OPEN ACCESS Freely available online

Journal of Clinical & Experimental Dermatology Research

Research Article

Prospective Randomized, Double-Blind Study to Evaluate Dietary Supplements for Impacts on Skin Appearance in Healthy Women

Paula Simpson, Rodney Benjamin*

Department of Research and Development, Bergstrom Nutrition, Vancouver, WA 98660, USA

ABSTRACT

Objective: Data suggests both Methylsulfonylmethane (MSM) and high dosage Hydrolized Fish Collagen (HFC) independently support skin health and reduce visible signs of aging. The goal of this study was to determine if MSM combined with HFC has benefits for skin health and if the combination acts synergistically to facilitate lower dosages of HFC and provide superior results to MSM alone.

Design and patients: A total of 58 females aged 41-65 participated in this double-blind placebo controlled study. They were randomly assigned to one of three groups; placebo, 1000 mg of MSM/day or combo 1000 mg+2500 mg of HFC/day. Efficacy was determined using instrumentation, expert (dermatologist) evaluation and subject self-assessment.

Results: Instrumental analysis showed near equal improvement in wrinkle reduction by Clarity Pro-3d evaluation by both the MSM and combination groups from baseline however, statistically significant improvement in elasticity as measured by cutometer (p=0.0097) was reached only in the combination group.

Conclusion: While both MSM and HFC reduce visible signs of aging, the combination of these two ingredients support lower dosing of HFC and may provide superior results to MSM alone.

Keywords: Methylsulfonylmethane (MSM); High dosage; Hydrolized Fish Collagen (HFC); Skin health; Photoaging; Extracellular Matrix (ECM); Collagen; Sulfur

INTRODUCTION

It can be said that skin is a direct reflection of what is going on inside the body and influenced by the diet and lifestyle one leads [1]. Skin is the largest organ of the body. As the primary organ and defense against the external environment, skin is a highly exposed organ to ultraviolet rays, chemical stressors and pollutants that may impair its natural biochemical homeostasis and physiological structure and function. Overtime, this chronic stress overloads skin physiology and accelerates the skin aging process [1,2].

In the effort to halt or slow aging, consumers often turn to interventions that may include cosmetic dermatology, over-the-counter products and dietary supplements. It has been estimated that in 2017, sales of products and services in this category hit $5.16 billion dollars [3]. According to Nielson, in 2018, Americans spent $12 billion dollars on beauty and personal care products, with hair, skin, and nails falling under this category [4].

Over the last two decades, there has been interest in research to determine the impact that diet and/or nutraceutical use may have on skin health and appearance. Alongside diet, targeted vitamins and minerals, antioxidants, phytonutrients, ceramides, collagen peptides and MSM are some ingredients used and studied within nutricosmetic research. Due to increasing consumer awareness and interest in nutritional influences on skin health, clinical research continues to broaden and advance their understanding on the systemic impact that nutrition and

Correspondence to: Rodney Benjamin, Department of Research and Development, Bergstrom Nutrition, Vancouver, WA 98660, USA, Email: RBenjamin@bergstromnutrition.com

Received: 31-Oct-2022, Manuscript No. JCEDR-22-19905; **Editor assigned:** 3-Nov-2022, PreQC No. JCEDR-22-19905 (PQ); **Reviewed:** 17-Nov-2022, QC No. JCEDR-22-19905; **Revised:** 24-Nov-2022, Manuscript No. JCEDR-22-19905 (R); **Published:** 01-Dec-2022, DOI: 10.35248/2155-9554.22.13.622

Citation: Simpson P, Benjamin R (2022) Prospective Randomized, Double-Blind Study to Evaluate Dietary Supplements for Impacts on Skin Appearance in Healthy Women. J Clin Exp Dermatol Res. 13:622.

supplementation can have on skin and appearance [2].

Though there are multiple signs of photoaged skin, wrinkles are perhaps the most tangible. Wrinkles are formed when there is a weakening of the Extracellular Matrix (ECM) within the dermis due to a breakdown of collagen rich connective tissue. Through this weakening, skin connective tissue thins and becomes more susceptible to stressors that may further degrade skin homeostasis [5]. The structural integrity of skin is dependent upon the Extracellular Matrix (ECM) of connective tissue. Composition and structure of the ECM vary considerably in the different types of connective tissues and result in distinctive functional and biological characteristics. ECM is formed by diverse protein families involved in several physiological functions. Collagen is one of the most recognized of these proteins. Type I collagen is the most abundant in human skin (80%) with type III collagen making up the remainder of skin collagen (15%). The collagen in the skin is mainly produced by fibroblasts, connective tissue cells in the dermis which are responsible for producing and organizing the collagen matrix [6]. It was originally believed that collagen supplementation directly improved skin health. However, it has been found that oral supplemented hydrolyzed collagen peptides have indirect mechanisms related to skin health once they reach the dermis. Three different indirect mechanisms have been suggested: (a) Collagen fragments can be a precursor for collagen synthesis in the skin; (b) Collagen fragments can stimulate collagen and proteoglycans production in the skin; and (c) Collagen and its fragments can increase skin turnover by induction of regulatory T cells (Tregs) and M2 macrophages [7]. As the physiological mechanism of ingested collagen peptides has become better defined, new interest in studies of additive ingredients in combination with collagen have emerged.

Despite the growing interest in multi ingredient formulations for skin health, there are only a small number of human clinical studies looking at the combined effect of collagen supplementation and other potential skin health ingredients, such as plant and marine derived antioxidants [8-10]. In a 12-week human clinical study, 2 mg/day of carotenoid antioxidant astaxanthin, along with 3 g/day of collagen hydrolysate significantly improved elasticity and barrier integrity in photoaged human facial skin after daily supplementation. The researchers concluded that the combination had additive effects for preventing or reversing the skin aging process through different mechanisms of action [10]. Although combination formulas have shown enhanced efficacy, to date, there are no studies reporting the synergistic and complementary actives within the ECM, such as hydrolyzed collagen peptides alongside MSM for skin health and appearance.

Methylsulfonylmethane (MSM) is an organosulfur found in a variety of foods including milk, grains, fruits, and vegetables in minimal amounts [11]. Earlier MSM research indicates it may be effective as a nutri-cosmetic by providing a bioavailable source of organic sulfur, reducing inflammation, and supporting the body's intrinsic antioxidant pathways. Sulfur 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 [12]. It is proposed that Methylsulfonylmethane, as a sulfur donor may increase disulfide bonding within proteins of ligaments and connective tissue, reinforcing the structural integrity and encouraging collagen production [13]. Collagen supplements have shown promise in improving the appearance of photoaged skin. However, there are concerns regarding the environmental impact and disease risk of the commonly used bovine and porcine sources. Therefore, collagen derived from fish has emerged as an alternative source of collagen because it has a lower environmental impact and risk of disease transmission. Further, marine fish collagen and collagen peptides have a high degree of homology to human structure and bioavailability through the gastrointestinal barrier reference. Studies conducted with marine fish collagen supplementation have shown significant improvements in skin wrinkles, elasticity, and hydration [8]. In a 2021 triple blind, placebo-controlled trial, women (aged 45 yrs-60 yrs) supplementing with 10 g of marine hydrolyzed collagen powder daily for 12 weeks, showed improvements in quantitative wrinkle scores and hydration, along with qualitative/self-reported improvements in elasticity, hydration, radiance, firmness and the appearance of fine lines and wrinkles. The researchers also concluded the supplement was safe and well tolerated by participants and suggested further studies are warranted to examine the synergistic effects of collagen supplementation along with other skin enhancing nutrients to advance the understanding and mechanism of action of nutricosmetic influences on skin health [14].

MSM and hydrolyzed fish collagen are two independent nutritionally supplemented ingredients each with clinical validation to promote healthy skin [15,16]. Although each has shown efficacy in reducing wrinkles, promoting elasticity, hydration and improving skin texture, MSM and HFC provide skin targeted benefits through different mechanisms. HFC improves skin health by providing the amino acid building blocks for collagen production, fulfilling specific nutritive needs for collagen synthesis, and stimulating the production of both collagen and Hyaluronic Acid (HA) [6]. Although MSM may slightly increase collagen levels, it primarily works by improving the cross-linking of collagen and elastin. MSM is 34% sulfur by weight, and supplementation increases the pool of sulfur available to the body for biochemical needs, sparing Sulfur-containing Amino Acids (SAAs) from being metabolized as a sulfur source [17]. MSM supports disulfide bonds within ECM proteins. During collagen synthesis, disulfide bonds align strands of pro-collagen, so they conform correctly [18]. An *in vitro* study using an engineered ligament model found that MSM improved the strength of collagen fibers [13]. This was especially true of ligaments subjected to estrogen, which is known to inhibit Lysyl Oxidase (LOX) and decrease collagen fiber strength. LOX is found in all connective tissue, including the dermis and epidermis and functions to cross-link collagen and elastin [19]. MSM appeared to offset the effect of estrogen in this model. The study indicates that MSM improves the cross-linking of collagen, likely through disulfide bonds and protection of LOX [13].

MSM may help to offset both intrinsic and extrinsic photo

damage. Oxidative damage from UV radiation, external toxins, and AGEs along with the subsequent inflammation plays a major role in skin aging. MSM supports the biochemical processes that protect skin cells and the ECM from damage. MSM supplementation is associated with improved antioxidative capacities, with multiple studies showing that MSM increases levels of endogenous antioxidant enzymes glutathione, super oxide dismutase, and catalase, possibly through upregulation of Nrf2 [20,21]. Through inhibition of NF-kB and NLRP3 activation, MSM decreases inflammation that inhibits collagen synthesis and stimulates MMP degradation [22-24]. Additionally, dermal genomic data indicates MSM influences several key genes, including MMPs, important to maintaining healthy, youthful-looking skin [14].

Based on the hypothesis that these two ingredients will work synergistically when taken together (albeit through separate mechanisms,) a nutraceutical combination of MSM and HFC would simultaneously increase the amount of collagen and HA with the ECM through fibroblast stimulation and improve the strength and structure of proteins through crosslinking. Additionally, the antioxidative and anti-inflammatory properties of MSM will protect newly formed ECM proteins from oxidative damage and degradation associated with skin aging.

Study objectives

The study intended to determine how the oral nutritional supplements, MSM and the combination of MSM and Hydrolized Fish Collagen (HFC), impact the characteristics and appearance of facial skin, determine if the combination of MSM and HFC could be efficacious for a lower dosage of collagen than previously reported in literature, and to obtain consumer perception of the materials following six and twelve weeks of supplementation.

MATERIALS AND METHODS

This human clinical study was conducted according to applicable ICH GCP standards by an independent clinical research laboratory (Eurofins CRL Inc, Piscataway, NJ, USA). The product formulas, study protocol, and Informed Consent Form were reviewed and approved by the Institutional Review Board (IntegReview IRB, Austin, TX, USA protocol number CRLNJ2019-0852 BI) before study initiation October, 2020 in accordance with Title 21 CFR Parts 50 and 56.

Study evaluations included Corneometer (Derma Unit SSC 3 Courage+Khazaka box with Courage+Khazaka electronic GmbH MP Corneometer CM825 probe) measurements, Cutometer (Courage+Khazaka Cutometer dual MPA 580 unit with Courage +Khazaka electronic GmbH 2 mm cutometer probe) measurements, dermatologist skin assessments by dually anchored likert scales in fine lines and wrinkles in a variety of areas on the face, BTBP Clarity Research 3D System imaging (BrighTex Bio-Photonics LLC Company Clarity Pro 2D+3D Research System) and analysis, DermaScan ultrasound (Cortex technology dermascan C USB Unit with dermascan 2D Probe), and likert scale outcome subject questionnaires.

A total of fifty-eight subjects were randomized and divided as follows: Group A (N=19) received a placebo, Group B (N=17) received 1000 mg of methylsulfonylmethane (OptiMSM® bergstrom nutrition, vancouver, WA USA), and Group C (N=22) received both 1000 mg of methylsulfonylmethane (OptiMSM® Bergstrom Nutrition, Vancouver, WA USA) and 2500 mg of Hydrolyzed Marine Collagen peptides (FCP) Ajinomoto Health and Nutrition North America Inc. Itasca, IL, USA). All products were formulated and packaged into stick packs using maltodextrin as a filler and a natural cherry flavor, so that stick pack contents were of the same total weight, color, taste, and texture. Participants were instructed to consume one stick pack per day by stirring into 8-12 ounces of any beverage or soft food (hot or cold), stir well, and consume entirely. Storage conditions instructed to store the products at room temperature (20°C-25°C or 68°F-77°F) and protect from moisture.

RESULTS

Skin moisture content when measured by cornometer showed no significant changes from baseline and no differences between the groups. Results from the cutometer appear to support the study rational as skin elasticity significantly improved (p=0.0097) from baseline in the MSM+HFC group after twelve weeks (Table 1) but failed to reach statistical significance in any of the other groups.

Clarity pro 3D analysis showed a significant decrease of wrinkle area in the nasolabial area for the placebo group after 12 weeks. The MSM and the combination groups both showed statistically significant improvement from baseline in reducing surface area of the Forehead and in Crow's Feet at both 6 and 12 weeks. Fine wrinkles surface area (%) of the forehead after 12 weeks. MSM reduced the nasolabial surface area (mm^2) after 12 weeks and the combination group's nasolabial surface area significantly reduced after 6 weeks. The percent surface area of the forehead reduced in the MSM group after twelve weeks and the combination group experienced a reduction in emerging wrinkle surface area percent of the forehead after 6 weeks (Figure 1).

Group	Baseline	Week 6	Week 12	p value 6 weeks	p value 12 weeks
A (placebo)	0.359 ± 0.0622	0.3737 ± 0.0788	0.3608 ± 0.0752	0.7164	0.9951
B (MSM)	0.3236 ± 0.0508	0.3203 ± 0.692	0.3379 ± 0.077	0.9649	0.5561
C (MSM +collagen)	0.3401 ± 0.1290	0.3482 ± 0.1116	0.3967 ± 0.1304	0.8797	0.0097*

Note: *The change, baseline to week 12 for the MSM+collagen was statistically significant.

Table 1: Cutometer measurements.

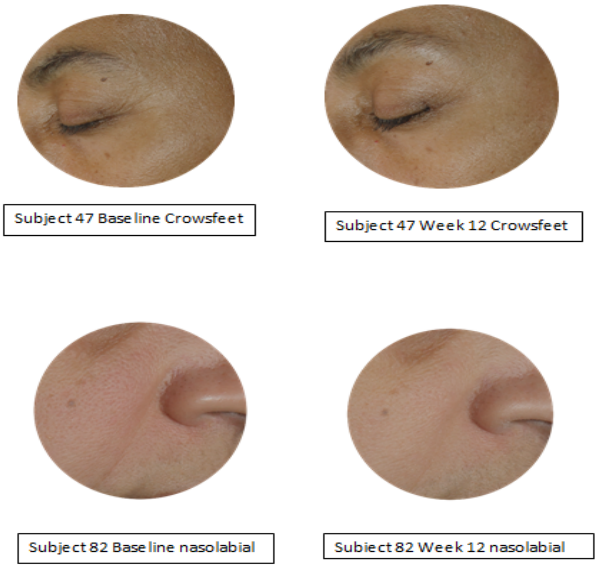

Figure 1: Objective outcome picture of two subjects from group C, before and after supplementation receiving the combination of MSM and HFC.

Dermatologist likert scale evaluation

Statistically significant improvement was seen across all groups in MSM and MSM+collagen groups showed statistically significant improvement from baseline at 12 weeks for: Visual crow's feet fine lines, visual crow's feet wrinkles, nasolabial folds visual fine lines, nasolabial folds visual wrinkles, visual fine lines of the forehead, visual wrinkles of the forehead, however tactile smoothness only showed significant improvement in the two treatment group at both six weeks and twelve weeks.

Subject likert scale questionnaires

Under the condition of this study and in this test population, the majority of subjects in all three groups, including the placebo group, elictited statistically favorable responses to the consumer perception questions.

DISCUSSION

The Placebo group had statistically significant improvement in many areas. This clinical trial took place during a global pandemic. Unprecedented measures were in place including lockdowns which very likely contribute to the overall strong showing for the placebo group. Many environmental aggressors were reduced during the pandemic. Air pollution was reduced. Many people spent more time indoors minimizing exposure to environmental pollutants, UVR, wind and temperature extremes.

While the exact mechanism of how Particle Matter (PM) air pollution affects skin remains unclear, PM produces Reactive Oxygen Species (ROS), thereby produciing pro-inflammatory cytokines, degrading collagens through the production and activation of metalloproteinase, and activating melanocytes, resulting in the disruption of barrier function and skin aging [25]. Direct dermal uptakes from airborne pollutants vary based on their PM size, with the hair follicles being a factor in providing the route for transdermal penetration [26]. In one study, it was reported that particles less than 1.5 μm in diameter do penetrate efficiently into the hair follicles up to a depth >2 mm. Such a transfollicular route may enable ambient particles and/or their surface bound constituents such as metal and PAHs, to reach viable cells, such as melanocytes, in deeper skin layers [27]. With the pandemic restrictions minimizing exposure to urban pollution, this likely influenced the significant skin improvements found in placebo group.

MSM is a naturally occurring organosulfur compound with broad biological effects. Based on previous clinical studies, MSM may preserve and potentially inhibit the breakdown of dermal collagen and elastin structure that lead to wrinkle formation and fragile skin, while improving nutrient uptake and retaining moisture *via* skin barrier function. Proposed mechanisms include: (1) Antioxidant/Anti-inflammatory-MSM was associated with increased plasma glutathione levels in humans [20], a primary antioxidant enzyme and defender against UVR and environmentally induced reactive oxygen species. Through upregulating glutathione, pro-inflammatory metabolites are potentially controlled in dermal tissue. In addition, MSM was shown to down-regulate certain genes associated with inflammation by suppressing the expression of NF-kB. In skin, inhibition of NF-kB benefits the ECM through reduced expression of inflammatory cytokines [22]. (2) As a source of bioavailable sulfur, MSM contributes to the cross-linking of proteoglycans and collagen within the Epidermal Collagen Matrix (ECM,) the primary site and root where wrinkles are initially formed. By maintaining healthy collagen, cross-linking or "hardening" of the tissue is inhibited allowing for healthy dermal function. The loss of ECM proteins highlights skin damage; disulfide bonds are required for structural adhesion and formation and Sulfur-Containing Amino Acids (SAA) are required for protein synthesis, and MSM is known to contribute important sulfur-containing amino acids including methionine, cysteine, cystine, homocysteine, homocystine and taurine [11]. (3) Barrier Function/TEWL-Instrumental analysis in previous clinical analysis suggests MSM may increase barrier function, creating greater nutrient and water exchange and minimizing Trans-Epidermal Water Loss (TEWL) [12].

As previously mentioned, there are three different probable mechanisms that have been suggested for oral intake of collagen peptides: (a) Collagen fragments can be a precursor for collagen synthesis in the skin; (b) Collagen fragments can stimulate collagen and proteoglycans production in the skin; and (c) Collagen and its fragments can increase skin turnover by induction of regulatory T cells (Tregs) and M2 macrophages [7]. Based on the physiological mechanisms for both MSM and collagen peptides *via* oral supplementation, it is not surprising that both ingredients revealed significant improvements in both the independent supplemented group and combination supplemented group. Based on the literature and clinical data available to date, it may be proposed that MSM is a superior ingredient to work along with collagen peptides to encourage crosslinking in collagen formation within ECM. Unlike other antioxidant ingredients studied with collagen peptides, MSM

has the ability to upregulate primary antioxidant enzymes to combat oxidative stress but also control proinflammatory mediators that degrade ECM. It is these combined mechanisms which make MSM a favourable and effacious nutraceutical ingredient for skin health, independently and in combination with marine collagen peptides.

CONCLUSION

The results of this study suggest that under these conditions and in this test population MSM and collagen work synergistically to support the extra-cellular matrix as evidenced by instrumental analysis. Cutometer results indicated a significant improvement in elasticity that was not experienced in either the placebo or MSM only groups. In addition clarity pro 3D analysis indicated similar improvement in both the MSM and combination treatment groups with significant improvement shown in six of eight areas, while the placebo group only had significant improvement in one of eight. The results also suggest that subjective consumer perception may be an unreliable measurement either due to a strong placebo effect or due more favorable environmental conditions experienced during pandemic lockdown.

REFERENCES

1. Cao C, Xiao Z, Wu Y, Ge C. Diet and skin aging-from the perspective of food nutrition. Nutrients. 2020;12(3):870.
2. Ahmed IA, Mikail MA, Zamakshshari N, Abdullah AS. Natural anti-aging skincare: Role and potential. Biogerontology. 2020;21(3): 293-310.
3. Revenue of beauty salons (hair, skin, nails) in the United States, 2012-2017.
4. Nielsen. The future of beauty. 2019.
5. Cui Y, Wang F, Voorhees JJ, Fisher GJ. Rejuvenation of aged human skin by injection of cross-linked hyaluronic acid. Plast Reconstr Surg. 2021;147(1S-2):43S-49S.
6. Sibilla S, Godfrey M, Brewer S, Budh-Raja A, Genovese L. An overview of the beneficial effects of hydrolysed collagen as a nutraceutical on skin properties: Scientific background and clinical studies. Open Nutraceuticals J. 2015;8(1):29-42.
7. Barati M, Jabbari M, Navekar R, Farahmand F, Zeinalian R, Salehi-Sahlabadi A, et al. Collagen supplementation for skin health: A mechanistic systematic review. J Cosmet Dermatol. 2020;19(11): 2820-2829.
8. de Luca C, Mikhal'chik EV, Suprun MV, Papacharalambous M, Truhanov AI, Korkina LG. Skin antiageing and systemic redox effects of supplementation with marine collagen peptides and plant-derived antioxidants: A single-blind case-control clinical study. Oxid Med Cell Longev. 2016;2016.
9. Genovese L, Corbo A, Sibilla S. An insight into the changes in skin texture and properties following dietary intervention with a nutricosmeceutical containing a blend of collagen bioactive peptides and antioxidants. Skin Pharmacol Physiol. 2017;30(3):146-158.
10. Yoon HS, Cho HH, Cho S, Lee SR, Shin MH, Chung JH. Supplementing with dietary astaxanthin combined with collagen hydrolysate improves facial elasticity and decreases matrix metalloproteinase-1 and-12 expression: A comparative study with placebo. J Med Food. 2014;17(7):810-816.
11. Parcell S. Sulfur in human nutrition and applications in medicine. Altern Med Rev. 2002;7(1):22-44.
12. Anthonavage M, Benjamin R, Withee E. Effects of oral supplementation with optimsm® on skin health and wrinkle reduction. Pharm Bull. 2009;32(4):651-656.
13. Avey A, Baar K. Methylsulfonylmethane reverses the effect of estrogen on engineered ligament function. 2018.
14. Evans M, Lewis ED, Zakaria N, Pelipyagina T, Guthrie N. A randomized, triple-blind, placebo-controlled, parallel study to evaluate the efficacy of a freshwater marine collagen on skin wrinkles and elasticity. J Cosmet Dermatol. 2021;20(3):825-834.
15. Anthonavage M, Benjamin RL, Withee ED. Effects of oral supplementation with methylsulfonylmethane on skin health and wrinkle reduction. Nat Med J. 2015;7(11):1-21.
16. Schwartz S, Withee E, Benjamin R. Oral supplementation of Methylsulfonylmethane (MSM) improves the appearance of skin, hair and nails at dosages as low as 1 gram/day. In: Integrative dermatology symposium. 2018:5.
17. Wong T, Bloomer RJ, Benjamin RL, Buddington RK. Small intestinal absorption of Methylsulfonylmethane (MSM) and accumulation of the sulfur moiety in selected tissues of mice. Nutrients. 2017;10(1):19.
18. Canty EG, Kadler KE. Procollagen trafficking, processing and fibrillogenesis. J Cell Sci. 2005;118(7):1341-1353.
19. Noblesse E, Cenizo V, Bouez C, Borel A, Gleyzal C, Peyrol S, et al. Lysyl oxidase-like and lysyl oxidase are present in the dermis and epidermis of a skin equivalent and in human skin and are associated to elastic fibers. J Invest Dermatol. 2004;122(3):621-630.
20. Nakhostin-Roohi B, Barmaki S, Khoshkhahesh F, Bohlooli S. Effect of chronic supplementation with methylsulfonylmethane on oxidative stress following acute exercise in untrained healthy men. J PharmPharmacol. 2011;63(10):1290-1294.
21. Mohammadi S, Najafi M, Hamzeiy H, Maleki-Dizaji N, Pezeshkian M, Sadeghi-Bazargani H, et al. Protective effects of methylsulfonylmethane on hemodynamics and oxidative stress in monocrotaline-induced pulmonary hypertensive rats. Adv Pharmacol Sci. 2012;2012.
22. Kim YH, Kim DH, Lim H, Baek D-Y, Shin H-K, Kim J-K. The anti-inflammatory effects of methylsulfonylmethane on lipopolysaccharide-induced inflammatory responses in murine macrophages. Biol Pharm Bull.2009;32(4):651-656.
23. Ahn H, Kim J, Lee MJ, Kim YJ, Cho YW, Lee GS. Methylsulfonylmethane inhibits NLRP3 inflammasome activation. Cytokine. 2015;71(2):223-231.
24. Tanaka K, Asamitsu K, Uranishi H, Iddamalgoda A, Ito K, Kojima H, et al. Protecting skin photoaging by NF-κB inhibitor. Curr Drug Metab. 2010;11(5):431-435.
25. Lee J, Oh SJ, Park S, Park JH, Lee JH. Anti-pollution skincare: Research on effective ways to protect skin from particulate matter. Dermatol Ther. 2021;34(4):e14960.
26. Fussell JC, Kelly FJ. Oxidative contribution of air pollution to extrinsic skin ageing. Free Radic Biol Med. 2020;151:111-122.
27. Lademann J, Schaefer H, Otberg N, Teichmann A, Blume-Peytavi U, Sterry W. Penetration of microparticles into human skin. Hautarzt. 2004;55(12):1117-1119.