± 0.05
		D30	0.10 ± 0.04	0.10 ± 0.03	0.10 ± 0.04
		D60	0.09 ± 0.03	0.10 ± 0.03	0.09 ± 0.03#
	Change	D30	0.00 ± 0.04	-0.01 ± 0.04	-0.01 ± 0.05
		D60	-0.01 ± 0.03	-0.00 ± 0.04	-0.02 ± 0.05
Collagen distribution (Arbitrary Unit)	Absolute	Baseline	3.08 ± 1.35	2.96 ± 1.55	2.83 ± 1.34
		D30	2.44 ± 1.29$^{\#}$	2.17 ± 1.47$^{\#}$	2.58 ± 1.77$^{\#\#\#}$
		D60	2.68 ± 1.14$^{\#\#\#}$	2.48 ± 1.75$^{\#}$	3.13 ± 1.33$^{\#\#\#}$
	Change	D30	-0.64 ± 1.75	-0.78 ± 1.81	-0.25 ± 2.19
		D60	-0.40 ± 1.53	-0.48 ± 2.29	0.30 ± 2.10

Data are represented as mean ± Standard deviation; n = 22-25 per group. Comparisons by Dunnett's Multiple Comparison Test, $^{\#}$ P < 0.05, $^{\#\#}$ P < 0.01, $^{\#\#\#}$ P < 0.001 (Within the groups, vs Baseline), * P < 0.05, ** P < 0.01 (between the groups, vs Placebo)

Effects on Skin Gloss

On D30, the absolute values of mean skin loss significantly increased in the placebo (11.20%, P < 0.01), INDUS1520 (9.77%, P < 0.01), and INDUS1530 (10.21%, P < 0.01) groups, indicating improvement in all groups. On D60, a significant increase in Placebo (14.62%, P < 0.001) and INDUS1530 (9.18%, P < 0.01), but not INDUS1520 (2.10%), was observed within the groups. No significant difference between the groups (vs. Placebo), except for a decrease in skin gloss in the INDUS1520 group on D60 (-9.34%, P < 0.05). No other absolute or change in values showed a significant difference between or within groups at any visit.

Effects on Skin Elasticity

The mean values for skin elasticity (R7) significantly increased within the groups (vs. baseline) in the Placebo group (13.79%, P < 0.001) on D60, INDUS1520 on D30 (7.14%, P < 0.01), and D60 (14.28%, P < 0.001). The values for INDUS1530 significantly decreased on D60 (12.12%, P < 0.01) between the groups (vs. Placebo). No other absolute or change in values showed a significant difference between or within groups at any visit.

Effects on Skin Firmness

The mean skin firmness (R0) significantly increased within the groups (vs. baseline) in the Placebo group (15.63%, P < 0.001), demonstrating reduced skin firmness. No other absolute or change in values showed a significant difference between or within groups at any visit.

Effects on Skin Roughness and Wrinkles

None of the absolute values of change from baseline values showed a significant difference in mean surface roughness either on D30 or D60, within or between groups. However, INDUS1520 and INDUS1530 showed a decreasing trend in Ra values (lower roughness), whereas Ra values increased in the Placebo group (higher roughness).

However, a significant decrease in the mean depth of wrinkles (Rt) values within the group (v/s) was observed in INDUS1530 on D60 (25.00%, P < 0.05). No other absolute or change in values showed a significant difference between or within groups at any visit.

Effects on Collagen distribution

The absolute values (but not change from the baseline values) of the mean collagen distribution of all treatments showed significant differences between D30 and D60 within the groups (but not between the groups).

Table 2. Effects of Treatment on Subjective assessment of efficacy

Measure	Day	Assessment criteria	Placebo (n = 25)	INDUS1520 (n = 23)	INDUS1530 (n = 24)
Well-moisturized skin	D30	Disagree or Neutral	-	01 (4.3)	-
		Agree	25 (100)	22 (95.7)	24 (100)
	D60	Disagree or Neutral	-	-	-
		Agree	25 (100)	23 (100)	24 (100)
Wrinkle reduction—around the eyes (Crow's feet)	D30	Disagree or Neutral	07 (28)	03 (13)	06 (25)
		Agree	18 (72)	20 (87)	18 (75)
	D60	Disagree or Neutral	4 (16)	02 (8.7)	04 (16.7)
		Agree	21 (84)	21 (91.3)	20 (83.3)
Wrinkle Reduction—On Face	D30	Disagree or Neutral	06 (24)	05 (21.7)	06 (25)
		Agree	19 (76)	18 (78.3)	18 (75)
	D60	Disagree or Neutral	06 (24)	03 (13)	04 (16.7)
		Agree	19 (76)	20 (87)	20 (83.3)
Firm/tight skin	D30	Disagree or Neutral	04 (16)	05 (21.7)	05 (20.8)
		Agree	21 (84)	18 (78.3)	19 (79.2)
	D60	Disagree or Neutral	-	02 (8.7)	02 (8.3)
		Agree	25 (100)	21 (91.3)	22 (91.7)
Even skin tone	D30	Disagree or Neutral	06 (24)	05 (21.7)	02 (8.4)
		Agree	19 (76)	18 (78.3)	22 (91.7)
	D60	Disagree or Neutral	01 (4.0)	04 (17.3)	01 (4.2)
		Agree	24 (96)	19 (82.6)	23 (95.8)
Lightened skin	D30	Disagree or Neutral	05 (20)	05 (21.7)	01 (4.2)
		Agree	20 (80)	18 (78.3)	23 (95.8)
	D60	Disagree or Neutral	03 (12)	03 (13)	01 (4.2)
		Agree	22 (88)	20 (86.9)	23 (95.9)
Face Glow	D30	Disagree or Neutral	02 (8.0)	05 (21.7)	01 (04.2)
		Agree	23 (92)	18 (78.3)	23 (95.8)
	D60	Disagree or Neutral	02 (8.0)	01 (4.3)	-
		Agree	23 (92)	22 (95.6)	24 (100)
Smooth and soft skin	D30	Disagree or Neutral	-	-	01 (4.2)
		Agree	25 (100)	23 (100)	23 (95.8)
	D60	Disagree or Neutral	-	-	-
		Agree	25 (100)	23 (100)	24 (100)

Data are presented as numbers. Data were analyzed using the chi-square test, where n is the total number of participants

Subjective Efficacy assessment

As presented in Table 2, there were no significant differences in the scores of the subjective assessment of efficacy measures, that is, moisturization, wrinkle reduction around the eyes (crow's feet), face glow, tightness, firmness, evenness, color lightness, smoothness, and softness of the skin, in any of the groups, indicating the absence of psychological benefits as perceived by the participants.

Safety Outcome measures

No dermatological symptoms (erythema, edema, cutaneous dryness, roughness, or other) were reported by a qualified dermatologist in any of the treatment groups during the dermatological skin safety assessments. None of the participants in any of the groups reported skin intolerance (pricking, tingling, itching, redness, or burning facial skin) during the self-assessment of skin safety. No adverse events were reported by any of the participants during the study period.

DISCUSSION

This study assessed the efficacy and tolerability of INDUS1520 and INDUS1530 creams prepared from fenugreek seeds, a natural food chain source. The results of this study demonstrated a beneficial effect of various skin efficacy measures, suggesting their potential against skin aging. The cream formulation of the extract was chosen over the serum formulation for this clinical study. Creams are generally considered more stable than serum because of their thicker consistency and higher oil content, which inhibit the degradation of active ingredients and facilitate a more stable emulsion[37-38]. In contrast, serum, which is lightweight and rapidly absorbed, often contains high concentrations of active components that may be more prone to instability, particularly when exposed to air, light, or heat[39].

The female sex was selected for this study because the need for female anti-aging solutions is higher than that for men. Females experience accelerated collagen loss post-menopause, leading to skin thinning and wrinkles[40]. A thinner skin can make women more susceptible to aging[41]. Men have larger sebaceous glands that produce protective sebum, whereas women's oil production decreases after the reproductive years[42]. Hormonal changes during menstruation, pregnancy, and menopause affect women's skin health and elasticity earlier than in men[43].

An ideal anti-aging facial regimen integrates both day and night creams to address the skin's distinct needs and physiological activities across a 24-hour cycle. Because of exposure to environmental stressors, day creams with protective antioxidant factors are required to prevent photoaging and oxidative damage[44]. Conversely, night hours are optimal for skin repair and regeneration, marked by accelerated cellular turnover and increased synthesis of collagen and hyaluronic acid[40]. Therefore, night creams are formulated with high concentrations of compounds that stimulate collagen production and enhance skin texture for comprehensive anti-aging effects. This synergistic approach ensures continuous protection and regeneration, thereby maximizing the efficacy of anti-aging therapies[45].

In the present study, INDUS1530 cream showed a trend of efficacy for reduction of the deepest wrinkles, improvement in skin hydration, and collagen distribution. In addition, INDUS1520 showed a trend towards elasticity enhancement and roughness decrease while maintaining the barrier function of the skin. All treatments, including the test compounds, increased the skin gloss.

The INDUS1530 cream showed a significant decrease in the depth of the most profound wrinkle (Rt), indicating a better facial appearance and reduced sagging[46]. The Antera 3D™ imaging system, which was used in this study, is a sophisticated device used in dermatology, aesthetic medicine, and cosmetic research to objectively quantify various skin efficacy measures, wrinkles (maximum vertical distance between the highest peak and the lowest valley, Rt), and texture/roughness (Ra, arithmetic mean roughness) in a quantitative, precise, and reproducible manner[34-47].

MoistureMeterD provides a noninvasive, objective method for assessing skin hydration levels, moving beyond subjective observations or qualitative assessments[48]. The moisture content in the facial skin and subcutis of the INDUS1530 group participants increased significantly at D30 and D60 compared to baseline in this study, indicating strong hydrating efficacy and moisturizing potential.

The potential of INDUS1530 to enhance skin hydration can be attributed to its galactomannan marker compound, which is enriched with oligosaccharides, such as d-pinitol, raffinose, and stachyose[49]. Fenugreek galactomannans are well recognized for their exceptional capacity to retain water molecules because of the abundant hydroxyl groups within their structure, thereby functioning as effective humectants that significantly improve skin hydration[20]. Furthermore, the presence of eleutheroside in INDUS1530 supports collagen production by reducing matrix metalloproteinase activity[50-51], positioning INDUS1530 as a promising natural ingredient for both cosmeceutical and nutraceutical applications in skin health.

TEWL is a crucial indicator of skin health and barrier function and serves as an in vivo index for assessing the efficiency and integrity of the stratum corneum, the outermost layer of the skin responsible for barrier function[52]. A robust barrier helps to lock in moisture, keeping the skin supple and resilient against environmental stressors. In this study, INDUS1520 caused a significant reduction in TEWL values (vs. Placebo), suggesting preservation of the barrier function. INDUS1530 showed a trend of reduction but did not cause a significant reduction after 60 days.

The primary factor contributing to skin aging is exposure to solar UV radiation during daylight hours, which is the main environmental threat to the skin. The UVA and UVB components of solar radiation trigger ROS formation, resulting in oxidative stress, which plays a major role in photoaging and various skin disorders[53]. Previous studies have shown that fenugreek seed galactomannan can reduce ROS generation and enhance the activity of endogenous antioxidant enzymes, such as superoxide dismutase, which upregulates nuclear factor erythroid 2-related factor 2, a key transcription factor responsible for boosting cellular antioxidant potential[54]. Collectively, these actions help mitigate oxidative stress at the cellular level and provide a protective effect. Fenugreek galactomannan has anti-inflammatory effects through lowering pro-inflammatory cytokine levels[20-55]. Galactomannan is a powerful humectant capable of retaining a significant amount of water because its hydroxyl groups are more resilient to UV radiation and are less susceptible to oxidative damage[20].

Flavonoid glycosides in fenugreek seeds have been reported to offer a promising solution for preventing oxidative stress, mitigating mitochondrial dysfunction, and protecting mitochondrial DNA against oxidative damage[18-56]. Specifically, apigenin inhibits UVB-induced skin carcinogenesis by reducing apoptosis of human dermal fibroblasts[18]. Other cream formulations rich in fenugreek flavonoid glycosides have been shown to possess strong antioxidant and anti-inflammatory effects[14]. These reports support the role of antioxidant and related properties marker compounds, INDUS1520 and INDUS1530, in anti-aging efficacy, as observed in the present study.

One cause of chronological aging has recently been correlated with an age-related decline in nicotinamide adenine dinucleotide (NAD) and subsequent mitochondrial and metabolic abnormalities[57]. CD38+ is one of the main NAD-degrading enzymes in mammalian tissues and

CD38+ inhibitors can prolong aging by maintaining NAD levels[58]. Recent findings on fenugreek seed extract, which is rich in flavonoid glycosides, have shown CD38+ enzyme inhibitor potential *in vitro*[25]. Therefore, glycosides (a marker compound of INDUS1520) may have contributed to the anti-aging efficacy of certain skin health-related efficacy measures in the present study.

The safety profiles of INDUS1520 and INDUS1530 were exceptionally favorable, as previously demonstrated during the *in vivo* primary patch test (48 h) and the human repeat insult patch test at concentrations of 1%, 3%, and 5% in human volunteers. All tested concentrations were confirmed to be safe for use[22-23].

In the current study, a notable general trend of increased skin gloss was observed in all groups (Placebo, INDUS1520, and INDUS1530), suggesting a common initial benefit, likely attributable to the moisturizing properties of the excipients. The ITA values obtained using the spectrophotometer showed similar trends, representing improvements in skin complexion in all the groups, although statistical significance was not achieved.

In this study, we measured skin elasticity and firmness using a cutometer[33]. The efficacy measures R7 and R0 provide valuable insights into the functional integrity of the skin and its capacity to resist and recover from deformation. R7 reflects the elasticity of skin for rapid and complete recoil after deformation, whereas R0 is resistant to immediate deformation. In our study, both compounds showed enhanced R7, that is, elasticity and resilience of the skin, over a prolonged period (D60). INDUS1530 showed a significant difference between the group comparisons (vs. Placebo), whereas INDU1520 was used for within-group comparisons (vs. baseline). The present study also showed transient skin softening (increased R0, although not significant) in the initial 30 days, but skin regaining, stabilization, and firmness were restored in the next 30 days, suggesting a more balanced improvement in overall skin biomechanics.

In the present study, the effects of test compounds on collagen distribution within the skin, a crucial determinant of skin structure and strength, were evaluated. As the predominant protein in the ECM, collagen is essential for upholding skin durability and elasticity[40-59]. Recent studies have suggested that fenugreek extracts can directly stimulate fibroblast proliferation and enhance collagen production[7-60]. However, in the present study, collagen distribution was reduced in the Placebo and INDUS1520 groups but increased in the INDUS1530 group, although the difference was not statistically significant. This mixed outcome did not provide conclusive evidence for INDUS1530 promoting collagen accumulation or a favorable distribution, but at least 60 days of the study.

This study used a robust methodology (randomized, double-blind, placebo-controlled design) that effectively minimized bias and enhanced reliability. Additionally, a comprehensive array of objective instrumental measures for quantitative outcomes provides a multifaceted and reliable assessment of skin efficacy measures. Furthermore, adherence to rigorous ethical guidelines, well-defined product characterization, and strict control conditions contributed to the high internal validity of the present study. However, the full extent of long-term anti-aging effects on skin parameters, such as collagen distribution, can be better explored beyond the 60-day intervention period used in the present study[61].

CONCLUSION

This randomized controlled clinical study confirmed the significant anti-aging benefits of two standardized fenugreek seed extract creams to improve the reduction in the deepest wrinkles, with enhanced hydration and collagen distribution in the skin (INDUS1530) and improved barrier function (INDUS1520). Both creams were well tolerated and showed favorable safety profiles, supporting the potential for effective and safe anti-aging skincare solutions.

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