ORIGINAL RESEARCH

Reversing Oxinflammation Associated with Glycative Stress and Formation of Advanced Glycation End Products with a Dietary Supplement Containing Rosemary Extract

by ANNA GUIOTTO, PhD; ALESSANDRA PECORELLI, PhD; ZOE DIANA DRAELOS, MD, FAAD; AUDREY GUENICHE, PharmD, PhD; MARGARITA YATSKAYER, MS; and DIANE B. NELSON, RN, MPH

Drs. Guiotto and Pecorelli are with the Department of Environmental and Prevention Sciences at the University of Ferrara in Ferrara, Italy. Dr. Draelos is with Dermatology Consulting Services, PLLC, in High Point, North Carolina. Dr. Gueniche is with L'Oréal Research and Innovation, Development in Chevilly Larue, France. Ms. Yatskayer is with L'Oréal Research and Innovation, Evaluation Intelligence in Clark, New Jersey. Ms. Nelson is with skinbetter science, a Dermatological Beauty brand of L'Oréal USA Inc., in Phoenix, Arizona.

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OBJECTIVE: Skin aging is accelerated by glycative stress, which promotes the accumulation of advanced glycation end products (AGEs) and impairs the extracellular matrix. A randomized, double-blinded, placebo-controlled trial evaluated a dietary supplement containing rosemary extract (BioR), demonstrating tissular and visible improvements in skin quality. The data reported herein evaluated markers associated with glycative stress and AGEs from skin biopsies and tape strips obtained following dietary supplement use. **METHODS:** Female participants (N=104), aged 40 to 65 years, with moderate-to-severe skin dullness and roughness/texture, and mild-to-moderate erythema, pore size, and uneven pigmentation were randomized to BioR (n=52) or placebo ([PLB] n=52). Capsules were taken with food over 12 weeks. Subjects (n=16, BioR; n=16, PLB) underwent 3mm punch biopsies (volar upper arm) and tape stripping (16 tape strips, each; volar forearm) at baseline and 12 weeks for analysis of 4-hydroxynonenal protein adducts (4HNE [oxidative stress marker]) and AGEs. **RESULTS:** Immunohistochemistry and ELISA revealed that levels of 4HNE protein adducts were significantly decreased from baseline in the BioR versus PLB group ($p<0.005$; biopsies) and significantly decreased from baseline in the BioR group alone ($p<0.05$; tape strips) at 12 weeks. Significant reductions in AGEs occurred in the BioR versus PLB group ($p<0.005$; biopsies) at 12 weeks. No significant changes from baseline occurred in 4HNE protein adduct levels or AGEs in the PLB group. **CONCLUSION:** After 12 weeks, a dietary supplement containing rosemary extract led to significant reductions in a marker associated with oxidative stress, a component of glycation, and AGEs versus placebo in skin in addition to visible improvements in skin quality. **KEYWORDS:** Glycation, oxidative stress, AGEs, rosemary extract, dietary supplement

The health and quality of our skin is a reflection of complex endogenous processes that are impacted by lifestyle choices, including diet, and extrinsic exposures to environmental insults, such as pollutants and ultraviolet (UV) radiation. These cumulative factors accelerate skin aging. Molecular processes that contribute to skin aging include excessive production of free radicals, mitochondrial dysfunction and mutations, cellular senescence, impaired immune functioning, and glycative stress.[1–4] Glycation is a spontaneous, non-enzymatic reaction of free reducing sugars with free amino groups of proteins, DNA, and lipids.[5] Glycative stress is characterized by the accumulation of cytotoxic byproducts called advanced glycation end products (AGEs) and the body's inability to counteract deleterious effects of protein degeneration and dysfunction caused by AGEs.[1,2,6,7] A recognized component of glycation is oxidative stress, or oxinflammation.[8] Oxinflammation refers to pro-oxidative mechanisms that occur as a result of crosstalk between inflammatory and oxidative stress mediators which lead to local or systemic damage, fostering an environment predisposed to inflammation.[8] All cells are exposed to some degree of glycative stress. As a result, AGEs are associated not only with skin aging, but also with many degenerative disorders, including Alzheimer's disease, diabetes, renal failure, and atherosclerosis.[2,6,9]

Extracellular matrix (ECM) proteins are a common site of glycation and a significant source of circulating AGEs.[6] ECM proteins with slow turnover rates, such as collagen, are particularly vulnerable to the effects of AGEs.[1,10,11] AGEs create intra- and inter-molecular crosslinks between adjacent proteins, altering and impairing their physical properties and functionality.[1,2,12] This weakens the biomechanical properties of collagen, causing a reduction in skin elasticity along with increased stiffness and a loss of flexibility.[1,13,14]

AGEs have a substantial overall effect on skin, obstructing wound healing, diminishing epidermal ceramides and cholesterol, promoting the production of melanin, and damaging the epidermal keratinocyte cell structure.[10,15] More than 20 species of AGEs have been identified in human skin, and each exerts differential effects on skin and tissue remodeling that promote accumulation in the ECM.[1,2,11,16] The accumulation of AGEs in the skin diminishes overall skin quality, clinically manifesting in visible skin dullness, sallowness, rough skin texture, and loss of elasticity.[16,17]

Counteracting glycation and AGEs are important antiaging strategies

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CORRESPONDENCE: Alessandra Pecorelli, PhD; Email: alessandra.pecorelli@unife.it

for maintaining healthy skin quality. Phytonutrients, such as carotenoids, flavonoids, and polyphenols, have unique antioxidant and anti-inflammatory properties, and there has been growing interest in understanding their roles and abilities in mitigating AGE accumulation.[18,19] Rosemary leaf (*Rosmarinus officinalis*) belongs to the botanical *Lamiaceae* family, which also includes thyme, lemon balm and sage, and is an abundant source of flavonoids, diterpenes, and phenolic acids. Rosemary leaf has been reported to possess anti-inflammatory, antibacterial, antimutagenic, astringent, and antiviral properties.[9,20] Both caffeic acid (CA) and its derivative rosmarinic acid (RA) are potent bioactive constituents of the rosemary leaf, along with other antioxidants including chlorogenic, ferulic and carnosic acids. *In-vitro* and *in-vivo* studies have examined the antioxidant and glycation-inhibiting activity of RA.[21,22] Purified RA and a lemon balm extract containing RA reduced the formation of pentosidine, a well-recognized AGE, along with decreasing glycation of collagen and elastin.[23] Additional *in-vitro* studies have demonstrated the ability of RA to reverse glycation and deglycate AGE crosslinked proteins.[5,12]

Rosemary is a non-toxic compound that is well absorbed via the gastrointestinal tract and skin. As a raw material, dried rosemary remains stable for extended periods of time and demonstrates consistency of composition across batches. A proprietary, multi-sequencing extraction process has been developed to preserve and optimize the beneficial natural cofactors of the rosemary leaf (COREextract™).[5,12,24,25] Utilizing bioguided extraction, fractions of the crude plant extract are screened to identify biologically active cofactors, which are then isolated and purified into a powder extract. A clinical trial investigated a dietary supplement comprised of COREextract (BioR; skinbetter science, Inc., Phoenix, Arizona) and reported significant improvements in global facial skin quality at 12 weeks.[26]

Herein, we describe our findings based on the analysis of markers associated with glycative stress and AGEs from skin biopsies and tape strips obtained in a subset of subjects enrolled in the double-blinded, randomized, placebo-controlled clinical trial.

METHODS

Clinical study design. A randomized, single-center, double-blinded, placebo-controlled clinical trial evaluated the safety and efficacy of a dietary supplement comprised of COREextract (BioR) and its effects on visible improvements in facial skin quality over 12 weeks.[26] All participants provided consent to participate in the study and to have their photographs appear in any publication stemming from the findings of the study. Female subjects, aged 40 to 65 years, with moderate-to-severe skin dullness and roughness/texture, and mild-to-moderate erythema, pore size and uneven pigmentation were enrolled in the trial. Eligible subjects were randomized to either the BioR treatment group (rosemary extract [300mg/capsule], biotin [2mcg], and zinc gluconate, [0.45mg]; n=52) or the Placebo (PLB) treatment group (glyceryl dibehenate, vegetable capsules; n=52). Subjects were instructed to take two capsules three times daily (breakfast, lunch and dinner) for Weeks 1 to 4, two capsules two times daily (breakfast and dinner) for Weeks 5 to 8, and one capsule two times daily (breakfast and dinner) for Weeks 9 to 12.

Among the 104 subjects enrolled in the clinical trial, a subset of 32 subjects (n=16, BioR; n=16, PLB) consented to undergo skin biopsies of the volar surface of the left upper arm and tape strip tissue samples of the left volar surface of the forearm at baseline and 12 weeks. The analyses assessed levels of 4-hydroxynonenal (4HNE) protein adducts, a marker of peroxidation and oxidative stress damage, and AGEs utilizing an assay that detects AGEs in tissues including Nε-(Carboxymethyl)-Lysine (CML), Nε-(Carboxyethyl)-Lysine (CEL), imidazole, and pentosidine.[26–30] Laboratory investigators and personnel were blinded to study treatment groups.

Skin biopsies—immunofluorescence for 4HNE protein adducts and AGEs. The study investigator obtained a 3mm circular punch biopsy from the volar surface of the left upper arm from subjects at baseline and 12 weeks. Following collection, skin samples were placed in a fixative solution (10% neutral buffered formalin [NBF]) and remained in preservative for at least 24 hours at room temperature (RT). Skin biopsies were then dehydrated through a series of ethyl alcohol solutions (70%, 80%, 90% and 100%), cleared with xylene, and finally embedded into paraffin blocks. For immunohistochemistry analysis, 4µm tissue sections were deparaffinized in xylene and rehydrated through an alcohol gradient. Antigen retrieval was performed using a 10mm sodium citrate buffer solution (pH 6.0; AP-9003500, ThermoFisher Scientific, USA) at 96°C for eight minutes. Tissues were washed in phosphate buffered saline (PBS) and blocked with 2% BSA in PBS solution at room temperature (RT) for one hour. Next, tissue sections were incubated overnight at 4°C with primary antibodies resuspended in PBS-BSA 0.25% at different dilutions based on the specific antibody, 4HNE (cat. AB5605, Merk Millipore, Germany 1:500) and AGE (cat. ab23722, ABCAM, USA, 1:200). The following day, sections were washed in PBS and incubated with fluorochrome-conjugated secondary antibodies (cat. A-11008, Goat anti-Rabbit IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 488; cat. A-11057, Donkey anti-Goat IgG (H+L) Cross-Adsorbed Secondary Antibody, Alexa Fluor™ 568, Thermo Fisher Scientific Inc, USA) at 1:1000 dilution in 0.25% BSA in PBS for 1 hour at RT. Nuclei were then stained with DAPI (4',6-diamidino-2-phenylindole; D1306, Invitrogen, ThermoFisher Scientific, USA) in PBS at RT. Slides were washed in PBS and mounted with coverslips using Fluoromount-G™ Mounting Medium (00-4958-02, ThermoFisher Scientific, Waltham, MA, USA). Images were acquired by epifluorescence on a Zeiss LSM10 microscope equipped at 40x magnification. Images were quantified using ImageJ software (National Institutes of Health, Bethesda, MD, USA).

Tape strips–ELISA assay for 4HNE protein adducts. Sixteen sequential tape strips (D-squame, 2cm x 1.95cm) were applied and removed from the same spot on the volar left forearm by the study investigator under a standard weight of 500g/cm^2 for three seconds using a pressure instrument. Tape strips were collected and stored in sterile 1.5mL Eppendorf tubes at −80 °C until further analysis.

The samples were thawed in ice, after which each adhesive strip was individually placed in 5mL Eppendorf tubes containing 1mL of cold buffer (0.1N NaOH with 1% SDS) and vortex for one minute at maximum speed. Extracted strips were placed on ice and centrifuged at maximum speed for two minutes at 4°C to collect any remaining liquid from the adhesive strip and the protein content of each sample was measured

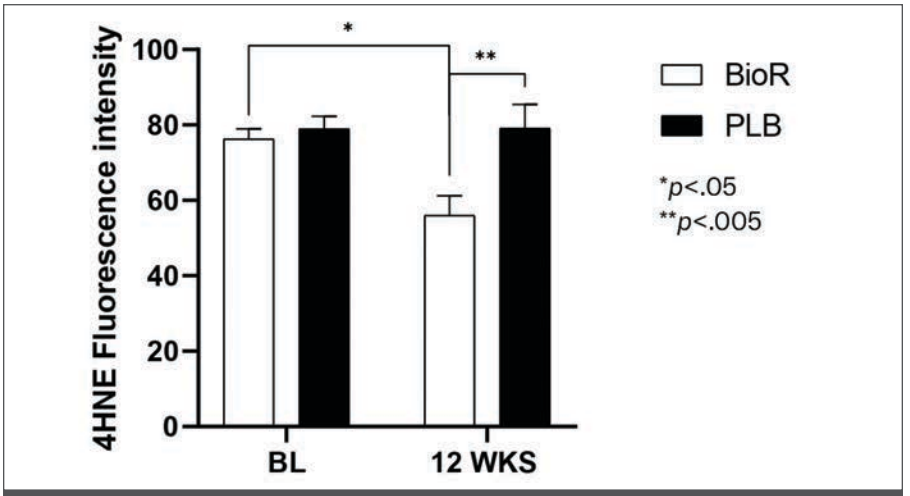

FIGURE 1. Significant reduction in 4HNE protein adduct levels were demonstrated in skin biopsies in the BioR Treatment Group (n=12) vs. PLB Treatment Group (n=14) at 12 weeks. No significant reductions occurred in 4HNE protein adduct levels in the PLB Treatment Group.

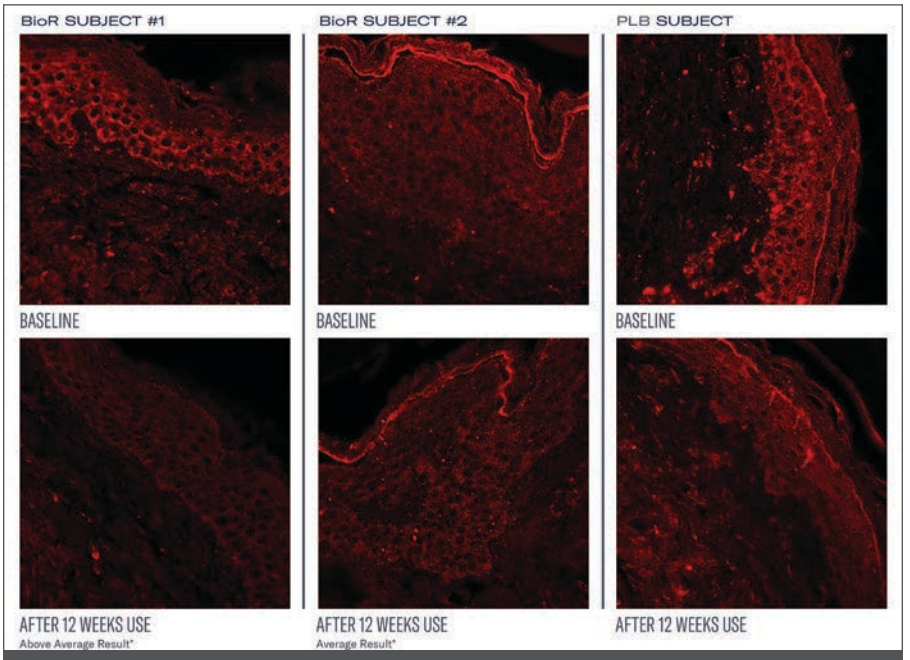

FIGURE 2. Red immunofluorescence staining demonstrated greater reductions in 4HNE protein adduct levels from subjects in the BioR Treatment Group vs. PLB Treatment Group. Image description averages were quantified based on mean 4HNE protein adduct levels in skin biopsies obtained at baseline and 12 weeks in a subset of subjects (n=12).

by colorimetric assay using Quick Start Bradford Protein Assay Kit (cat. 5000201, Bio-Rad Laboratories, Inc., Hercules, CA, USA) and read at 595nm by spectrophotometer.

4HNE protein adduct levels were measured from the obtained extracts using the 4HNE ELISA kit (cat. NBP2-66364, Novus Biologicals, Centennial, CO 80112, USA), according to the manufacturer's instructions. The final optical density was measured with microplate reader set to 450nm. 4HNE protein adduct concentrations were reported as ng/mL, and the Gen5 2.0 software (BioTek, Agilent, Santa Clara, CA, USA) was used for the detection.

Statistical analysis. Statistical analysis was performed using GraphPad Prism (GraphPad Software Inc., La Jolla, CA, USA). Statistical analysis for each assessment involved two-way ANOVA followed by Tukey's post-hoc comparison test. A p-value <0.05 was considered significant. All data are reported as mean ± SEM.

RESULTS

Decreased 4HNE protein adduct levels and AGEs were demonstrated in the BioR treatment group at 12 weeks. Immunofluorescence on skin tissue biopsies revealed that levels of 4HNE protein adducts were significantly decreased in the BioR treatment group versus the PLB treatment group at 12 weeks (p<0.005; Figures 1, 2). Significant reductions were also observed in levels of 4HNE protein adducts in the BioR treatment group alone from baseline at 12 weeks (p<0.05). No significant reductions occurred in 4HNE protein adduct levels in the PLB treatment group.

Significant reductions in AGEs were demonstrated in the BioR treatment group versus the PLB treatment group at 12 weeks (p<0.005), and from baseline to 12 weeks in the BioR treatment group alone (p<0.0001; Figures 3, 4). No significant reductions occurred in AGEs levels in the PLB treatment group.

Decreased 4HNE protein adduct levels were demonstrated in tape strips in the BioR treatment group at 12 weeks. Levels of 4HNE protein adducts were significantly decreased from baseline in the BioR treatment group alone at 12 weeks (p<0.05; Figure 5). Although greater reductions in 4HNE protein adduct levels occurred in the BioR treatment group versus the PLB treatment group, these were not statistically significant. No significant reductions occurred in 4HNE protein adduct levels in the PLB treatment group.

DISCUSSION

Glycation is an inevitable aspect of aging and can negatively affect the health and quality of skin. The consequent accumulation of AGEs promotes oxinflammation, which further exacerbates and contributes to skin aging and clinical manifestations of dullness, sallowness, rough skin texture, and loss of elasticity.[8,16,17] AGE accumulation is exacerbated by exposure to UV radiation and pollutants.[17] Thus, minimizing extrinsic exposure to environmental insults can aid in reducing the accumulation of AGEs and mitigate visible effects on the skin. Further, as with all living tissues, skin requires internal nourishment. Ideally, foods that are rich in phytonutrients can help prevent the

accumulation of AGEs and reduce glycation and oxinflammation in the skin.[31] Diets that are low in sugar and fried or baked foods, and high in fruits, vegetables, and herbs, and that include plants rich in polyphenols can help combat the glycation process, supporting skin health and aging.

Rosemary leaf is a rich source of antioxidant compounds, including rosmarinic and caffeic acids.[20] A number of studies have reported the antiglycation benefits of rosemary extract and the ability of RA to reverse glycation and deglycate AGE crosslinked proteins.[5,9,12,20,21,32,33] COREXtract is derived from a proprietary extraction process that preserves and optimizes key natural bioactive cofactors of the rosemary leaf and has been shown to have greater ability (2.4 times more) to reverse glycation and deglycate AGE crosslinked protein compared to pure RA alone.[25] Clinical findings from the current double-blinded, placebo-controlled study evaluating the visual effects of BioR on facial skin quality demonstrated significant reductions in skin dullness, roughness/texture, erythema, and pore size at 12 weeks, along with significant improvements in global skin quality in the BioR treatment group versus the PLB treatment group.[26] Results from skin biopsy and tape strip analyses obtained in a subset of subjects demonstrated the ability of BioR to counteract oxidative stress, a component of the glycation process, and significantly decrease AGE levels in the skin. Significant reductions in 4HNE protein adduct levels that occurred in subjects in the BioR treatment group suggest that BioR has the ability to reduce oxidative stress damage in the skin, a major mechanism involved in the glycation cycle and the accumulation of AGEs. Moreover, the significant decrease in AGEs observed in subjects in the BioR treatment group at 12 weeks demonstrated the ability of BioR to reverse AGE crosslinked proteins in the skin. Future studies regarding specific types of AGEs and their biochemical, structural, and clinical impact on the skin would further contribute to our understanding of the effects of glycation on the skin and offer possible insights into prevention and treatment.

The formation of AGEs, which are produced endogenously and derived exogenously, has been associated with alterations in the quality of skin and skin aging.[34] This study demonstrated the effects a dietary supplement containing rosemary extract and its natural bioactive cofactors (COREXtract) had in significantly reducing glycative stress and reversing AGEs in the skin, leading to clinical improvements in skin dullness, texture, erythema and pore size, and global skin quality at 12 weeks. Taken together, the strength and consistency of the clinical and histological findings from this study provide substantial evidence demonstrating the effects a dietary supplement containing rosemary extract had on mitigating glycation and supporting skin health.

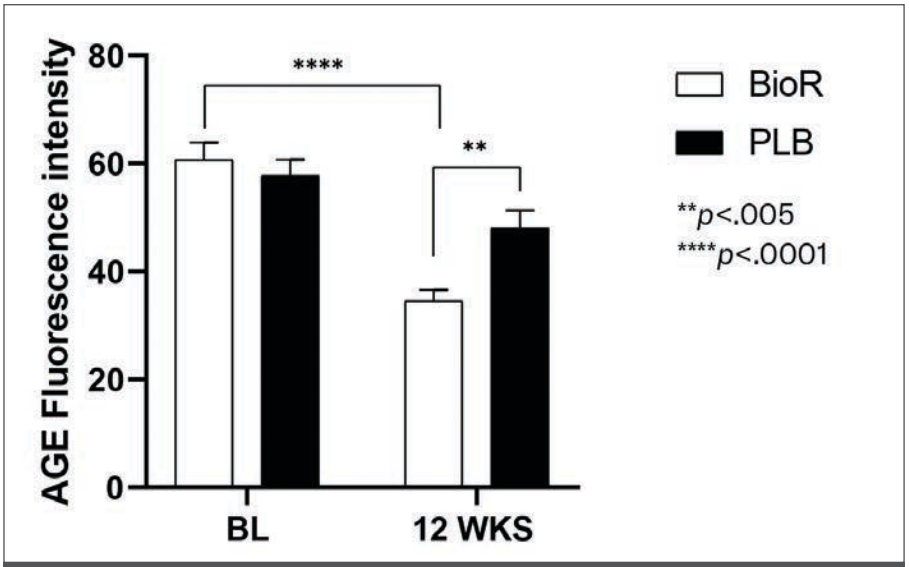

FIGURE 3. Significant reduction in AGE levels were demonstrated in skin biopsies in the BioR Treatment Group (n=11) vs. PLB Treatment Group (n=12) at 12 weeks. No significant reductions occurred in AGE levels in the PLB Treatment Group.

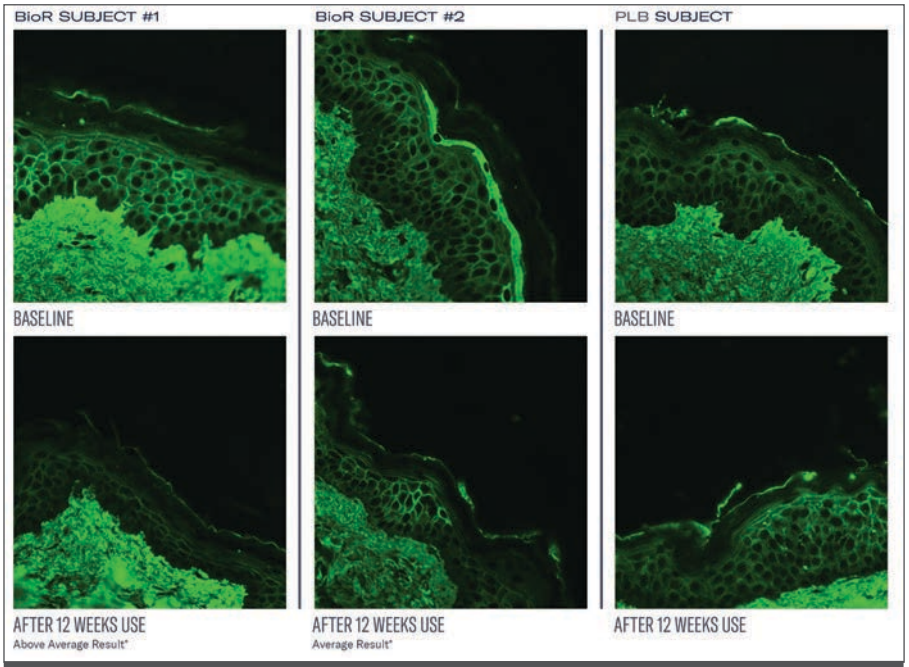

FIGURE 4. Green immunofluorescence staining demonstrated greater reductions in AGEs from subjects in the BioR Treatment Group vs. PLB Treatment Group. Image description averages were quantified based on mean AGE levels in skin biopsies obtained at baseline and 12 weeks in a subset of subjects (n=11).

CONCLUSION

A dietary supplement containing rosemary extract and its natural cofactors led to significant reductions in markers associated

with glycative stress and AGEs compared to placebo at 12 weeks.

ETHICAL STATEMENT

This study received ethical approval from the Allendale Investigational Review Board, Old Lyme, Connecticut.

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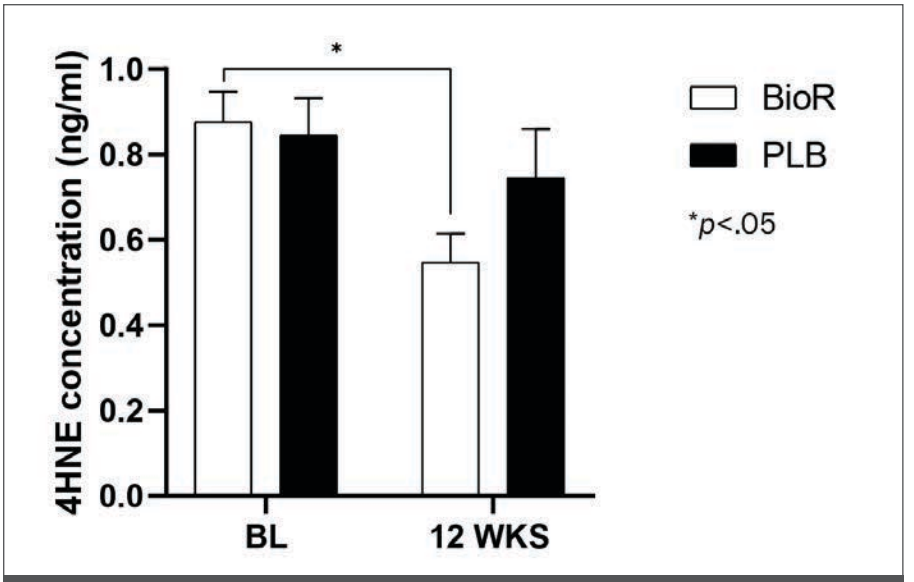

FIGURE 5. Significant reduction in 4HNE protein adduct levels were demonstrated in tape strip samples in the BioR Treatment Group from baseline at 12 weeks (n=11). No significant reductions occurred in levels of 4HNE protein adducts in the PLB Treatment Group (n=10).

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