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Brief Communication

Efficacy and safety of a proprietary *Punica granatum* extract in skin health - a randomized, placebo-controlled clinical study in healthy volunteers

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Abstract: Objectives: The concept of beauty from within is a growing trend in the market and people now look for oral supplements that can enhance the well-being of skin from within. Within this principle, a proprietary pomegranate extract (Grantria®), standardized to ellagic acid, punicic acid and punicalagin, was developed using ADOP (Advanced Oil-Powder) technology and was clinically evaluated for its efficacy and safety in healthy adults. Methods: This evaluation was carried out as a randomized, placebo-controlled clinical study for 60 days at a daily dose of 300 mg. This study involved a total of 60 subjects randomized in the ratio of 1:1 to test group and placebo group. Multiple skin health parameters were evaluated before and after the intervention. Results: Data from this study indicated that *Punica granatum* extract significantly reduced crow's feet wrinkles, tactile roughness, forehead fine lines, forehead wrinkles and improved skin radiance compared to the placebo in 60 days. Other skin health attributes like pores, spots and UV pigmentation were also observed to exhibit significant changes. The test group showed a significant improvement in skin tone evenness, skin moisturisation, elasticity and firmness compared to the baseline. The Tyrosinase biomarker levels were observed to drop by 3% in the Grantria® supplemented group. Conclusions: Grantria® was found to be effective, safe, and well accepted by the subjects making it a potential candidate for use in the supplements intended for maintaining healthy and glowing skin.

Keywords: *Punica granatum*, Grantria, skin health, wrinkles, skin radiance, tactile roughness

Introduction

Extended life expectancy worldwide has changed the perception of aging and has propelled scientific anti-aging research leading to a multitude of anti-aging treatments. Over the past several years, professional systems and technologies for non-invasive anti-aging treatments have become the gold standard in professional clinics worldwide. Years of medical research have focused on both the internal and external factors of skin aging. The internal causes of aging skin are similar to those experienced by the rest of our internal organs, including the normal changes in hormone levels, particularly estrogen, as well as the decline in metabolic activity and cell regeneration as we grow. External causes that affect our skin's appearance include exposure to UV rays, environmental pollution, and smoking. While the scientific research has categorized age-inducing factors as internal or external, increasing evidence demonstrates their interdependencies; specifically, the research is now showing that external factors may actually accelerate the internal aging process [1]. The collagen and elastin fibers in our skin decrease every year, changing the structure and appearance of our skin. The dermal layer of our skin contains fibroblasts, the cells that maintain the skin structure and produce collagen. Research on anti-aging shows that the number of fibroblasts in the skin decreases and skin metabolism slows down as we age. These structural changes to our skin appear as fine lines, wrinkles and sagging facial skin [2].

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Emotional health, quality of life self-perception and interactions with others were shown to be impacted by one's skin [3]. Therefore, people use cosmetics in the quest to make them look younger and feel confident and comfortable. Traditional cosmetics and skin care products like creams work on the surface of the skin and they are applied topically. There is a growing trend in the use of oral supplements in the maintenance of healthy and glowing skin. Collagen peptides, astaxanthin, resveratrol, tomato and rosemary extracts are available in the supplement market as ingredients of the products being promoted as "Beauty from within" that are intended to maintain skin health via oral supplementation as opposed to the topical use of traditional cosmetic products. Parameters such as crow's feet wrinkles, tactile roughness, skin radiance, forehead fine lines, wrinkles, pores, spots, skin tone evenness, elasticity and firmness are used to evaluate the quality of ingredients or products intended to maintain healthy and glowing skin. The primary objective of our work is to evaluate the efficacy and safety of Grantria®, a proprietary *Punica granatum* extract in a randomized, placebo-controlled clinical study for the management of skin health.

Several other studies have revealed corroborating evidence with regards to the positive dermal health demonstrated by *Punica granatum.* Skin erythema and redness, along with melanin pigmentation were found to be decreased in a study conducted by Parvin et al, where the extract of *Punica granatum* was administered topically [4]. Some of the key compounds in this extract, namely punicalagin and ellagic acid are known for their skin whitening activity which is demonstrated through the prevention of melanin formation [5]. Hydrolysable tannins in the pomegranate extract control sebum production in skin, thereby preventing acne [6]. The polyphenols found in pomegranate extract have proven protective effect against ultraviolet radiation which is believed to be due to the inhibition of NF-kappa B activity [7].

Methods

Study design

The study was designed as a randomized, open label, placebo-controlled study and conducted at a single centre in compliance with ICMR ethical guidelines, the ICH 'Guidance on Good Clinical Practice', NDCT Rule (The New Drugs and Clinical Trials, 2019) and Declaration of Helsinki. The study was initiated after approval from the study centre's institutional ethics committee and was registered in Clinical Trials Registry - India (CTRI) with registration number CTRI/2023/02/050063 dated 24/02/2023. All subjects who agreed to participate in the study provided documentation of fully executed informed consent to the investigator prior to study related procedures being conducted. Randomization process was followed for the allocation of the recruited subjects into the test and placebo groups. Computer generated randomization was employed by utilizing a pseudo-random number generator where each participant was assigned to either test or placebo group in a manner that minimized selection bias and balanced potential confounding variables across both groups. No subjects were allowed to use any topical drug or cosmetic product or apply bleach/turmeric on their face and neck during the study duration. All subjects were asked to inform the investigator before using any treatment, which may interfere with the study assessments. For monitoring the subject's compliance, proper instructions were given to all subjects regarding study before giving the consent. All subjects were evaluated on Day 1 (before treatment), Day 15, Day 30 and Day 60 (at the end of the treatment). Evaluation on Day 1 and Day 60 involved visits to the study centre. Evaluations on Day 15 and Day 30 were carried by telephonic communication. On every evaluation, the study coordinator conducted an enquiry related to compliance of the study protocol. Compliance checks included counselling of the subjects and subject's diary review.

Participants

Non-pregnant females aged between 35 and 65 years were screened for inclusion in the study. Only subjects who were willing to give voluntary written informed consent for participation in the study and willing to comply as per the protocol requirements were included in the study after being screened and when found suitable for participation. They were included if they had dark spots, pimple marks and facial pigmentation with skin phototype IV to VI. Subjects with minimum grade 2 of crow's feet wrinkles as per skin aging atlas and those sub-

jects having stable hormonal status as declared personally were included. All eligible subjects underwent urine pregnancy test on day 1 to check if they were not pregnant before inclusion in the study and females with childbearing potential were asked to use acceptable methods of contraception.

The list of study exclusion criteria was extensive, including multiple factors. Subjects willing to become pregnant, lactating mothers, those with active/inflamed pimples or any active lesions on the face, those undergoing any treatment of any skin condition on their face/body, and those with any significant skin pathology in the test area. Additionally, patients were excluded if they had chronic illness or major surgery within the last 12 months, including any significant ophthalmic illness or if they have undergone eye surgery in the past 6 months, as well as any individuals who had nose piercing/facial piercing within the past 6 months. Other reasons for non-admittance to the study were patients with known hypersensitivity to any of the study products or constituents or cosmetics, with allergies or sensitivities to bar cleansing products, creams/lotions, artificial jewellery, or anything else, anyone who had participated in any other clinical trials within 1 month prior to participation in the study, as well as individual using medications including food supplements, which the investigator believed may influence the interpretation of the data and those who used any topical or systemic treatment(s) such as NSAIDs, corticosteroids, retinoids, or vitamins 30 days prior to participation in the study. Participants were asked not to use any topical drugs or cosmetic products (without prior approval by the investigator) and not to apply bleach/turmeric on their face and neck. They were also asked to inform the investigator before using any treatment which may interfere with the study assessments and inform the investigator before using any systemic treatment (drug or dietary supplement) which may interfere with the study assessments.

Interventions

The test product Grantria® and placebo capsules were supplied by Zeus Hygia Lifesciences, India. Grantria® and placebo capsules were identical in appearance to the test tablets. Each test product capsule contained 300 mg of the proprietary pomegranate extract. Grantria® is an innovative herbal ingredient developed by Zeus Hygia Lifesciences using proprietary ADOP technology and was standardized to contain optimized quantities of pomegranate bio actives ellagic acid, punicic acid and punicalagin. Each capsule of placebo contained 300 mg of microcrystalline cellulose. All subjects were asked to take one capsule per day before food, for 60 days.

Outcomes

Primary outcomes of the study included changes in the clinical scores of crow's feet wrinkles, tactile roughness, skin radiance, forehead fine lines and forehead wrinkles assessed by a dermatologist and changes in the pores, spots, skin tone evenness and elasticity and firmness using skin topography assessment. Crow's feet wrinkles were scored from grade 0 to 5 by the dermatologist with the help of skin aging atlas by BAZIN and FLAMENT on Day 1 (before treatment) and Day 60 (at the end of the treatment). During baseline visit, the scoring of the side (left/right) having highest grades was captured. The same site was chosen for scoring at subsequent visits. Forehead fine lines and wrinkles were also assessed by a dermatologist using the skin aging atlas by BAZIN and FLAMENT and were graded from 0 to 7. Tactile roughness was scored by the dermatologist between 0 to 9 where, 0 means completely smooth, 1-3 corresponds to mild roughness, 4-6 indicates moderate roughness and 7-9 severe roughness. Skin radiance was assessed by the dermatologist using the skin radiance scale with the scores ranging from 0 to 9. Pores, spots, skin tone evenness and elasticity and firmness were measured using Visioscan® 1000D (Courage + Khazaka Electronic GmbH, Germany) on Day 1 (before treatment) and Day 60 (at the end of the treatment). Elasticity and firmness were measured using Cutometer (Derma Lab® Combo, Derma Lab Series, Elasticity Probe no: C05440.02-338, Cortex Technology Aps, Plastvaenget 9-9560 Hadsund-Denmark) on Day 1 and Day 60. The number of adverse events were considered as the secondary outcome and was assessed by the principal investigator throughout the study.

Statistical methods

The sample size for this study was calculated using G power software, factoring in the mean

Table 1. Baseline demographics

Parameters	Test Product-1 (N=40)	Placebo (N=40)
Gender - Females, N (%)	40 (100.0)	40 (100.0)
Age (Years)[a]	44.58±8.05	47.65±9.47
Height (cm)[a]	153.12±6.66	151.90±7.43
Weight (kg)[a]	58.65±10.00	57.73 (9.36)

[a]Each value represents mean±SD of n=40.

values of the hydration parameter observed in two treatment groups from a previous study [3]. With the aim of achieving a statistical power of 90% and maintaining a significance level of 5%, the sample size was initially determined to be 37 for each group. To account for the possibility of participant attrition, this figure was subsequently adjusted to 40. The Quantitative data obtained at time points (t) were subjected to tests of normality (Shapiro wilk test). Depending upon the nature of distribution of the data, the appropriate descriptive and inferential statistics are chosen. Data that is normally distributed was described in terms of mean and standard deviation while non-normally distributed data were described using median and interquartile range. The null hypothesis was rejected when a *p*-value less or equal to 0.05 (5% significance level) was revealed by the statistical procedure.

Results

Recruitment, participant flow and demographic details

A total of 80 subjects were assessed for eligibility as per the inclusion and exclusion criteria and all 80 subjects were found eligible and thus recruited into the study after giving informed consent, before initiating the study. All the recruited subjects were randomly assigned to the test group and placebo group in the ratio of 1:1 with 40 subjects in the test group and 40 subjects in the placebo group. There were no dropouts from the study. Baseline demographic data of the subjects involved in the study is given in **Table 1**. All the subjects completed the study without any deviation from the study protocol and therefore data from all the subjects were included for the analysis.

Effect on crow's feet wrinkles

At Day 1 (Pre-treatment), the Crow's feet wrinkle values were similar for both Test group (3.00±0.88) as well as Placebo group (3.00± 1.01). Post supplementation, the Crow's feet wrinkles significantly (P<0.001) decreased to 1.55±0.60 on day 60 in the test group compared to the placebo group, which had shown a slight increase to 3.30±1.02. Within group analysis showed that both the groups showed a significant (P<0.05) difference at the end of the study compared to the baseline. As presented in the below graph (**Figure 1**), the statistically significant changes in test group indicates the effectiveness of the test product.

Effect on tactile roughness

The study data reflects that the test substance significantly (P<0.001) decreased the tactile roughness from 4.45±1.11 on day 1 to 2.52± 0.68 on day 60 compared to the placebo group (Clinical score of 4.35±1.08 on day 1 and 4.65±1.00 on day 60). A significant (P<0.05) difference was observed within the groups compared to their baseline at the end of the study. Similar to the findings for Crow's feet wrinkles, the test group showed improvement in reducing the tactile roughness to around 43.3% at the end of the study compared to baseline (**Figure 1**).

Effect on skin radiance

In line with the improvements in wrinkles and skin roughness, skin radiance was also found to be improved significantly (P<0.001) in the test group, from 5.30±1.16 on day 1 to 7.58± 0.64 on day 60, compared to the placebo group, which showed 5.10±1.41 on day 1 and a decline to 4.90±1.39 on day 60. Within the groups, both the test substance group and the placebo showed significant (P<0.005) differences in skin radiance at the end of the study compared to baseline levels. These study findings underline the effectiveness of test product in improving skin radiance compared to placebo (**Figure 1**).

Effect on forehead fine lines

The test product exhibited efficacious superiority by significantly (P<0.001) outperforming

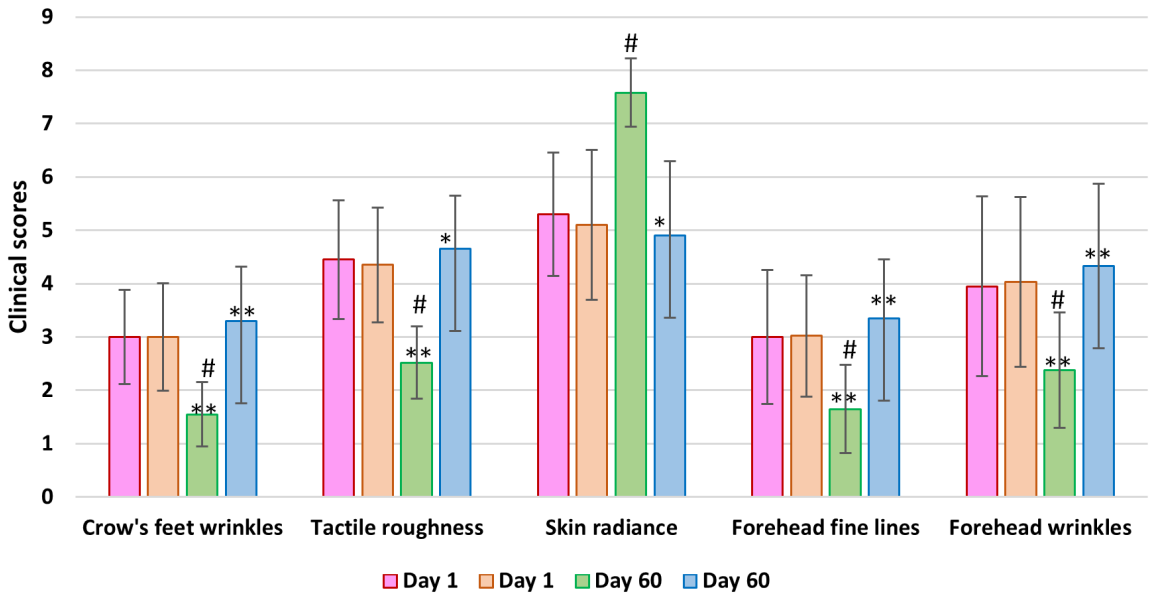

Figure 1. Effect of Grantria® on clinical scores. Each value represents mean±SD and n=40; Significant compared to the baseline - *P<0.005 and **P<0.001; Significant compared to the placebo - #P<0.001; Clinical scores assessed by dermatologist using skin aging atlas.

the placebo group in improving forehead fine lines at the end of day 60. As presented in **Figure 1**, there was a statistically significant drop in the score for forehead fine lines (P<0.001), from 3.00±1.26 on day 1 to 1.65±0.83 on day 60 in the case of the test group. However, the placebo group did not show any notable benefits during the study (Day 1; 3.02±1.14 and 3.35±1.10 on day 60). The difference within the groups, both the test and the placebo products were significant (P< 0.005) at the end of the study compared to their baseline levels.

Effect on forehead wrinkles

Compared to baseline, the test product significantly (P<0.001) decreased the forehead wrinkles on day 60. The observed changes in clinical scores were from 3.95±1.69 on day 1 to 2.38±1.08 on day 60 as compared to the placebo group, which showed a slight increase from 4.03±1.59 on day 1 to 4.33±1.54 on day 60. Significant (P<0.05) difference was observed within the groups compared to their baseline at the end of study. Significant reductions in forehead wrinkles underline the effectiveness of test product in the studied subjects (**Figure 1**).

Effect of Grantria® on elasticity, firmness, skin hydration, moisturization, pores, spots, wrinkles, UV pigmentation, skin tone evenness and tyrosinase levels

Grantria® significantly (P<0.05) improved the elasticity and firmness compared to its baseline values, which seemed to be better than placebo, however there was no significant difference between the groups at the end of the study. Skin moisturization was significantly (P<0.05) improved by Grantria® but the same was significantly decreased by the placebo indicating the importance of Grantria® in improving skin moisturization. Skin hydration measured by TEWL using tewameter did not shown any significant difference within each group and between the groups. Grantria® significantly (P<0.05) reduced pores and spots and increased the skin tone evenness as assessed using skin topography (Visioscan®) at the end of the study compared to its baseline. Placebo did not show such decrease in pores and spots while a little worsening of skin tone evenness was observed at the end of the study compared to its baseline values. Grantria® showed significantly less UV pigmentation compared to its baseline but has not shown any difference on wrinkles as assessed using

skin topography (Visioscan®). On the other hand, UV pigmentation and wrinkles were significantly worsened in the placebo at the end of the study compared to its baseline. There was no significant difference observed between the groups at the end of the study in any of these parameters. We did not find any statistically significant difference in the tyrosinase levels at the end of the study within each group and between the groups, however, there was 3% drop in the tyrosinase levels in the Grantria® group when compared to the baseline (**Table 2**).

At the end of 60 days, a statistically significant difference was observed in the change in mean scores from baseline to the end of the study between the Grantria and placebo groups for pores, spots, wrinkles, UV pigmentation, and skin tone evenness. The Visioface assessments were consistent with the dermatologist's clinical scoring, which also revealed a statistically significant difference in the clinical scores between the two groups in terms of fine lines, wrinkles, and skin radiance.

In conclusion, these results suggest that the Grantria capsule significantly enhances skin health by effectively reducing wrinkles, fine lines, pores, and spots, as well as mitigating UV pigmentation and promoting a more even skin tone. This improvement underscores its potential as a beneficial addition to skincare regimens aimed at achieving a healthier and more radiant complexion.

Grantria® is safe with no adverse events

At the end of study, 97.5% of the subjects in the test group reported improvements in the skin radiance, whereas only 35% of the subjects reported improvement in the placebo group. All subjects in the test group reported that their skin was dewy and fresh, hydrated, and felt smooth and soft, light weight and non-greasy, and more lifted and firmer. More than 77% of the subjects in the test group reported reduction in the appearance of fine lines and wrinkles and felt that their skin looked younger. Only 12.5% reported reduction in the appearance of fine lines and wrinkles in the placebo group. All subjects in the test group agreed that the test product made their skin appear to look more even and less blotchy, moisturized, look refreshed, feel protected and nourished and improved the texture of the skin, and improved the overall health and look of the skin. Also, all the subjects slightly agreed that the use of the test product made their skin to look and feel rejuvenated. None of the subjects in the test group reported any adverse events during the study period.

Discussion

Skin aging is a complex process that affects the structure and function of the skin, leading to changes in its appearance and tactile properties. Crow's feet wrinkles are the fine lines and wrinkles that are seen around the eye socket. These wrinkles appear during facial expression and become permanent as we age. They are caused by the contraction of fibers of the orbicularis oculi, a circumferential muscle that surrounds the eye [8]. Pomegranate extract at a daily dose of 250 mg containing 75 mg of punicalagin reduced facial wrinkle severity in 28 healthy adult male and female subjects in 4 weeks [9]. In the present study, the Grantria® significantly ($P<0.001$) decreased crow's feet wrinkles (48%) compared to the placebo group at the end of the study.

Tactile roughness is the perception of the surface texture of an object by touch. Accumulation of corneocytes, i.e., the dead skin cells in the outermost layer of the skin contributes to the tactile roughness and skin aging and reduces the ability of skin to retain moisture and nutrients. Degradation of collagen and elastin, which are proteins that provide strength and elasticity to the skin also affects tactile roughness and skin aging, wherein the collagen and elastin fibres become disorganized and fragmented as a result of intrinsic (genetic) and extrinsic (environmental) factors, such as sun exposure, smoking, pollution, and stress [10]. We have seen significant ($P<0.001$) reduction in the tactile roughness at the end of the study compared to the placebo group possibly due to pomegranate extract's antioxidant [11, 12] and collagen supporting properties [13]. Pomegranate extract has been reported to modulate collagen and hyaluronic acid metabolism in normal conditions in human fibroblast Hs68 cells and positively influenced hyaluronic acid metabolism and reduced reactive oxygen species levels in UV-exposed cells [12]. Pomegranate extract and its active constituent puni-

Table 2. Results of elasticity, firmness, skin hydration, moisturization, pores, spots, wrinkles, UV pigmentation and skin tone evenness

Parameters	Grantria [Mean (SD)]		Placebo [Mean (SD)]		Change from Baseline [Mean (SD)]		*P* value#
	Day 1	Day 60	Day 1	Day 60	Grantria	Placebo	
Cutometer VE (MPa)[a]	3.02±3.57	3.54±1.86	4.25±9.26	3.59±1.49	0.52±3.63	-0.66±9.52	0.466
Cutometer E (MPa)[a]	2.71±2.83	3.44±0.78	2.50±2.32	3.27±0.59*	0.73±2.69	0.77±2.37	0.937
Cutometer (Retraction Time) (ms)[a]	2898.60±2625.98	540.88±765.39****	2616.40±2492.27	408.25±482.06*	-2357.72±2800.49	-2208.15±2604.38	0.805
Skin moisturization[b]	193.30±103.92	240.62±108.47**	200.75±134.21	266.70±123.76**	47.31±102.83	65.95±146.05	0.511
Skin hydration (TEWL)[c]	7.43±3.92	19.88±66.54	7.99±7.49	16.28±40.47	2.44±67.07	8.29±39.59	0.737
Pores[d]	2.62±0.60	2.50±0.59****	2.62±0.61	2.65±0.56	-0.12±0.15	0.03±0.23	0.001
Spots[d]	2.16±1.03	2.10±0.99***	2.00±1.21	2.00±1.21	-0.06±0.13	0.00±0.10	0.016
Wrinkles[d]	7.01±3.41	6.95±3.42	6.72±2.56	6.78±2.55***	-0.06±0.24	0.06±0.11	0.008
UV pigmentation	6.43±1.51	6.35±1.51*	6.24±1.72	6.35±1.72****	-0.08±0.20	-0.08±0.20	<0.001
Skin tone evenness[d]	6.13±1.63	6.06±1.61****	5.61±1.41	5.66±1.39***	-0.07±0.12	0.05±0.10	<0.001
Tyrosinase[e]	394.69±81.23	382.92±68.42	382.50±62.76	383.16±59.75	-11.78±48.80	0.66±54.10	0.455

Each value represents mean±SD and n=40 for all parameters except tyrosinase for which n=18 in the test substance group and n=22 in the placebo group; *P* value* - Statistical significance for intra group comparison between baseline and end of the study (Paired T test); *P* value# - Statistical significance for inter group comparison between baseline and end of the study (Independent two sample T test); Significance compared to the baseline - *P<0.05, **P<0.01, ***P<0.005 and ****P<0.001; a - assessed using cutometer; b - assessed using corneometer; c - assessed using tewameter; d - assessed using skin topography (Visioscan®); e - assessed in blood sample.

calagin has been reported to support collagen by inhibiting collagenase activity, positively influencing the expression levels of collagen degradation enzymes (MMP-9 and MMP-13) and by increasing the expression levels of the type I collagen protein, COL1A1. These activities were supported by molecular docking studies [13].

Forehead fine lines and forehead wrinkles are the signs of aging. The difference between forehead fine lines and wrinkles are the depth of the crease in the skin. Fine lines are very mild, while wrinkles are deeper set. Fine lines are often one of the first signs of aging and they usually occur in the most expressive areas of your face, such as around the eyes, mouth and forehead. Wrinkles can form anywhere a fine line does, and vice versa. Disorganised collagen and elastin fibres weakens the structure underlying the epidermis, leading to wrinkles, sagging, and loss of firmness. In this study, Grantria® showed a significant ($P<0.001$) reduction in the forehead fine line and forehead wrinkles at the end of the study compared to the placebo group. Oral supplementation of a powder containing concentrated pomegranate juice has reduced skin wrinkles and increased skin water content, collagen type I, and hyaluronan contents in UVB irradiated hairless mice. The test substance also showed anti-inflammatory effects by lowering UVB induced increase in the interleukin 1β levels and protected against UVB-induced GSH depletion [9]. Pomegranate extract at a daily dose of 250 mg containing 75 mg of punicalagin was found to reduce facial TEWL (Transepidermal water loss) and wrinkle severity in a subgroup of subjects with higher level of Eggerthellaceae in their gut microbiome [9]. These findings underline the anti-wrinkle properties of triple bioactives of Grantria® as observed in the current study.

Skin radiance is the look of healthy, vibrant, and dewy skin that reflects light. It can be influenced by skin tone, luminosity, firmness, discolouration, smoothness, and cell turnover. In this study, a significant ($P<0.001$) improvement in skin radiance was observed (42.8%) at the end of the study for the Grantria® group compared to the placebo group. A fermented pomegranate extract as a drink form, when taken at a daily dosage of 50 ml for 8 weeks was found to improve skin moisture, brightness, elasticity, and collagen density in a randomized, double-blind, placebo-controlled study involving 40 healthy subjects. The same extract as topical application on the face for 4 weeks was shown to have enhanced skin moisture, brightness, elasticity, and reduced spots and UV spots in another randomized, double-blind, placebo-controlled study involving 40 healthy subjects [14]. A 4-week oral supplementation of an ellagic acid rich pomegranate extract was found to protect skin from UV-induced skin pigmentation in terms of skin luminance, melanin values and erythema values in a randomized, double-blind, placebo-controlled study involving healthy adult females [15].

Pores, spots, UV pigmentation, skin tone evenness, skin moisturisation, elasticity and firmness are some of the attributes that affect the quality of skin. Pores are the openings of the hair follicles on the skin. They secrete sebum, which is a natural oil that moisturizes and protects skin. Pores can become enlarged or clogged due to excess sebum production, skin debris, aging, or sun damage. Spots are small areas of discoloured skin that can be caused by various factors, such as acne, inflammation, infection, hormonal changes, or sun exposure. Spots can be red, brown, black, or white in colour and can vary in size and shape. Skin tone evenness refers to uniformity in the surface colour of the skin. Uneven skin tone can result from hyperpigmentation or hypopigmentation, which are conditions where some areas of our skin produce more or less melanin than others. Uneven skin tone can also be caused by sun damage, inflammation, scarring, or aging [16]. Pomegranate extract has been reported to inhibit tyrosinase activity with an IC_{50} value of 394.7 μg/mL [12]. A pomegranate extract containing 90% ellagic acid has been reported to have inhibited mushroom tyrosinase in vitro, inhibited UV-induced skin pigmentation on the back of brownish guinea pigs upon oral administration and reduced the number of DOPA-positive melanocytes in the epidermis of UV-irradiated guinea pigs. These effects show the potential of using the extract as a skin whitening supplement [17]. A pomegranate peel extract was reported to have antioxidant properties and inhibited tyrosinase and TRP-2 in B16F10 melanoma cells and showed an inhibitory effect on MMP-2 [11]. Elasticity is the ability of our skin to stretch and bounce back to its

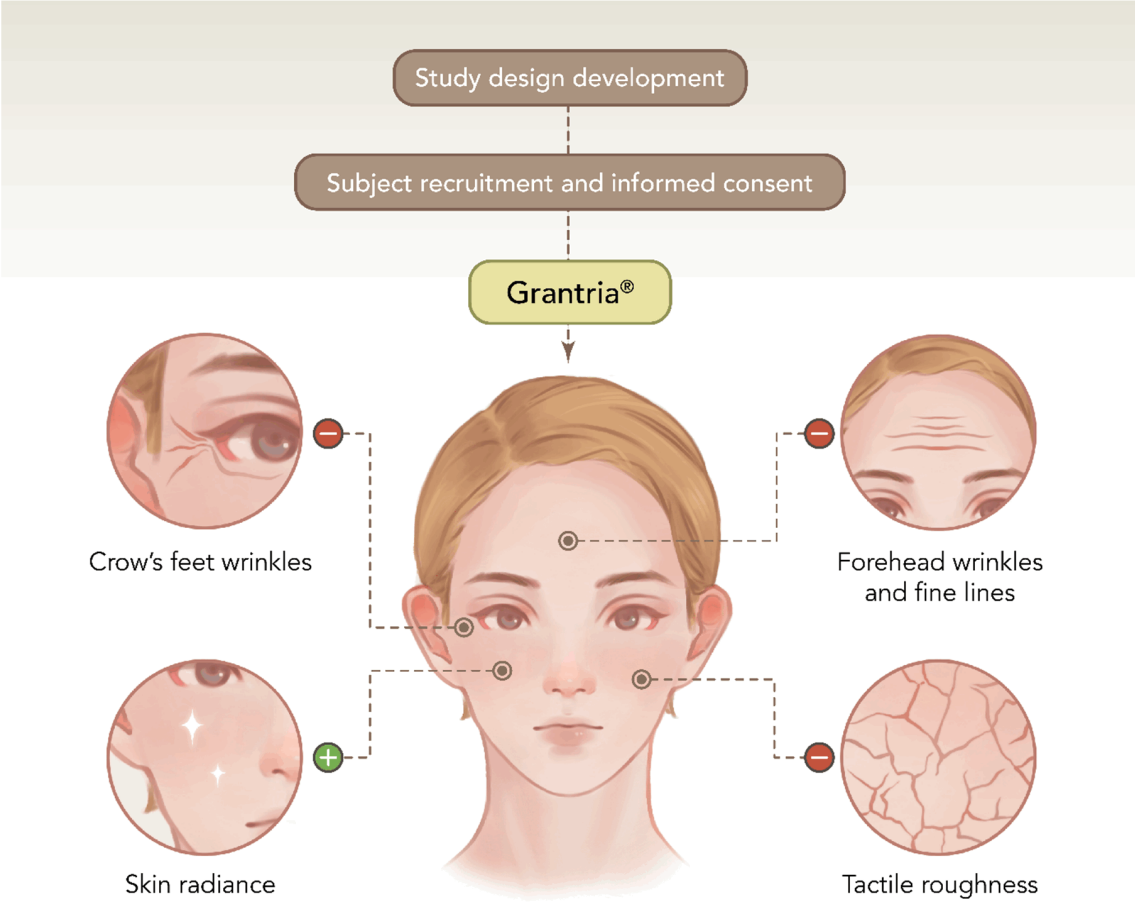

Figure 2. Efficacy of Grantria® in various skin conditions.

original shape. Elasticity depends on the amount and quality of collagen and elastin fibers in the skin. Firmness is the degree of tightness and smoothness of the skin. Firmness is related to elasticity, but also depends on the amount of fat and muscle tissue under the skin. Grantria® significantly ($P<0.001$) reduced pores, spots, UV pigmentation and increased skin tone evenness, elasticity and firmness, as well as skin moisturization compared to the baseline values. However, we did not see any significant effect on wrinkles as assessed using skin topography, skin hydration measured by TEWL (transepidermal water loss) using tewameter and in the tyrosinase levels upon oral supplementation of the test substance, which needs further evaluation.

Grantria® is standardized to ellagic acid, punicic acid and punicalagin as all the three bioactives have been reported to play a critical role in skin health [16, 18, 19]. Oral use of ellagic acid has been reported to protect skin from UV-induced pigmentation in healthy subjects [20]. An ellagic rich pomegranate extract has been reported to accelerate healing of burn wounds in rats [18-20]. Punicalagin was reported to protect DNA from oxidative damage, reduce toxicity to keratinocytes induced by oxidative stress, enhance wound healing rate and promote skin cell adhesion and migration [19]. Pomegranate seed oil containing high amounts of punicic acid has been reported to help maintain the integrity of epidermis [20]. Overall, Grantria® was found to be effective and safe in the current study (**Figure 2**) and in the absence any treatment (i.e., placebo), skin health has deterioration in terms of Crow's feet wrinkles, tactile roughness, forehead fine lines, forehead wrinkles, skin radiance, wrinkles, UV pigmentation and skin tone evenness. A limitation of the study is that the sample size for this study was calculated only based on one primary outcome parameter.

Conclusions

This randomized, double-blind, placebo-controlled clinical study demonstrated the potential of Grantria® as an effective and safe supplement in maintaining healthy, glowing skin in healthy adults and was found beneficial in managing crow's feet wrinkles, tactile roughness, forehead fine lines and forehead wrinkles. The antioxidant, and collagen supporting actions of Grantria®, a proprietary pomegranate extract, along with its protective action against UV-induced skin pigmentation could be a reason for its skin health maintenance properties. The three biologically active constituents, viz. ellagic acid, punicic acid and punicalagins contribute to the effectiveness of Grantria®. In conclusion, Grantria® proves to be a potentially safe and effective plant ingredient which can be formulated into supplements intended for maintaining healthy and glowing skin. Further extension of studies may be carried out to objectively assess the skin health benefits of Grantria®.

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Disclosure of conflict of interest

None.

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