Original Communication

Beauty from within: Oral administration of a sulfur-containing supplement methylsulfonylmethane improves signs of skin ageing

Neelam Muizzuddin[1] and Rodney Benjamin[2]

[1] Skin Clinical Research Consultants
[2] Bergstrom Nutrition

Abstract: *Background*: Methylsulfonylmethane (MSM) is an organosulfur compound with known benefits for joint health, sports nutrition, immune function, and anti-aging formulations and is gaining popularity as a nutritional supplement for the support of hair, skin and nails. *Methods*: The study was conducted in two steps; in Part I (pilot study) a panel of 20 participants ingested either 3 g a day of MSM or placebo capsules for 16 weeks. Visual and subject self assessment of wrinkles and skin texture as the predominant sign of ageing was observed. In Part II (dose-response study), 63 participants ingested either 1 g or 3 g per day of MSM for 16 weeks. Expert clinical grading, instrumental measurements and consumer perception was used to evaluate skin conditions like lines and wrinkles. Additionally, instrumentational analysis was conducted using corneometer and cutometer for investigation of skin hydration, firmness and elasticity. *Results*: Part I of the study clearly indicates that oral ingestion of MSM (3 g/d) reduces signs of ageing like facial wrinkles ($p < 0.05$) and skin roughness ($p < 0.05$) as compared to placebo. Detailed analysis in Part II instrumentation assessments showed a significant ($p < 0.05$) improvement from baseline in the severity of facial wrinkles, as well as improved skin firmness, elasticity and hydration with MSM. Some of these parameters exhibited a good dose-response indicating that the higher (3 g/d) of the supplement was more effective than the lower dose of 1 g/d, but generally the lower dose of 1 g/d appeared to be sufficiently effective in reducing the facial signs of ageing. *Conclusion*: This study indicated that MSM is effective in reducing visual signs of skin ageing even at a low dose of 1 g/d.

Keywords: MSM; methylsulfonylmethane, wrinkles, skin, ageing, firmness elasticity, hydration

Introduction

Health and a youthful, glowing, healthy appearance is a common desire of the ageing population and is reflected in the billions of dollars spent each year on vitamins, minerals, botanical extracts, and antioxidants in an effort to maintain a youthful appearance of the skin and promote overall well-being. The concept of health and wellness offers a composite of several specialty categories with an emphasis on prevention and maintenance rather than on therapy. This concept of beauty "inside-out" approach using nutrition and nutraceuticals to support skin function is gaining popularity [1]. Nutricosmetics refer to innovative ingestible products that are marketed specifically for beauty benefits [1]. Products that address "beauty from within" provide endogenous support to reduce the effects and manifestations of aging. These products currently include antioxidants like polyphenols, phytonutrients, and vitamins C and E, as well as structural components like hydrolyzed collagen and hyaluronan, bioactive peptides, oligosaccharides, plant polyphenols, carotenoids, and polyunsaturated fatty acids. [2, 3]. Supplementation with these products has shown evidence of changing signs of ageing like dermal wrinkles as well as protection from UV radiation ageing in several human trials [2, 4].

Methylsulfonylmethane (MSM) is a natural constituent of the environment available in a variety of foods, including milk, grains, fruits, and vegetables [5]. It is a normal oxidation product of dimethyl sulfoxide (DMSO) and may be part of the natural global sulfur cycle, so it may provide a source of sulfur for essential animal methionine [6].

Sulfur is the third most abundant mineral element in the body derived almost exclusively from proteins. Only two amino acids; methionine and cystein contains sulfur. Methionine, cannot be synthesized in the body and therefore has to be supplied by the diet. On the other hand cysteine, is synthesized by the human body, but the process

requires a steady supply of sulfur. MSM represents an organic form of sulfur [5] which plays an important role in many body organs and systems. Plants concentrate MSM available in the soil and from the atmosphere, from where it becomes available in many foods. It has long been associated with skin health because of its fundamental role in physiological processes, including the synthesis of collagen, hyaluronic acid, and keratohyalin – the most abundant matrix molecules in the skin [8–10].

Sulfur amino acids contribute substantially to the maintenance and integrity of the cellular systems by influencing cellular redox state and the capacity to detoxify toxic compounds, free radicals and reactive oxygen species [11]. Any dietary excess is readily oxidized to sulfate, excreted in the urine (or reabsorbed depending on dietary levels) or stored in the form of glutathione (GSH). There is evidence that MSM sulfur can be incorporated into the sulfur-containing amino acids methionine and cysteine to provide a source of dietary sulfur and MSM may affect the compartmentalization and metabolism of sulfur [6].

MSM is known to be a beneficial nutrient and a therapeutic substance for the treatment of acne, arthritis, muscle pain, weak nails, dry or rough skin, and other ailments. In addition, a variety of health-specific outcome measures have been demonstrated to improve with MSM supplementation, including inflammation, joint/muscle pain, oxidative stress, and antioxidant capacity [12–16]. It has become a popular dietary supplement as an antioxidant and anti-inflammatory agent. When administered orally it is rapidly absorbed, well distributed, and efficiently excreted from the body [5, 17]. Oral supplementation with MSM has been shown to influence skin on a genetic level, by regulating a select number of genes responsible for inflammation, skin barrier, and moisturization, as well as those genes involved in the structural integrity of the skin which are associated with the aging process [18]. MSM is *Generally Recognized As Safe* (GRAS) approved substance. It is well-tolerated by most individuals at dosages of up to four grams daily, with few known and mild side effects [16] and has been reported to be non-toxic [5, 19].

Hormonal imbalance, inflammation, smoking, exposure to UV radiation, and environmental stressors contribute to the aging of the skin by production of reactive oxygen species (ROS) that can potentially damage cell membranes, proteins, and DNA. Free radicals are composed of oxygen molecules with an unpaired electron and are induced by several exogenous and endogenous factors, including UV exposure, pollution, stress, smoking and normal metabolic processes. Studies show that free radicals induce alterations in gene expression pathways, which in turn contribute to the degradation of collagen and the accumulation of elastin emblematic of photo-aged skin [20, 21]. MSM supports the body's natural antioxidant pathways through increased levels of glutathione, superoxide dismutase, and catalase [22].

This overload of oxidative stress and a production of free radicals can eventually break down connective tissues and collagen, and release chemicals that lead to cellular and molecular events that are evident as signs of aging, such as the formation of wrinkles, uneven skin tone, dyspigmentation, inflammation, immunosuppression, photoaging, photocarcinogenesis, and sagging skin. Nutricosmetics provide nutritional antioxidant supplementation to support endogenous antioxidant enzymes that may help to internally regulate oxidative stress and help to achieve a healthier skin appearance from the inside out. [1] Among the ingredients used in nutricosmetics, antioxidants represent the most crucial. The best-known antioxidants are carotenoids (beta-carotene, lycopene, lutein, zeaxanthin, and astaxanthin) and polyphenols (anthocyanidins, catechins, flavonoids, tannins, and procyanidins) [2].

Inflammation is a known contributor to the degradation of collagen, elastin and hyaluronic acid; thus, reducing inflammation is another integral approach to preventing wrinkle formation. Anti-oxidants and free radical scavengers protect the skin via reducing skin inflammation by directly acting on cytokine and growth factor receptors in dermal cells and keratinocytes [23–27]. Interventions that suppress, prevent, or alter the dynamics of chronic inflammation hold great promise for treating or preventing multiple age-related pathologies.

The anti-inflammatory properties of MSM have great potential in supporting skin health by reduction of damage through inflammatory cascades. Studies have indicated that MSM can reduce the production of interleukin (IL)-1, IL-6, tumor necrosis factor-α (TNF-α), nitric oxide (NO), prostaglandin E2 (PGE2), and nuclear factor (NF)-κB [28–31]. Since MSM can inhibit NF-κB transcriptional activity, it reduces the expression of enzymes and cytokines involved in ROS production. Downregulation of COX-2 and iNOS reduces the amount of superoxide radical ($O2^-$) and nitric oxide (NO), respectively [29].

Previous studies have clearly indicated that 16 weeks of oral administration of 3 g/d MSM is highly effective in reducing fines lines and wrinkles and improvement of the appearance and condition of the skin [18]. This study was designed to determine if it was effective at a lower dose and the most efficacious dosage of this nutrient in improving skin quality.

Methods

The study was conducted in two steps, Part I and then Part II.

Part I: Pilot study

Oral product #1 OptiMSM 1 g: 1 g hydroxypropyl methylcellulose (HPMC) capsules with 1000 mg of 100% Methylsulfonylmethane. The participants consumed three 1000 mg capsules a day. Oral Product #2 Placebo: HPMC capsules with 875 mg rice flour; (filled to volume to resemble MSM capsules).

A total of 20 participants completed the study, 11 using OptiMSM and 9 using Placebo. The participants were instructed to take 3 g of capsules in the morning with or without food.

This was a 4 month, double blinded (the participants and evaluators were unaware of the identity of the samples), in use study. Measurements were obtained before treatment and after 8 and 16 weeks of use. At each time point the following measurements were obtained:

- Expert Visual grading using a 1–10 cm scale where 1 was none and 10 was extreme for the appearance of lines/ wrinkles (crows feet), texture/smoothness (visual),
- Subject self assessment via questionnaire with approval rating scale of: 1-strongly agree, 2- agree, 3 neither agree nor disagree, 4 disagree and 5 strongly disagree. The numbers were expected to come down with improvement.

The participants were instructed to refrain from using any facial treatments and procedures such as Botox® and fillers during the study period. They continued using their favorite facial products and color-cosmetics but were instructed not to change products during the course of the study. Participants who used nutritional supplementation regularly (within the last 2 weeks) were excluded. The participants were not participating in any other clinical studies involving the face.

The participants were all females between ages of 35 to 59 years old Fitzpatrick Skin Type I-IV with lines and wrinkles in crows feet region and significant loss of facial skin firmness and elasticity.

The participants were healthy with no acute or chronic disease or medical condition, including dermatological problems, which could put them at risk in the opinion of the Principal Investigator or compromise study outcomes. They exhibited the ability to read, understand and sign an informed consent form (including HIPAA and State requirements). They were willing and able to co-operate and follow all study directions, attend study visits as scheduled and willing to accept the restrictions of the study.

Participants with a history of allergic reactions, skin sensitization and/or known allergies to cosmetic ingredients, toiletries, sunscreens, etc. as well as those who were immunocompromised, on Hormone Replacement Therapy or oral contraception for less than three months before the screening visit were excluded as were pregnant and lactating women. Employees of testing lab or other testing firms/ laboratories, cosmetic or raw goods manufacturers or suppliers were not included in the subject panel.

The study was conducted in accordance with FDA GCP regulations and ICH guidelines in as much as they apply to cosmetic research. The study was overseen by Allendale Institutional Review Board to ensure the protection of the rights, safety, and well-being of participants.

Part II: dose-response study

After a thorough study of data from Part I a more comprehensive study was designed to determine if a lower concentration of MSM was effective in improving skin. The same subject instructions as well as inclusion and exclusion criteria were employed in this part of the study. The test product was used as follows:

Group A: Oral Product #1 (OptiMSM®)-3 g HPMC capsules with 1000 mg of 100% Methylsulfonylmethane. The participants consumed three 1000 mg capsules a day.

Group B: Oral Product #2 (OptiMSM®)-1 g HPMC capsules with 1000 mg of 100% Methylsulfonylmethane. The participants consumed one 1000 mg capsule a day.

A total of 63 participants completed the study. The panel was divided into two groups of 31–32 each. Group A received 3 grams a day (g/d) of the test material and Group B consumed 1gram a day. The participants were instructed to take the capsules in the morning with or without food.

This was a 4 month, in use study. Measurements were obtained before treatment and every month for the course of the study. At each time point the following measurements were obtained:

- Expert Visual grading using a 1–10 cm scale where 1 was none and 10 was extreme for the appearance of lines/wrinkles (crows feet), texture/smoothness (visual), radiance/luminosity, firmness and elasticity (tactile) at Weeks 4, 8, 12 and 16.
- Skin elasticity using a Cutometer (Courage and Khazaka, Cologne, Germany).
- Skin moisturization using a Corneometer (Courage and Khazaka, Cologne, Germany).
- Photographs were obtained using a 2D Clarity pro (BrighTex Bio-Photonics, San Jose California, USA) followed by analysis of wrinkles in the crows feet area. Data for the 8-week time point is missing due to instrument malfunction.
- Subject self assessment via questionnaire.

The study was overseen by Allendale Institutional Review Board to ensure the protection of the rights, safety

and well-being of participants (Part I-IRSI 3778BN0114 and Part II-IRSI 4194BN0118).

Statistics

Data was normalized so all measurements started at the same baseline using "if" formula. Students t test was used as a statistical indicator of significance. T test was conducted for all time points vs baseline (before use). Microsoft excel datasheet statistical software was used for all statistical analysis including data distribution (summary statistics) and equality of variance.

Results

Part I: Pilot study

Figure 1 illustrates the average effect of oral treatment of MSM on facial lines and wrinkles. Visual grading of facial lines and wrinkles by an expert clearly shows a significant reduction with use of the oral supplement (Figure 1A). The placebo group also appears to show a slight improvement, but the difference was not statistically significant. Subject self assessment (Figure 1B) indicates that on average the participants noticed a significant reduction in their facial lines and wrinkles after using the MSM product, but a very slight change by the participants who used the placebo.

Figure 1C showing the expert grading of skin texture indicates a steady and significant reduction in skin roughness with product use of MSM as well as placebo ($p < 0.001$). However, subject approval (Figure 1D) clearly indicates that the participants on MSM noticed a much more significant ($p < 0.05$) improvement in skin texture as compared to the group on placebo.

Part II: Dose-response study

Figure 2 demonstrates the average effect of oral treatment of MSM on facial lines and wrinkles. Visual grading of facial lines and wrinkles by an expert, shows that lines and wrinkles reduced with use of the oral supplement and the decline continued over the course of the study (Figure 2A). The higher concentration of the supplement was consistently more effective having statistically significant reduction in lines and wrinkles after 16 weeks of use. Subject self assessment (Figure 2B indicates that twelve participants on 3 g/d of MSM agreed that their lines and wrinkles improved after 4 weeks of use and by 16 weeks nineteen participants out of 31 approved. The participants on the lower concentration of the supplement also agreed that their lines and wrinkles reduced with product use with 13/32 approvals at the

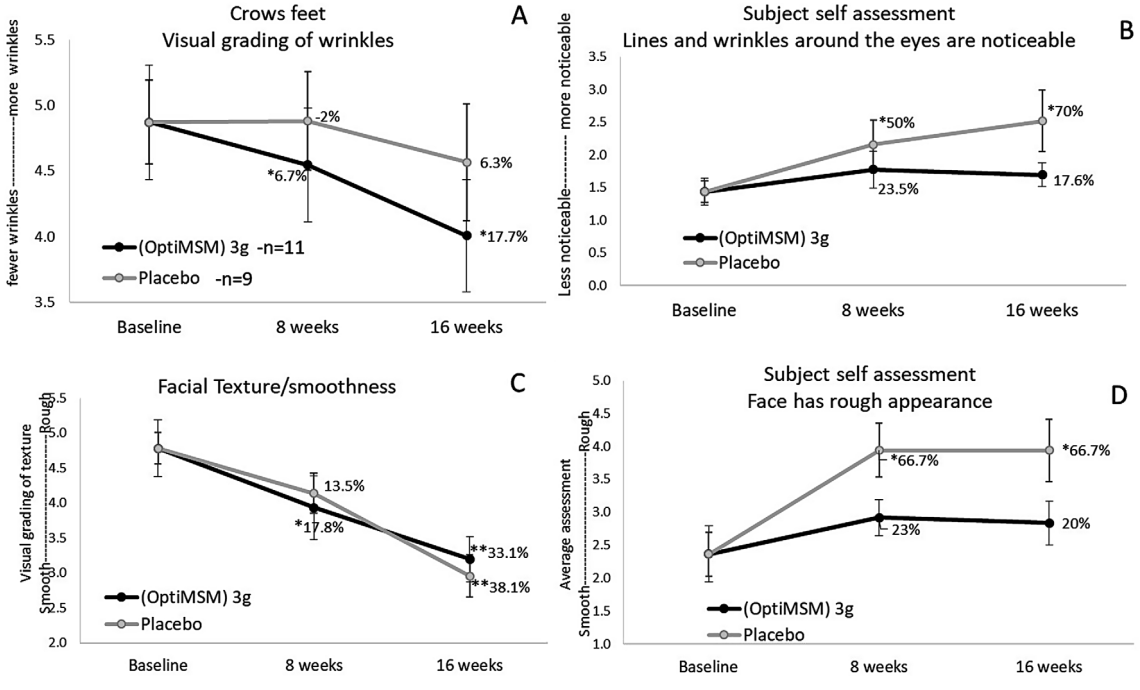

Figure 1. Study part I: facial lines and wrinkles and facial skin texture. Error bars represent standard error of mean. A: there was a clear and consistent reduction in facial lines and wrinkles after MSM use (n = 11) and only a slight change with the placebo (n = 9). Statistical significance * is *p* value of < 0.05 and ** is < 0.001. B: Subject self assessment of wrinkles. C: Visual grading of skin texture with use of MSM and placebo. D: subject approval of skin texture.

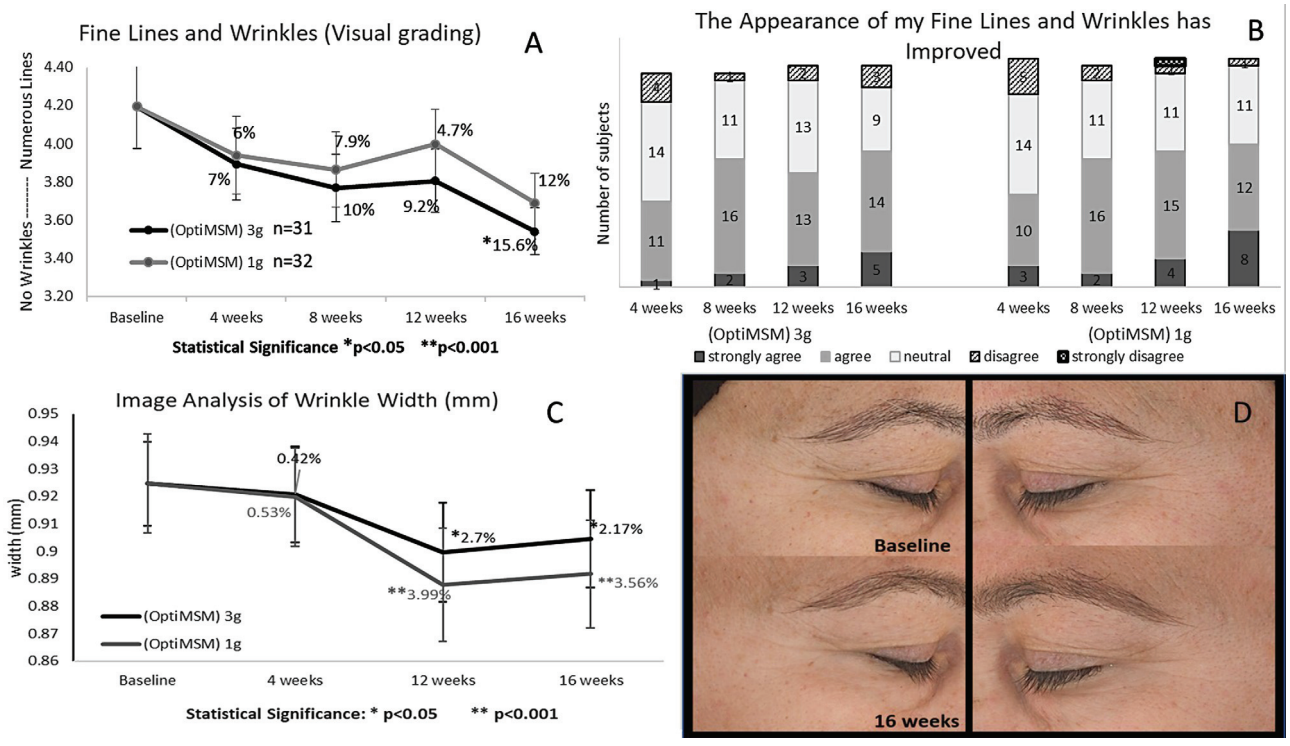

Figure 2. Study part II: facial lines and wrinkles. Error bars represent standard error of mean. A: visual grading of facial lines and wrinkles. B: subject self assessment and C: image analysis of photographs. D: Photographic example of a subject on the lower concentration of 1 g/d of the supplement clearly shows a softening of the crows feet area.

4 week time point that increased to twenty out of 32 after 16 weeks of use.

Image analysis of photographs in Figure 2C clearly indicate a statistically significant ($p < 0.05$) reduction in skin wrinkle width after 12–16 weeks of using the high concentration of 3 g/d of the oral MSM supplement. However, the lower concentration of the product appeared to exert an even higher effect ($p < 0.001$). An example of the wrinkle reduction of 1 g/d of the oral supplement is clearly observable in the photograph (Figure 2D).

Figure 3A showing the expert grading of skin texture clearly indicates a steady and significant reduction in skin roughness with product use ($p < 0.001$). Both doses of the supplement appeared to be equally effective. Subject approval (Figure 3B) appears to correlate with the visual grading of skin texture. Out of 31 participants on the high dose of 3 g/d, twenty-two showed approval as early as after 4 weeks of use. The group on the lower concentration also showed a high subject approval with twenty-two participants out of 32 in agreement that their skin texture improved as early as after 4 weeks of use.

Facial skin Radiance and Luminosity (Figure 4A and B) also significantly improved ($p < 0.05$) after 4 weeks of use and continued to improve for both groups for the course of the study with a highly significant improvement after 16 weeks of use ($p < 0.001$). Out of 31 participants on the 3gram supplement, fourteen agreed on an improvement after 4 weeks which increased to twenty-two after 16 weeks. Out of 32 participants that used 1 g/d of the supplement, seventeen agreed on an improvement after 4 weeks and twenty-six after 16 weeks.

Skin firmness and elasticity as measured with expert grading, instrumental measurement and subject self assessment is reported in Figure 5. Skin firmness clearly improved after product use (Figure 5A). Both doses of the product appeared to be equally effective, initially, however at the 16-week time point the lower concentration of the supplement appeared to be slightly more effective ($p < 0.001$) as compared to the higher concentration of 3 g/d ($p < 0.05$). Cutometer measurement of R0 (Uf) looks at the maximum amplitude of distended skin and represents the passive behavior of the skin to force (firmness). Figure 5B clearly exhibits no significant change in this parameter with product use. Nevertheless, subject self assessment (Figure 5C) indicates that twenty-one participants out of 31 agreed that their facial skin was firmer with the higher dose of the supplement as early as after 4 weeks of use. Fourteen participants on 1 g/d of MSM noticed an improvement in skin firmness after 4 weeks of use and this increased to twenty after 16 weeks of use.

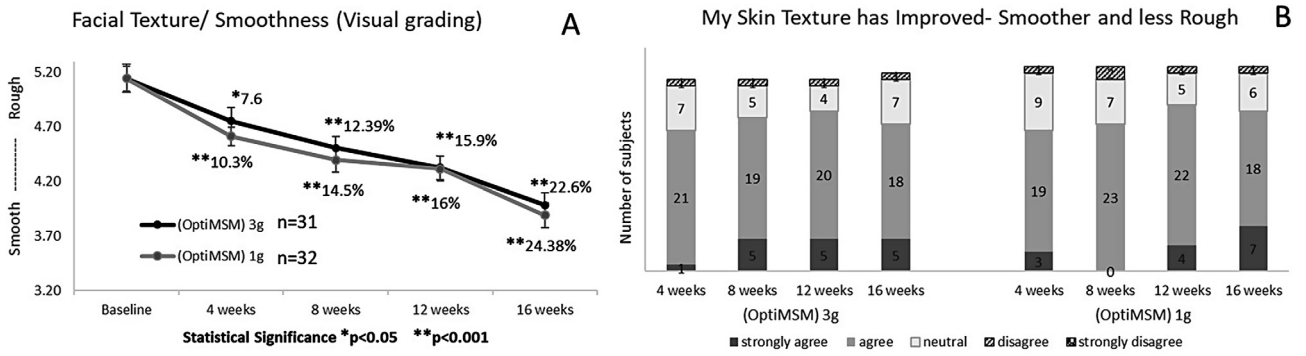

Figure 3. Study part II: n = 32 for 1 g MSM and n = 31 for 3 g MSM daily dose. A: Skin texture. Error bars represent standard error of mean. B: Subject self assessment. Most participants observed an improvement in skin texture with use.

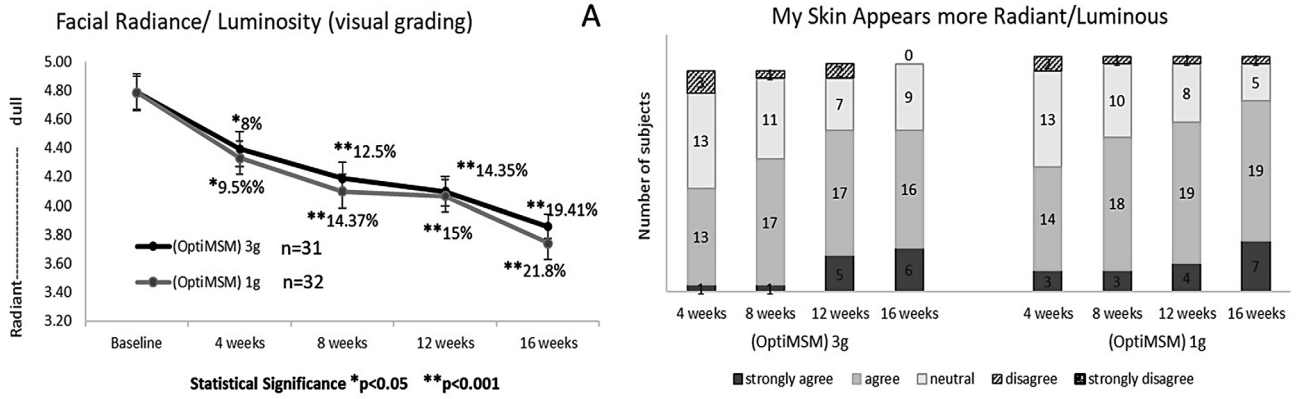

Figure 4. Study part II. n = 32 for 1 g MSM and n = 31 for 3 g MSM daily dose. A: Visual grading of facial Radiance and Luminosity. Error bars represent standard error of mean. Both treatments appeared to be equally effective. B: Subject self assessment. Most participants observed an improvement in skin radiance with use.

Expert grading of skin elasticity also indicated that both doses of the product were equally effective, initially, while the lower concentration of the supplement was slightly more effective (Figure 5D). Instrumental measurement of R5 (Ur/Ue) is net elasticity which is elastic portion of the suction part versus the elastic portion of the relaxation part (Figure 5E). This parameter clearly improved with product use for both groups. Subject self assessment of skin elasticity (Figure 5F) indicated that seventeen participants out of 31 agreed that their facial skin was more elastic with the higher dose of the supplement as early as after 4 weeks of use and this increased to twenty-one after 16 weeks of use. Sixteen participants on 1 g/d of MSM noticed an improvement in skin elasticity after 4 weeks of use and this increased to twenty-one after 16 weeks of use.

Skin hydration was measured with a Corneometer as well as self-assessed by the participants (Figure 6). Figure 6A clearly exhibits that the 3 g/d dose of MSM increased skin hydration ($p < 0.05$) within 4 weeks after which it increased some more after 8 weeks ($p < 0.001$) and then plateaued for the course of the study. The lower dose of 1 g/d MSM was slightly slower to hydrate skin, but the improvement continued for 12 weeks after which it plateaued. Subject self assessment (Figure 5B) indicates that twenty-two out of 31 participants agreed that the 3 g/d dose of MSM improved their skin hydration within 4 weeks of use, and this increased to twenty-six after 16 weeks of use. Twenty three out of 32 participants agreed that 1 g/d treatment was effective in hydrating their skin and this increased to twenty-six after 16 weeks of use.

Discussion

Youthful appearance is a serious desire of the ageing population. The passage of time is reflected in the appearance of facial lines and wrinkles; by a slackening of tissue; a loss of skin elasticity; a dry/leathery appearance; uneven skin

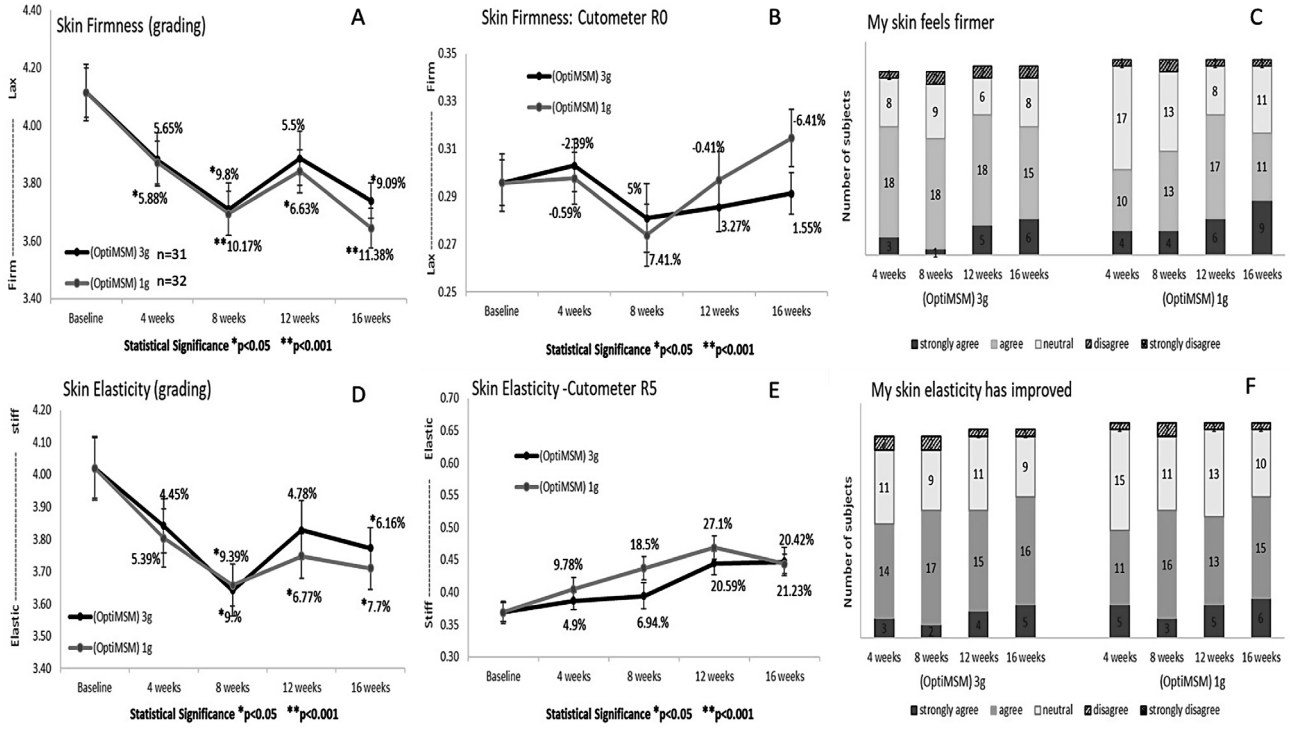

Figure 5. Study part II: n = 32 for 1 g MSM and n = 31 for 3 g MSM daily dose. Error bars represent standard error of mean. A: Visual grading of facial skin firmness and elasticity. B: Cutometer measurements. C: Subject self assessment. D: subject grading of facial skin elasticity. E: Cutometer measurements. F: Subject self assessment.

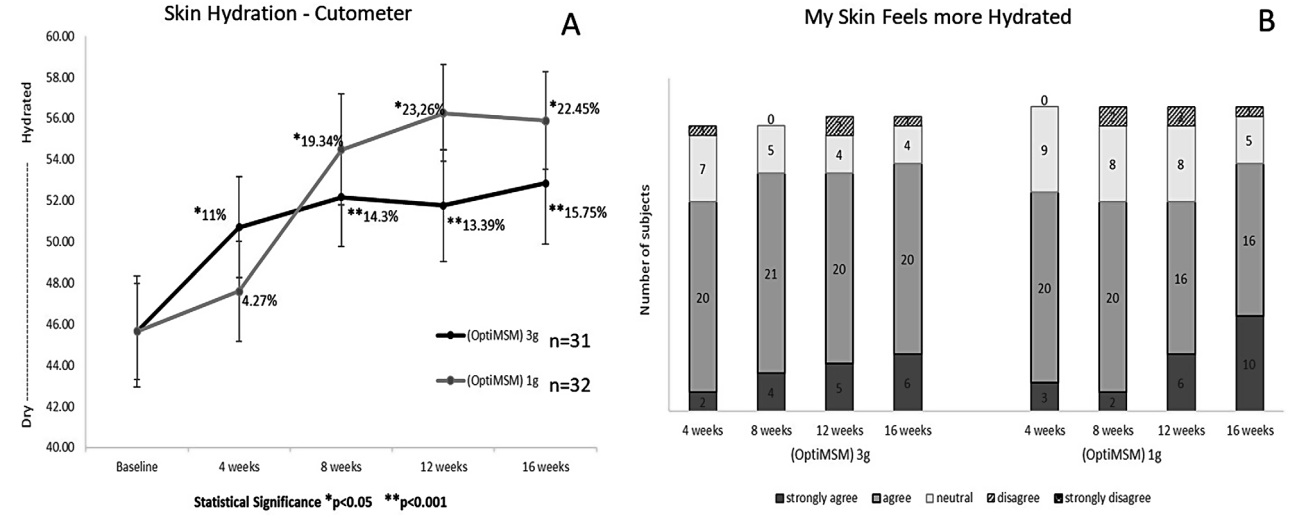

Figure 6. Study part II. n = 32 for 1 g MSM and n = 31 for 3 g MSM daily dose. Error bars represent standard error of mean. A: Visual grading of skin moisturization. B: Subject self assessment.

pigmentation and a general dullness. At the histological level, skin damage from photoaging is shown in tangled, thickened, abnormal elastic fibers and decreased collagen. The aging process also results in thinning and deterioration of the skin. There is a reduction in cells and in blood supply, and a flattening in the junction between the dermis and epidermis [32–34].

Treatments designed to prolong or promote youthful appearance include various nutraceuticals and dietary supplements. Oral treatments that address all the challenges of ageing skin skin can be unsuccessful due to their constituents being broken down by acid and enzymes in the gut; nevertheless several studies have shown positive effects of anti-oxidants [35], vitamins [36] and even

hydrolyzed collagen [37, 38] which is absorbed in the gut and then delivered to skin and joints through the blood stream. The current study demonstrated the effect of MSM on visible signs of skin ageing. Since facial wrinkles and rough texture are the most significant signs of chronological as well as actinic ageing, the pilot study addressed these signs to determine if oral use of MSM could change them versus placebo pills. Results of part I of this study are consistent with reports of significant improvement in skin appearance and condition after MSM treatment [18].

Part II further demonstrated that oral supplementation with MSM resulted in significant improvements in skin's appearance and condition as evaluated by expert grading, instrumental measures, and participant self assessment. This study indicated that the lower dose of 1 g/d appeared to be sufficient in reducing the facial signs of ageing.

Although the exact mechanism of action is not well understood, studies have indicated that MSM could be involved in altering gene expression of key genes that affect moisturization and barrier function, extracellular matrix production, and inflammation control [18]. Inflammation, oxidation, and gene expression in skin cells are highly interconnected, and it has been demonstrated that MSM has a positive effect on all three [31, 39]. Human aging is characterized by a chronic, low-grade inflammation, and this phenomenon has been termed as "inflammaging", thus management of low-level inflammation can help reduce the signs of ageing and it is possible that the reduction of signs of ageing in this study was partially due to the anti-inflammatory effect of this supplement. MSM has become a popular dietary supplement as an anti-oxidant and anti-inflammatory agent. It is known to inhibit activation of pro-inflammatory mediators through downregulation of NF-κB and decreasing the expression of TNF-α, and IL-6 [29, 40] as well as selective inhibition of NLRP3 inflammasome activation [41]. The anti-ageing effect of MSM could be due to its anti-inflammatory action.

MSM is also known for its effect on modulation of oxidative stress and antioxidant defense [22, 42, 43]. Hormonal imbalance, inflammation, smoking, exposure to UV radiation, and environmental stressors contribute to the aging of the skin by production of ROS that can potentially damage cell membranes, proteins, and DNA [5, 7, 17, 44, 45].

The process of aging is most often associated with its visible effects on the skin. The skin mirrors the aging process both physiologically and socially [46]. Endogenous factors like genetics, inflammation, hormone levels, and lack of proper nutrition as well as exogenous factors like increased exposure to ultraviolet (UV) radiation, environmental pollutants, and ROS play a significant part in enhancing the visible signs of ageing [47] including wrinkles, mottled pigmentation and loss of firmness and elasticity [48]. These perceptible symptoms can be easily determined through visual examination. Subject self-perception, and via the use of laboratory instruments. The strength of the present study was the assessment of skin health utilizing all three permutations. Expert grading indicated improvements in several markers, especially for the presence of crows feet. Participant self assessment questionnaires indicated overall satisfaction with skin health in both groups. Instrumentation assessments showed a significant improvement from baseline in the severity of facial wrinkles, as well as improved skin firmness, elasticity and hydration. Some of these parameters exhibited a good dose response indicating that the higher (3 g/d) of the supplement was more effective than the lower dose of 1 g/d, but generally the lower dose of 1 g/d appeared to be sufficiently effective in reducing the facial signs of ageing.

The studies reported were well designed to observe the effect of MSM supplementation on skin using a three aspects of assessment i.e. instrumental measurements, expert grading as well as subject self assessment. This multi prong approach imparted strength and validity to the data presented in this manuscript. Although this study exhibited a good indication of the effect of MSM on reducing signs of ageing, the results do not explain the mechanism of action. Additional controlled studies are warranted to further validate efficacy and hypothesized mechanisms of action.

Based on the confines and conditions of this study oral supplementation with MSM resulted in significant improvements in skin's appearance and condition as evaluated by expert grading, instrumental measures, and participant self assessment. The results of this study suggest that MSM taken orally may be beneficial for skin health and the reduction of fine lines and wrinkles, at a dose as low as 1 grams a day.

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Conflict of interest
Mr. Benjamin reports personal fees from Bergstrom Nutrition – Study Sponsor, outside the submitted work. In addition, Benjamin has a patent, US Patent No. 8,217,085 and its foreign counterparts licensed to Biogenic Innovations, a patent, US Patent No. 8,546,373 licensed to Biogenic Innovations, and a patent, US Patent 8,841,100 and its foreign counterparts licensed to Biogenic Innovations. Ms Muizzuddin reports personal fees from Bergstrom Nutrition, for assisting in the drafting of this manuscript.

Ethical approval
The study was approved by IRB.

ORCID
Rodney L. Benjamin
https://orcid.org/0000-0002-7190-6788

Rodney L. Benjamin
Bergstrom Nutrition
1000 West 8th Street
Vancouver, Washington 98660
USA
rbenjamin@bergstromnutrition.com