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ORIGINAL ARTICLE

The synergistic effect of retinyl propionate and hydroxypinacolone retinoate on skin aging

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Abstract

Background: Aging is responsible for the majority of skin and soft tissue remolding in humans. Retinol and its derivatives or retinoids effectively intervene skin aging process. Nevertheless, retinoids usually induce skin intolerance, especially among the Chinese, and thus, their application to prevent skin aging is yet to be well accepted. The study of optimal composition and concentration of retinoids is necessary to offer strong antiaging efficacies with minimum irritations. Therefore, a better understanding of retinol and its derivatives is acutely needed to develop strategies to combat skin aging.

Objective: In this study, we aimed to determine the optimal ratio of two retinol derivatives—hydroxypinacolone retinoate (HPR) and retinyl propionate (RP) in terms of dermal remodeling and skin aging prevention—and to investigate their synergistic antiaging effects both in vitro and in vivo.

Methods: An in vitro human foreskin fibroblast (HFF-1) cell model was established to evaluate the cell viability of HPR and/or RP treatment. In addition, the antiaging and retinol receptor genes expressions in HFF-1 cells cotreated with HPR and RP were quantified. The in vivo adverse reaction evaluation of skincare serums containing various levels of retinol or the optimal HPR and RP combination termed Gravi-A was performed by 24 h patch tests in 33 subjects prior to the clinical research. Last but not the least, clinical research with 42 Chinese urban women was conducted to assess the in vivo antiaging efficacy of the skincare serum containing this optimal retinoid combination.

Results: The combination of HPR and RP at the weight ratio of 5:9 was shown to achieve the optimal in vitro antiaging performance. Coadministration of 5 μg/mL HPR and 9 μg/mL RP to HFF-1 cells promoted their proliferation at 24 h and synergistically enhanced the expressions of type IV collagen, CRBP-I, and RARB genes. In addition, the skincare serum containing HPR and RP combination at 5:9 weight ratio demonstrated superior in vivo anti-wrinkle and skin elasticity improvement benefits without

Qianqian Wang and Fan Hu are co-first authors as they provided equal first-author-level contribution to this paper.

any adverse reactions, while retinol in the same concentration exerted much higher adverse effect. Skin wrinkles, skin smoothness, TEWL, skin elasticity R2 and R5 were improved by 8.3%, 11.9%, 25.7%, 14.5%, and 22.6%, respectively, after 8-week use. **Conclusion:** Our results indicated the advanced antiaging effect of HPR and RP combination both in vitro and in vivo. In addition, little adverse effect was observed in this study, in comparison with retinol. This combination named as Gravi-A is a potential therapeutic strategy to prevent skin aging, especially for Chinese women.

KEYWORDS
antiaging, Hydroxypinacolone retinoate, retinoid, retinyl propionate, synergistic

1 | INTRODUCTION

The skin is the largest organ of the human body and is mainly composed of epidermis, dermis, and subcutaneous tissue.[1] In the process of aging, these three skin layers go through deteriorative changes, where the dermis layer has the most obvious degeneration. Wrinkles and lower-skin elasticity are typical skin aging phenomena attributed to the progressive atrophy of the dermis. It is well-believed that the main mechanism of dermal atrophy is the reduction in the amount of extracellular matrix (ECM), especially collagen in the dermis.[2] In aged skin, the collagen synthesis decreases while its degradation increases, resulting in the disorganized ECM.

Retinoids, such like retinoic acid and retinol, have been widely tested in the treatment of skin aging. Studies showed that topical application of retinoic acid leads to increased dermal collagen synthesis, as well as blocking collagenase activity, thereby preventing collagen degradation.[3] This seems to be the molecular mechanism of retinoids antiaging efficacy. However, both retinoic acid and retinol treatments caused skin irritations, such as burning, scaling, and dermatitis.[3,4] One clinical study among volunteers of various ethnic origins revealed that the Chinese is the most susceptible to retinoid irritation.[5] Clearly, these drawbacks of retinoids limit their wide therapeutic application to prevent skin aging.

Recently, vitamin A ester has been a popular choice over retinol and retinoic acid thanks to its better chemical stability and safety profile. Retinyl propionate (RP) is a vitamin A ester analog and has been reported to have antiaging efficacy with minimal irritation.[6] Hydroxypinacolone retinoate (HPR), another cosmetic grade ester of vitamin A, is the latest developed which binds directly with retinoic acid receptors (RARs) without the need for biological transformation to retinoic acid forms. It has also been demonstrated to be more stable and causes less skin irritation than retinol.[7]

In this study, we investigated the effects of RP and HPR on the antiaging and retinol receptor genes expressions using an in vitro human foreskin fibroblast (HFF-1) cell model. Furthermore, the optimal weight ratio between HPR and RP was identified, and we named this optimal retinoid combination as Gravi-A. The objective of this study was to evaluate the antiaging efficacy and mildness of Gravi-A both in vitro and in vivo, in order to find an antiaging treatment more suitable for the Chinese.

2 | MATERIALS AND METHODS

2.1 | Cell viability

Cultured human foreskin fibroblast (HFF-1) cells were from the China Center for Type Culture Collection (CCTCC). The HFF-1 cells were cultured in complete medium consisting of 89% minimum essential medium (MEM: Cellmax, Sweden)/10% fetal bovine serum (FBS: Biological Industries, United States) supplemented with 1% Penicillin–Streptomycin solution (Solarbio, China) at 37°C in a humidified atmosphere with 5% CO_2.

The cells in the exponential growth phase were taken to make a single cell suspension, seeded on a 96-well plate at a density of 3×10^3 cells/mL and were cultured in medium containing 10% fetal bovine serum at 37°C for 24 h. The final culture volume was 100 μL. The supernatant was discarded, and then, the freshly prepared samples (serum-free) were added and incubated for 24/48/72 h. A 10 μL of CCK-8 (Nuo Yang Bio, China) solution was added to each well, vortexed, and continued to culture at 37°C. After 2 h, the absorbance OD value of each well was measured at a wavelength of 490 nm to observe the effect of the test substance on cell growth.

2.2 | In vitro genes expressions evaluation

The cells in the exponential growth phase were taken to make a single-cell suspension, seeded on a 6-well plate at a density of 1×10^5 cells/mL and were cultured in medium containing 10% fetal bovine serum at 37°C for 24 h. The final volume was 2 mL, and the supernatant was discarded. The freshly prepared samples were added and incubated for 24/48/72 h. The total cellular RNA was extracted from each well, and qPCR was used to quantify Col I, Col III, Col IV, CRBP I, and RARB mRNA expressions.

2.3 | Adverse reaction evaluation

The safety of skincare serums containing various levels of retinol or HPR and RP combination at 5:9 weight ratio was evaluated by 24 h patch tests in 33 subjects to detect potential adverse reactions. The evaluation was carried out in Intertek Shanghai, and the protocol had

passed reviewed by the Ethical Commission of Intertek. All participants signed a copy of the informed consent. Thirty-three female and male healthy subjects between the ages of 18 and 60 were enrolled in the patch test. The patches (Finn Chambers) with 20–25-μL serum formula was applied to the upper back and removed after 24 h, and the readings were recorded at three time points 30 min, 24 h and 48 h after removal. The criteria of International Contact Dermatitis Research Group were used for the assessment of the patch test results.

2.4 | Clinical research

The clinical research was performed in Shanghai China-norm Quality Technical Service Co., Ltd. The research protocol was examined and approved by the China-norm Ethics Committee for Clinical Research. Benefits, risks, and potential complications were explained to the subjects. All subjects voluntarily participated in this study and signed an informal consent form. Forty-two Chinese urban women with wrinkles or fine lines, enlarge pores and lack of skin elasticity, the clinical score of marionette and nasolabial lines ≥2, between the ages of 25 and 40 were enrolled in the study. Exclusion criteria are subjects who had externally or internally used retinoids, such as retinol, retinoic acid, tazarotene, and adapalene, within 3 months prior to enrollment; subjects who were pregnant, breastfeeding, or planning a pregnancy; subjects who had a history of cosmetic allergies or other serious allergies history; and subjects with systemic diseases or severe skin diseases. The subjects were instructed to apply the serum formulation once every day. The duration of treatment is 8 weeks, and subjects were evaluated at baseline, Week 1, Week 2, Week 4 and Week 8. While sitting quietly in a standard constant temperature and humidity environment (temperature 20–22°C, humidity 40%–60%) for at least 20 min, their skin texture was analyzed by Visioscan VC20, skin elasticity was measured by Cutometer (Courage & Khazaka, Germany), and transepidermal water loss (TEWL) was measured by Vapometer (Delfin, Finland). The overall antiaging efficacy was tracked by VISIA-CR (Canfield Scientific, United States). At Week 8, each subject filled in the self-assessment questionnaire, which is a form of the affective test to study preferences and dislikes of consumers regarding the Gravi-A serum. The antiaging efficacies including skin smoothness, radiance, plumpness, Crow's feet, and fine lines reduction, as well as pore size improvement, were evaluated by using a five-point scale: 1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, and 5 = strongly agree. All subjects received active product and no placebo was employed in the study. This method of study design is more concerned with the overall efficacy of the final product focusing on the improvement brought by the serum after use than before using the serum.

2.5 | Statistical analysis

All statistical analyses were performed using Excel and GraphPad Prism7 software package. Results were presented as the mean ± SEM. One-way analysis of variance (ANOVA) was performed between groups. The student's *t*-test was used to calculate significance. A p value of <0.05 was considered statistically significant.

3 | RESULTS

3.1 | Cell viability

HFF-1 cells were incubated with HPR and/or RP for 24, 48, and 72 h, and the cell viability results were shown in Figure 1. The coadministration of 5 μg/mL HPR and 9 μg/mL RP significantly increased HFF-1 cell viability by approximately 40% after 24 h compared to control and individual treatment. Negligible toxicity was observed in each retinoid treatment group across all timepoints. At 72 h, all retinoid groups slightly enhanced cell viability compared to control. Obviously, at all the tested concentrations, the vitamin A esters are safe to fibroblasts.

3.2 | In vitro antiaging and retinol receptor genes expressions evaluation

Cotreatment of 5 μg/mL HPR and 9 μg/mL RP with HFF-1 cells for 24/48/72 h, and the mRNA of Col I, Col III, Col IV, CRBP I, and RARB were collected and quantified. The results were presented in Figure 2. Compared to control, retinoids cotreatment at 24 h could increase the expressions of Col I and Col III mRNA in HFF-1 cells although there was no statistically significant difference. In contrast, at 48 h Col I and Col III mRNA expressions were significantly enhanced by more than fourfolds and 73.0%, respectively, in the cotreatment group. At 72 h, the retinoids cotreatment still could significantly boost Col I mRNA expression in HFF-1 cells by more than 3.5-folds.

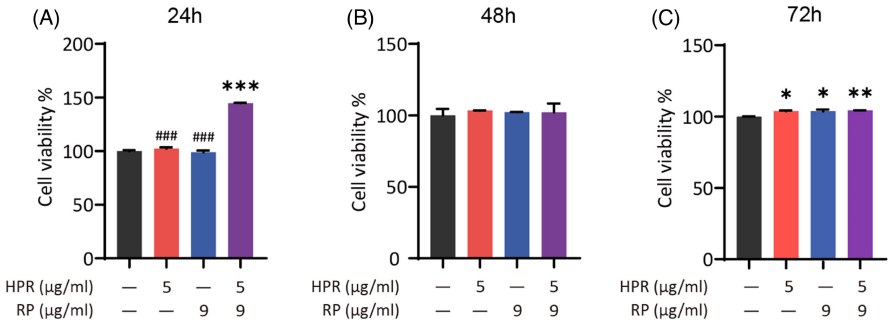

FIGURE 1 Cell viability of HFF-1 after 5 μg/mL HPR and/or 9 μg/mL RP treatment assessed at 24, 48, and 72 h.

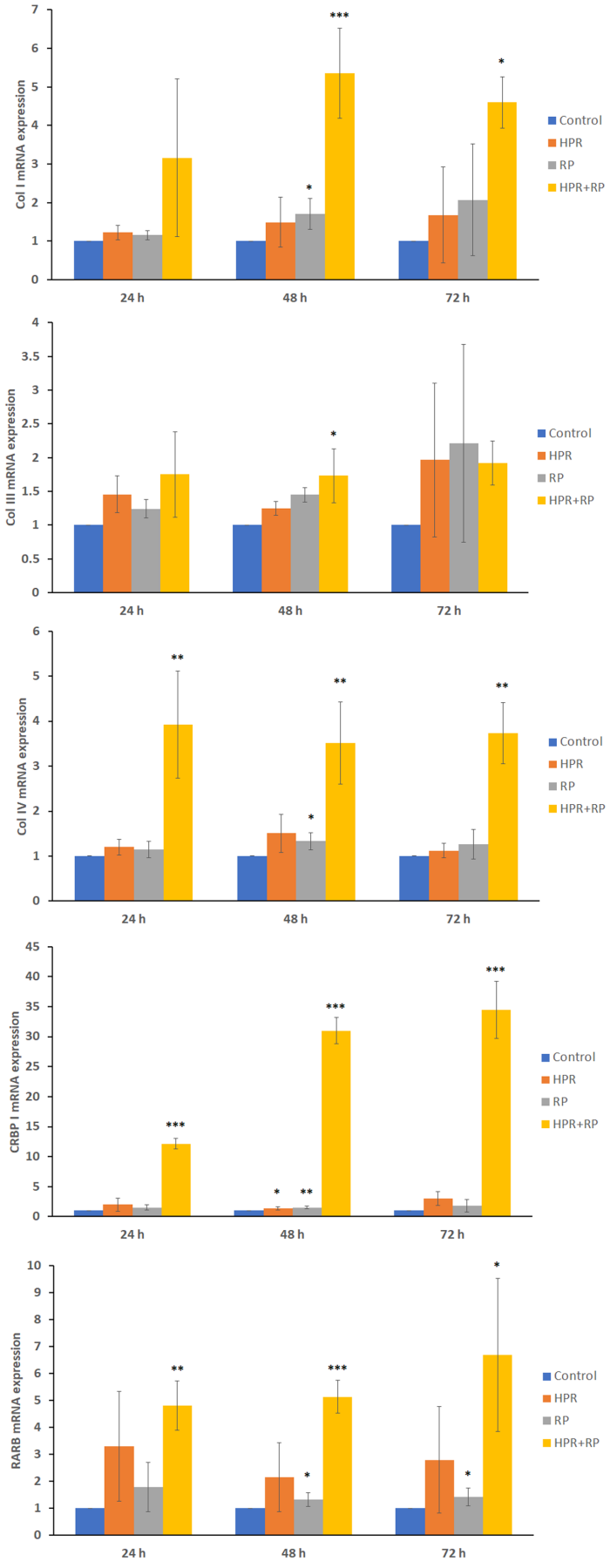

FIGURE 2 Antiaging and retinol receptor genes expressions in HFF-1 treated with 5 μg/mL HPR and/or 9 μg/mL RP for 24, 48, and 72 h. The data were presented as means ($n \geq 3$). Compared with the control group $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Compared with HPR or RP single treatment, 5 μg/mL HPR and 9 μg/mL RP cotreatment synergistically enhanced Col IV mRNA expressions from 24 to 72 h in HFF-1 cells. All single treatment groups did not significantly boost Col IV synthesis except for the RP group at 48 h, while the retinoid cotreatment significantly promoted Col IV synthesis by more than 2.5-fold from 24 to 72 h. Similarly, CRBP I and RARB expressions were also synergistically increased from 24 to 72 h. Individual treatment of HPR or RP did not increase CRBP I expression at 24 or 72 h, but their cotreatment synergistically promoted CRBP I expression by approximately 11-fold, 30-fold, and 33-fold from 24 to 72 h, respectively. The RARB expression was enhanced by roughly fourfold by HPR and RP cotreatment at both 24 and 48 h, and this enhancement advanced to 5.7-fold at 72 h.

The synergistic stimulation of Col IV, CRBP I, and RARB synthesis of 5 μg/mL HPR and 9 μg/mL RP cotreatment was summarized in Figure 3. The synergy of Col IV synthesis was mainly shown at 24 h, while the synergy became progressively stronger from 24 to 72 h in the case of CRBP I and RARB synthesis. Among all the genes, the synergy of CRBP I was the strongest, consistent with the observations from Figure 2.

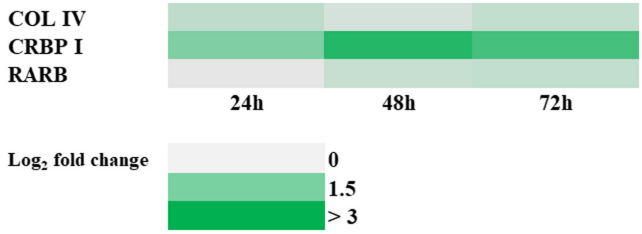

FIGURE 3 The synergistic boosting effect of 5 μg/mL HPR and 9 μg/mL RP combined treatment on the mRNA of Col IV, CRBP I, and RARB.

3.3 | Adverse reaction evaluation

To evaluate and compare the safety profile of retinol versus the optimal HPR and RP combination, skin patch tests of formulas containing various levels of retinol or retinoids were conducted, and the results were summarized in Figure 4. In general, the higher the retinol concentration, the more irritating it is. At 0.1% retinol, there were six out of 33 subjects showing mild reaction with a bit of redness. The number of subjects with this mild adverse reaction increased from six to seven as the retinol concentration rose from 0.1% to 0.5%. At both 0.75% and 1% retinol, there were seven out of 33 subjects showing mild reaction with a bit of redness and two out of 33 subjects showing positive yet weak reaction associated with mild red rashes. This clearly suggests that the Chinese skin is not well-tolerated retinol treatment.

In contrast, HPR and RP combination at 5:9 weight ratio was significantly much milder; only one out of 33 subjects showed mild reaction with a bit of redness even at the highest 1% concentration. There was 0 adverse reaction at both 0.5% and 0.75% Gravi-A. This

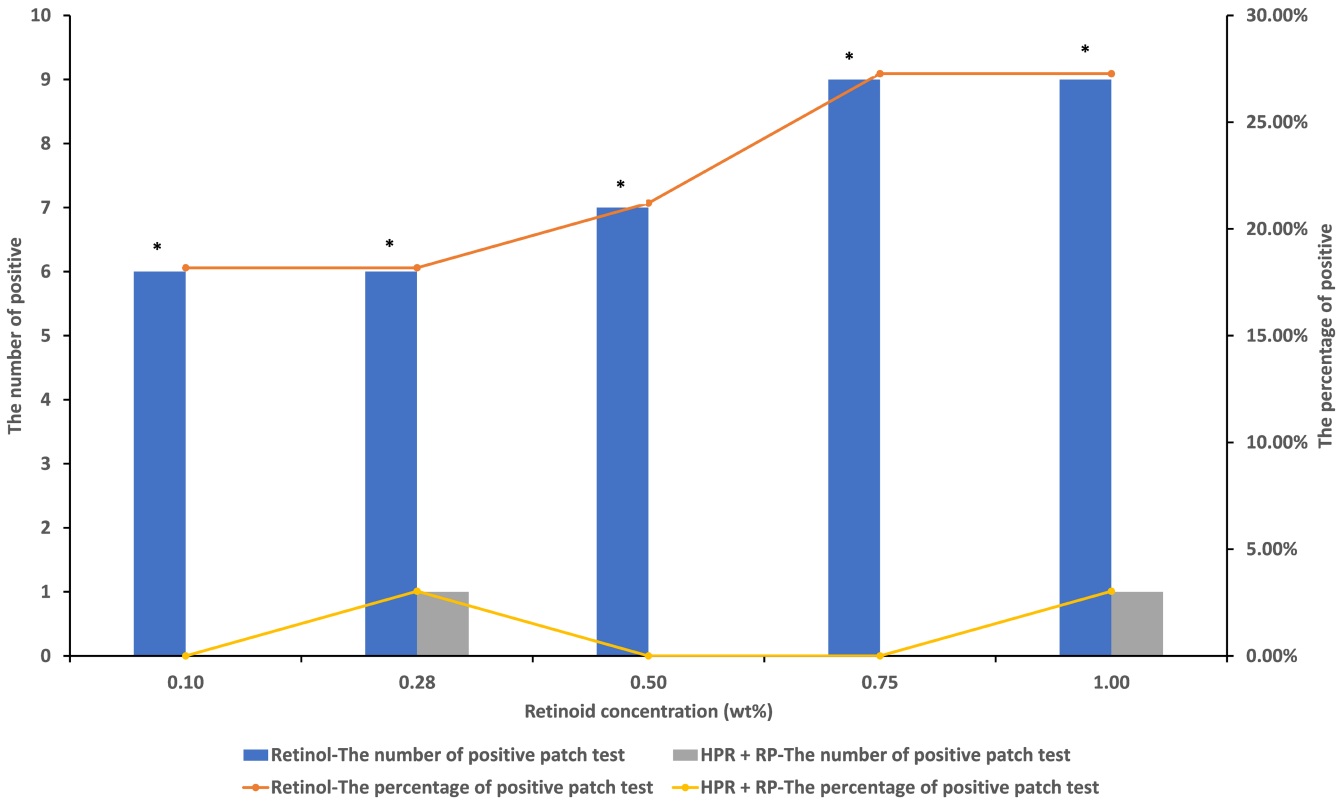

FIGURE 4 The skin patch test results of retinol versus HPR and RP combination at 5:9 weight ratio. Compared with the retinol group *$p < 0.05$.

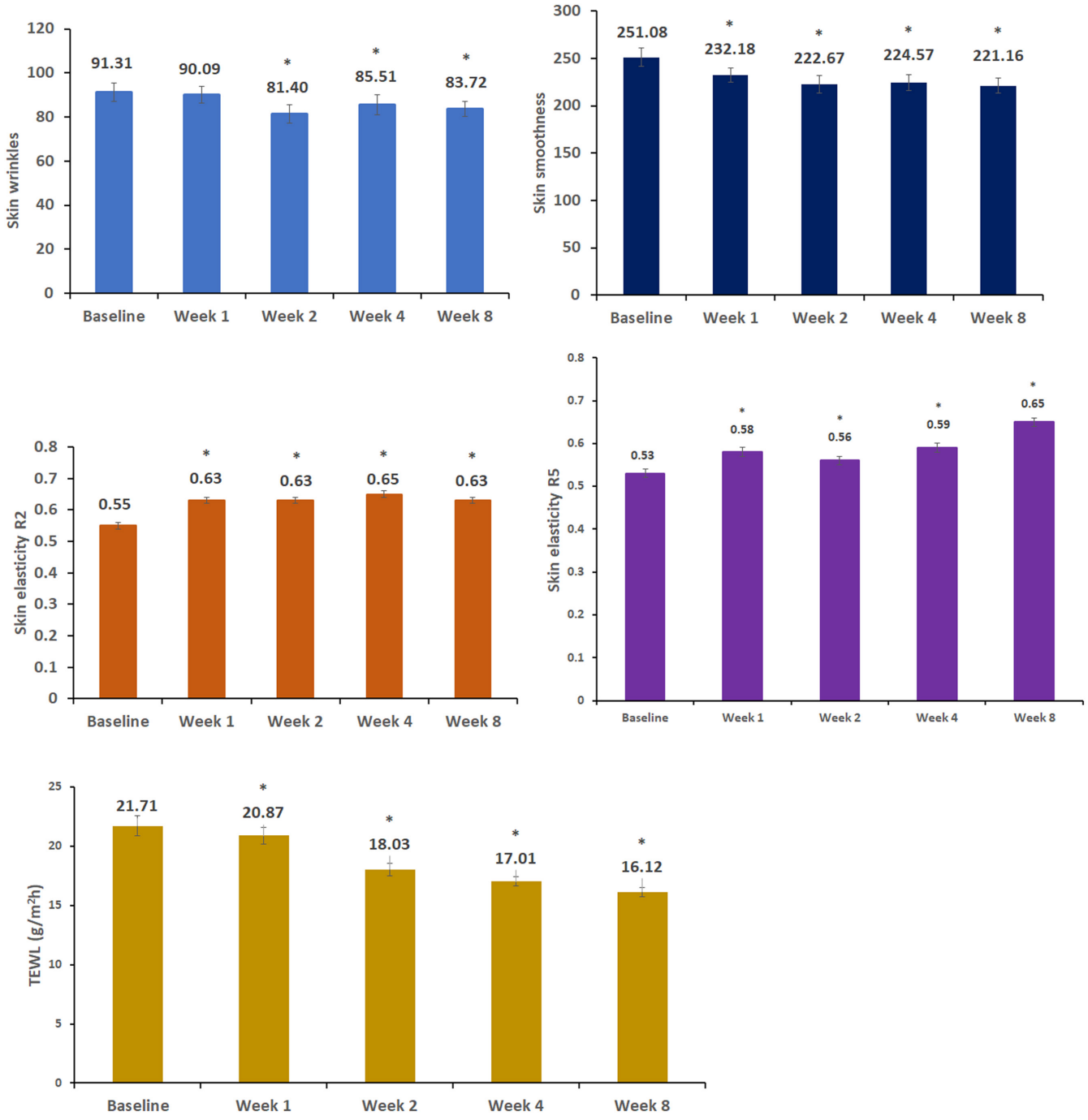

FIGURE 5 The in vivo instrumental analysis of antiaging efficacy of the skincare serum containing optimal HPR and RP combination. Compared with the baseline $^*p < 0.05$.

indicates the superior safety profile of HPR and RP combination, implying tolerance establishment might not be necessary when applying this retinoid combination.

3.4 | Clinical research

3.4.1 | Instrumental evaluation

The in vivo instrumental evaluation results were summarized in Figure 5. Compared to baseline, skin wrinkles have showed significant improvement ($p < 0.05$) since Week 2. The skin wrinkle value decreased by 10.9% from 91.31 to 81.40 at Week 2 and kept approximately constant from Weeks 4 to 8. Furthermore, skin smoothness, elasticity, and TEWL have all significantly improved since Week 1. Compared to baseline, skin smoothness value improved by 7.5% at Week 1 and continued to improve by 11.9% at Week 8. Cutometer results indicated that elasticity R2 and R5 increased by 14.5% and 9.4%, respectively, at Week 1 compared to baseline, and they reached peak values at Week 8. Regarding TEWL measurement, Gravi-A serum treatment resulted in lower TEWL since Week 1. The TEWL was reduced by 21.6% at Week 4 and 25.7% at Week 8. This indicates that

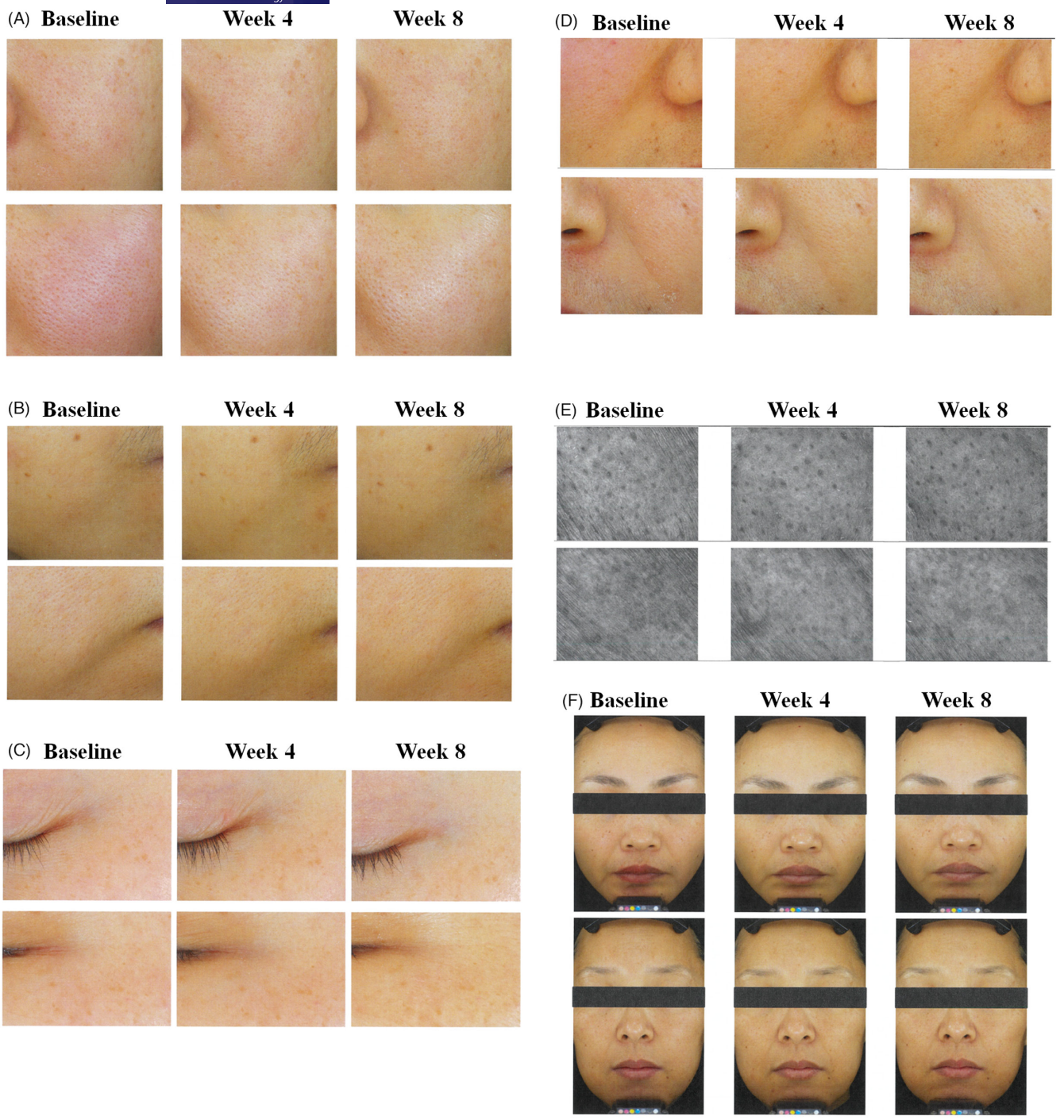

FIGURE 6 The examples of in vivo antiaging efficacy of the skincare serum containing the optimal HPR and RP combination (A: pore improvement, B: marionette lines reduction, C: Crow's feet reduction, D: nasolabial lines reduction, E: skin texture and smoothness improvement, and F: skin tone and radiance enhancement).

the optimal HPR and RP combination strengthened skin barrier function unlike other retinoids. Moreover, as indicated by VISIA-CR and Visioscan VC20 (Figure 6), the overall skin complexion improvement was quite remarkable, including pore improvement, Crow's feet, marionette and nasolabial lines reduction, skin texture, and smoothness improvement, as well as skin tone and radiance enhancement. Taken together, the instrumental evaluation results clearly demonstrated Gravi-A's in vivo anti-wrinkle efficacy without any adverse reactions.

3.4.2 | Subject self-assessment

The change from baseline of antiaging efficacy self-assessment was conducted at Week 8. The participants noticed significant improvement from baseline in facial skin conditions. After 8-week use, 97.6% of subjects reported their skins were smoother, more radiant, plumped, and supple. In addition, 95.2% of subjects noticed fine lines, Crow's feet and pore size were reduced.

4 | DISCUSSION

Retinoids play an important role in epidermal and dermal homeostasis, such as normalizing cellular proliferation and differentiation, as well as regulating the biosynthesis of ECM components particularly collagen, and maintaining dermal thickness. Shao et al.[8] revealed that topical retinol treatment stimulated keratinocytes proliferation by epidermal-specific upregulation c-Jun transcription factor in aged human skin. In this study, we additionally found that fibroblasts proliferation could be enhanced by either individual retinoid or combined esters treatment, consisting with the literature report of vitamin A regulating cell growth. At the optimal 5:9 HPR:RP weight ratio, they increased the proliferation of fibroblasts at 24 h by approximately 40%, following boosting the synthesis of Col I and III by approximately fourfold and 73%, respectively, at 48 h and synergistically stimulated the synthesis of Col IV by 2.7-fold at 72 h.

Types I and III collagens are the major constitutes of dermal extracellular matrix while type IV collagen is a type of collagen that is found primarily in the skin within the basement membrane zone.[9] Collagen fibrils in young skin are abundant, tightly packed, and intactly well-organized. In contrast, they are fragmented and coarsely distributed in aged skin.[10] In the aging process, collagen biosynthesis is reduced while collagen degradation is increased. Such deviant collagen homeostasis leads to skin wrinkles, roughness, and loss of elasticity, which are the major concerns of aged skin.

Topical retinol has been reported to improve aged dermal ECM microenvironment through enhancement of TGF-β/CTGF pathway in the dermis.[8] TGF-β/CTGF pathway is the principal regulator of ECM homeostasis, and retinol is able to enhance it through increasing the expression of TGF-β1/CTGF and suppressing the inhibitory Smad7 of TGF-β signaling.[8] Since, RP can be biologically converted to retinol by skin cells, and HPR was reported to be active without the need for any biological transformation,[7] we believe Gravi-A stimulates the ECM proteins production via a similar mechanism as retinol does. In addition, an improved ECM microenvironment is more suitable for the dermal homeostasis, which may promote fibroblasts proliferation.

CRBP and RAR are two of the most important proteins mediating vitamin A metabolism and biological functions. CRBP or cellular retinol-binding protein is a small cytosolic binding protein for retinol and retinaldehyde,[11] which can enhance retinoid translocation into the target cells through high-affinity binding. It has been reported that the expression of CRBP is upregulated by both retinoic acid and retinol in human skin,[12] which is caused by the conversion of retinol to ATRA.[13] Therefore, CRBP is involved in the regulation of retinoid metabolism by controlling the availability of certain active retinoids.

It is now well known that the active retinoids are mediated by bound to their corresponding nuclear receptors, one of which belongs to the RAR or retinoic acid receptor family. Upon activation by a specific ligand, for example, ATRA, the RAR complex dissociates from accessory proteins and translocates into the nucleus to activate downstream gene expressions.[12] Such changes in gene expression and ultimately in ECM protein products are responsible for the antiaging effects of retinoids.

In our study, HPR and RP combination at 5:9 weight ratio synergistically enhanced CRBP I and RARB expressions of fibroblasts from 24 to 72 h. CRBP I mRNA expression increased from 11-fold to 33-fold compared to control from 24 to 72 h, while it was from 3.8-fold to 5.7-fold in the case of RARB. Due to the key roles played by CRBP and RAR proteins in the metabolism and biological effects of vitamin A, we hypothesized the upregulation of retinol/retinoic acid metabolism pathway accounts for the in vitro synergistic antiaging efficacy of HPR and RP cotreatment at 5:9 weight ratio. Compared to retinol, RP has a more "skincare-efficient" metabolic profile and higher retinoid-related bioactivity over retinol because RP is metabolized primarily into retinol in the viable epidermis and dermis, whereas retinol is esterified into retinyl palmitate and metabolized into the skincare inactive retinoid form—14-hydroxy-4,14-retro-retinol.[14] In contrast to retinol, HPR does not need to convert to ATRA and can bind directly with RARs.[7]

As a result, the upregulation of CRBP I and RARB is positive as they cooperatively promote the transportation of Gravi-A within the cytoplasm and the binding of the metabolic product of RP and HPR with the receptors. The *in vitro* synergistic antiaging efficacy of HPR and RP cotreatment is hypothesized to be mediated through enhanced retinoid response by facilitating RP to bind better with CRBP and promoting HPR and RP metabolites to bind better with RAR as illustrated in Figure 7, thereby upregulating the retinol/retinoic acid metabolism pathway and contributing to the in vivo antiaging effects observed in the clinical study. Clearly, additional studies are warranted to verify this hypothesis, and we are currently investigating it via genomic methods.

The study conducted by Goh et al.[5] indicated that the Chinese were the most susceptible group when evaluated for irritation signs induced by adapalene or tretinoin, while the Caucasians appeared to be the least sensitive among the four ethnic groups tested in the study. Besides irritations, the signs of skin erythema, desquamation, and dryness, as well as the increase in TEWL value, were the most severe among the Chinese too. It is well known that retinol and retinoid treatments also cause temporary skin barrier disruption. Therefore, regular retinol treatment is not suitable for the Chinese.

Microencapsulation technology is a common method to improve the mildness of actives by controlled release mechanism. For example, Ye et al.[15] formulated an eye cream containing a supramolecular retinol with 0.1% active concentration plus 3% acmella oleracea extract to address the skincare concerns of urban Chinese eye skin. Retinol was encapsulated through cavitation in hydroxypropyl γ-cyclodextrin, which was then associated with the associating agent through intermolecular force to form the supramolecular retinol structure.[15] The supramolecular retinol was reported by the authors to improve stability and reduce irritation of retinol in the eye cream formula. Indeed, their patch result showed 0 skin adverse reactions among the 31 volunteers. Nevertheless, their 6-week clinical study indicated tolerance establishment was still necessary as six subjects showed mild adverse reactions, such as slight redness, itching, and tingling around the eyes

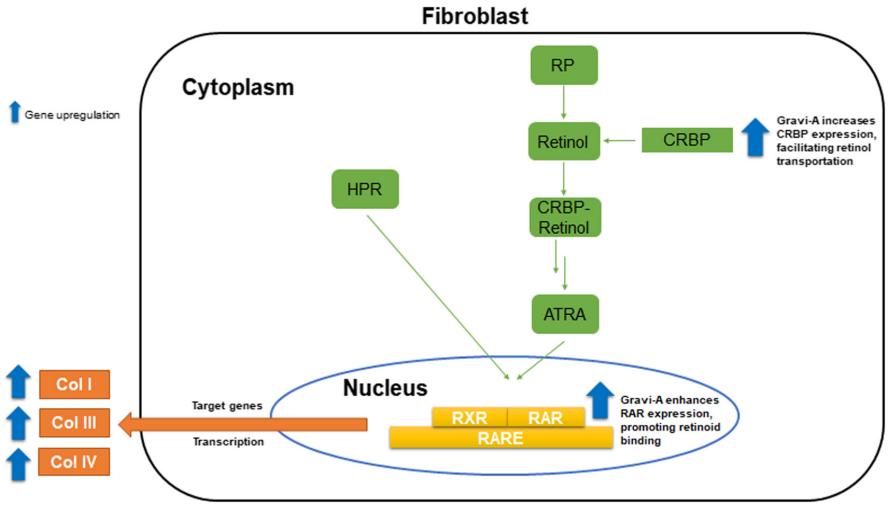

FIGURE 7 The proposed synergy mechanism of the optimal HPR and RP combination.

during the first week of using the eye cream.[15] Alternatively, in this study we demonstrated that the optimal HPR and RP combination treatment strengthened skin barrier function unlike other retinoids as the TEWL value had started decreasing since the first week use of the serum. In addition to the superior patch test result, there was no adverse reaction reported in this 8-week clinical study among 42 Chinese volunteers. This further supported the better safety profile of Gravi-A compared to retinol for Chinese consumers, and the tolerance establishment may not be needed for the optimal HPR and RP combination.

Not only did Gravi-A serum render mildness unlike regular retinol product, it also achieved appealing antiaging clinical efficacies. All the antiaging attributes, including skin wrinkles, smoothness, and elasticities, had started showing statistically significant changes since Week 2 use of the serum. At both Week 4 and Week 8, skin pore improvement, various wrinkles reduction and overall skin tone and radiance enhancement were confirmed by the VISIA-CR characterization. Furthermore, the antiaging performance of the Gravi-A serum confirmed by the instrumental analysis could be perceived by the volunteers in the clinical study based on their self-assessment results. This promising clinical result clearly indicates that Gravi-A treatment unlike regular retinol is the optimal antiaging approach for the Chinese.

5 | CONCLUSION

The combination of HPR and RP at 5:9 weight ratio termed Gravi-A was shown to be the optimal retinoids to maintain the skin intracellular homeostasis in this study. Their joint action directly increased CRBP I and RARB mRNA transcriptional levels, positively regulating antiaging signaling pathways. Their treatment on aging skin significantly induced dermal collagen synthesis. Compared with individual retinoid treatment, the combination of HPR and RP at 5:9 weight ratio demonstrated both short- and long-term effectiveness in terms of promoting collagen regeneration. Unlike retinol causes skin irritations, the optimal HPR and RP combination showed excellent safety profile. This was further supported by the clinical research of the skincare serum, which revealed its antiaging benefits without any adverse reactions. Since literature suggests the Chinese is the most susceptible to retinoid irritations, our study indicated that the combination of retinyl propionate and hydroxypinacolone retinoate is a potent therapeutic strategy suitable for the Chinese with high safety profile to prevent skin aging.

AUTHOR CONTRIBUTIONS

Q.W. designed the research study and performed the research. F.H. analyzed the data and wrote the original draft. X.H. collected and analyzed the data. Y.X. designed and supervised the research. L.D. supervised the research and contributed essential reagents and tools. R.Y. revised the draft.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST STATEMENT

The authors have no other conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICAL APPROVAL

The research protocol was examined and approved by the China-norm Ethics Committee for Clinical Research. Benefits, risks, and potential complications were explained to the subjects. All subjects voluntarily participated in this study and signed an informal consent form.

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