

THE EFFICACY OF 2% COPPER PEPTIDE (GHK-Cu) SERUM FOR EYEBROW HYPOTRICHOSIS: A RANDOMIZED, DOUBLE-BLIND, VEHICLE-CONTROLLED, SPLIT-FACE COMPARATIVE STUDY

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ABSTRACT

Background: Eyebrows contribute significantly to facial aesthetics, expression, and personal identity. Sparse or thinning eyebrow hair may negatively affect appearance and self-confidence. Copper peptides, particularly glycyl-L-histidyl-L-lysine copper complex (GHK-Cu), have demonstrated wound-healing, anti-inflammatory, and hair growth-promoting properties; however, evidence regarding their effectiveness for eyebrow enhancement remains limited.

Objective: To evaluate the efficacy and safety of 2% copper peptide (GHK-Cu) serum for improving eyebrow hair growth and density.

Materials and Methods: A randomized, double-blind, placebo-controlled, split-face clinical trial was conducted in 18 healthy participants aged 18–40 years. Each participant applied 2% GHK-Cu serum to one eyebrow and placebo serum to the opposite eyebrow twice daily for 12 weeks. Eyebrow hair count, hair diameter, and global photographic assessment scores (GPAS) were evaluated using standardized photographic assessments. Participant satisfaction and adverse effects were also assessed.

Results: The GHK-Cu serum-treated side demonstrated significant improvement in eyebrow hair count and diameter compared with the placebo side, particularly at week 12. Hair count significantly increased from baseline on the treated side ($p < 0.05$), while no significant changes were observed on the placebo side. Hair diameter also showed significant improvement after 12 weeks of treatment. GPAS and participant satisfaction scores were significantly higher on the GHK-Cu-treated side throughout the follow-up period. No serious adverse effects or allergic reactions were reported.

Conclusion: Topical 2% GHK-Cu serum was safe, well tolerated, and effective in improving eyebrow hair count, thickness, and overall appearance, suggesting its potential as a non-invasive cosmetic option for eyebrow enhancement.

Keywords: Eyebrow Hypotrichosis, Copper Peptide (GHK-Cu), Eyebrow Hair Growth, Split-Face Study, Randomized Controlled Trial, Topical Serum

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INTRODUCTION

Eyebrows possess the ability to protect our eyes from perspiration and dust, serving a protective function. They also play a significant role in facial expression, nonverbal communication, and personal identity. Together with other coordinated facial movements, eyebrows are capable of expressing a variety of emotions, including surprise, anger, and happiness. Additionally, they assist in facial attractiveness and contribute to sexual dysmorphism through their distinct color, shape, intensity, and distribution (Sadr et al., 2003). For those reasons, eyebrows are an important part of the facial characteristics, and people often undergo aesthetic procedures to recreate them. Eyebrow hypotrichosis is an undesirable condition that could impact a person's self-confidence and also have an effect on psychosocial interactions (Zaky et al., 2023). Although eyebrow hypotrichosis can have a negative influence on physical characteristics, it does not get as much attention as scalp hair loss. In clinical practice, it could become a challenging issue as a primary complaint or a positive finding during a routine physical examination (Velez et al., 2007). Causes of eyebrow hypotrichosis may vary from idiopathic or secondary to underlying conditions, such as primary dermatoses, endocrine disorders, autoimmune diseases, infections, trauma, neoplasms, nutritional disorders, etc. (Velez et al., 2007). Currently, there are only a few options available for eyebrow hypotrichosis treatment because of the limitations of the recommended medications. Cosmetic camouflage techniques such as microblading, tattooing, eyebrow transplantation, and topical medications are among the potential therapeutic approaches; however, their effectiveness can vary greatly (Chanasumon et al., 2018). The human copper-binding peptide GHK-Cu (glycyl-L-histidyl-L-lysine-Cu²⁺) is a small, naturally occurring tripeptide found in human plasma, saliva, and urine. It can be released during proteolytic degradation of proteins in the extracellular matrix following tissue injury (Pickart, 2008). Numerous studies have demonstrated its efficacy in wound healing and its ability to stimulate the synthesis of collagen, elastin, proteoglycans, and glycosaminoglycans. It also possesses anti-inflammatory, antioxidant, and hair growth-promoting properties (Schagen, 2017). Due to its exceptional benefits, synthetically derived GHK-Cu complexes are widely utilized in various skin care products, including those for rejuvenation, anti-aging, anti-wrinkle, after-sun care, skin moisturization, and hair growth (Schagen, 2017; 刘林 et al., 2013). The positive impact of GHK-Cu on hair growth has been shown through various mechanisms. One study demonstrates its potency as a stimulator of follicle growth and preservation in animal models (Trachy et al., 1991). Moreover, numerous studies suggest that GHK-Cu stimulates the proliferation of dermal papilla cells, which play a crucial role in regulating hair follicle growth cycles. Additionally, it can increase the expression of growth factors, such as vascular endothelial growth factor (VEGF), which promotes blood vessel formation and thus supports the nourishment and growth of hair follicles (Namjoshi et al., 2008). Overall, GHK-Cu holds promise as a potential therapeutic agent for promoting hair growth and addressing hair loss concerns. However, its efficacy specifically for eyebrow hair stimulation remains unknown. Conducting a study would provide valuable information regarding the potential therapeutic benefits of GHK-Cu for eyebrow hypotrichosis and possibly providing an effective solution for people who want to improve the appearance of their eyebrows.

LITERATURE REVIEWS

Anatomical Structure and Physiology of Eyebrow Hair

Eyebrow hair shares similar anatomical and physiological characteristics with other body hair. The hair follicle is composed of lower, middle, and upper segments, while the hair shaft consists of three layers: the medulla, cortex, and cuticle, which contribute to hair structure, pigmentation, and protection (Park et al., 2018). Eyebrow hair growth follows a cyclical process consisting of anagen, catagen, and telogen phases (Nguyen, 2014). Compared with scalp hair, eyebrow follicles have a relatively short anagen phase of approximately 2–4 weeks, which limits hair length and growth potential (Park et al., 2018). In addition, only a small proportion of eyebrow follicles remain in the

active growth phase at a given time. Hair growth and cycling are influenced by multiple factors, including hormones, cytokines, age, nutrition, and environmental conditions (Wolfram, 2003).

Eyebrow Hypotrichosis: Etiology and Treatment

Eyebrow hypotrichosis is a condition characterized by reduced eyebrow hair density or complete absence of growth, often causing significant cosmetic and psychological distress (Chanasumon et al., 2018). Although its exact prevalence is unclear, studies in related conditions such as alopecia areata show variable involvement of the eyebrows, ranging from mild thinning to complete loss (Nguyen et al., 2023). The condition may be idiopathic or associated with a wide range of underlying causes, including dermatological, endocrine, autoimmune, infectious, traumatic, neoplastic, nutritional, drug-induced, and genetic disorders (Velez et al., 2007). Current treatment options for eyebrow hypotrichosis include cosmetic camouflage, microblading, tattooing, hair transplantation, and topical therapies (Zaky et al., 2023). Cosmetic approaches such as brow pencils, tattooing, and microblading can improve appearance but require maintenance and may be associated with complications including irritation, allergic reactions, or infection (Marwah et al., 2021; Ortiz & Alster, 2012). Hair transplantation provides a more permanent option but is technically demanding and dependent on surgical expertise (Klingbeil & Fertig, 2018). Among topical therapies, bimatoprost and minoxidil have demonstrated beneficial effects on eyebrow growth and patient satisfaction (Lee et al., 2014; Suchonwanit et al., 2019). In addition, management of underlying medical conditions, such as dermatitis, hypothyroidism, or autoimmune diseases, may contribute to eyebrow regrowth and improved outcomes (Nguyen et al., 2023).

Copper Peptide (GHK-Cu) and Its Role in Skin and Hair Regeneration

GHK-Cu (glycyl-L-histidyl-L-lysine copper complex) is a naturally occurring peptide first identified in human plasma, recognized for its strong affinity for copper ions and its important role in tissue repair and regeneration (Pickart et al., 1973). It is produced during normal tissue turnover and following injury, although its levels decline with age. Due to its small molecular size, GHK can readily interact with cellular receptors and facilitate copper transport into cells, enabling a wide range of biological effects. As a result, GHK-Cu has been widely incorporated into skincare and hair care products for its ability to promote collagen synthesis, improve skin elasticity and firmness, reduce wrinkles and photodamage, and enhance hair growth and follicle size (Dou et al., 2020; Pickart & Margolina, 2018). Extensive research has demonstrated that GHK-Cu plays a significant role in wound healing, tissue remodeling, angiogenesis, and anti-inflammatory and antioxidant processes. It promotes extracellular matrix formation, stimulates collagen production, and accelerates wound healing, including improved outcomes in chronic ulcers (Maquart et al., 1993; Mulder et al., 1994). Furthermore, GHK-Cu enhances angiogenesis by upregulating growth factors such as VEGF and bFGF, thereby supporting tissue repair (Pollard et al., 2005). Its antioxidant and anti-inflammatory properties help reduce reactive oxygen species and inflammatory mediators, while also preventing protein glycation and maintaining skin integrity (Cebrián et al., 2005; Sakuma et al., 2018). Clinical studies further support its efficacy in skin rejuvenation, demonstrating improvements in skin density, thickness, and wrinkle reduction, highlighting its value as both a therapeutic and cosmetic agent (Badenhorst et al., 2016; Leyden et al., 2002). In addition to its dermatological benefits, GHK-Cu and related copper peptides have shown significant potential in promoting hair growth through multiple biological mechanisms. Both intradermal injection and topical application have been found to stimulate hair follicles and enhance follicular cell proliferation, partly by reducing apoptosis and promoting cell survival through pathways such as Bcl-2/Bax regulation and caspase inhibition (Pyo et al., 2007; Trachy et al., 1991). Experimental studies also suggest that copper peptides can convert vellus hairs into thicker terminal hairs and prolong the anagen phase, with effects comparable to minoxidil (Uno & Kurata, 1993). Additionally, GHK-Cu supports stem cell activity and keratinocyte proliferation by influencing markers such as p63 and PCNA (Kang et al., 2009). Clinical evidence further demonstrates increased hair count in patients treated with GHK-containing compounds, while GHK-Cu-based products have also been shown to improve post-hair transplantation outcomes by accelerating regrowth and enhancing healing, underscoring their promising role in hair restoration (Lee et al., 2016; Pickart, 2008).

From the literature review, the conceptual framework can be drawn as shown in Figure 1.

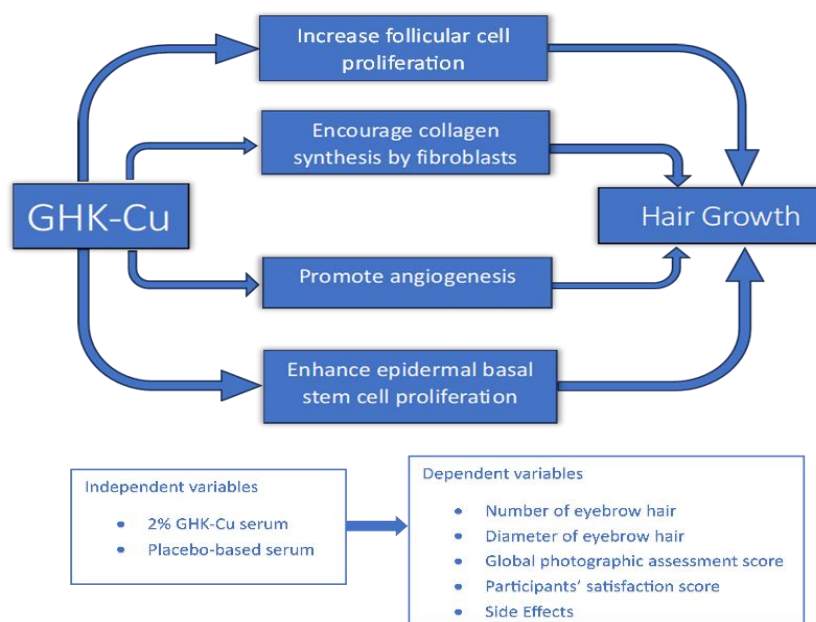


Figure 1 Conceptual Framework

RESEARCH METHODOLOGY

This study was designed as a randomized, double-blind, placebo-controlled, split-face clinical trial to evaluate the efficacy of 2% GHK-Cu serum in improving eyebrow appearance. A split-face design allowed direct comparison between treated and placebo areas within the same participant, improving reliability and minimizing inter-individual variability. A total of 18 participants aged 18–40 years with idiopathic eyebrow hypotrichosis were included in the study, which was conducted at Mae Fah Luang University Hospital, Bangkok. Participants were selected based on predefined inclusion and exclusion criteria to ensure suitability and safety for study participation. The inclusion criteria were as follows: participants aged 18–40 years; healthy male and female volunteers residing in Bangkok, Thailand; individuals seeking to improve eyebrow hair growth and density; those diagnosed by a research doctor with eyebrow hypotrichosis graded as 1 or 2 on the 4-point GEBA scale (1 = very sparse, 2 = sparse, 3 = full, 4 = very full) without significant underlying medical causes; and individuals who were able to comply with study procedures for 3 consecutive months and provided voluntary consent. The exclusion criteria included individuals with underlying medical conditions affecting hair growth, such as primary dermatoses (e.g., atopic dermatitis, seborrheic dermatitis), thyroid disorders, autoimmune diseases (e.g., alopecia areata, discoid lupus erythematosus, frontal fibrosing alopecia), infectious diseases (e.g., leprosy, secondary syphilis), psychiatric-related hair disorders (e.g., trichotillomania, trichotemnomania), and genetic conditions (e.g., ectodermal dysplasia). Individuals who had used medications affecting hair growth within the past 6 months—such as minoxidil, finasteride, dutasteride, spironolactone, phenytoin, cyclosporin, or steroids—were also excluded. Additional exclusions included a history of chemotherapy or radiotherapy, significant systemic illnesses (e.g., cardiovascular, renal, hepatic diseases, or malignancy), scars or trauma in the eyebrow area, prior cosmetic procedures (e.g., tattooing, microblading) or eyebrow transplantation, pregnancy or breastfeeding, and known allergy to copper peptide.

Potential participants received a comprehensive explanation of the study, and the consent process ensured that they fully understood the study before agreeing to take part. After obtaining consent, baseline measurements were performed. A straight-angle photograph of each participant's

eyebrows was taken using the VISIA® Skin Analysis System to assess the global photographic score. In addition, a 1 cm² region of each eyebrow, located along the mid-pupil line, was photographed using the Visioscan® VC 20plus. Each hair within the captured image was counted, and the diameter of the eyebrow hair was determined by measuring the width at the base of each follicle. The same measurement procedures were repeated at weeks 4, 8, and 12 following serum application to evaluate changes in eyebrow density, hair count, and diameter over time. Randomization was performed using a fixed block method to assign either the 2% GHK-Cu serum or placebo to the left or right eyebrow, ensuring balanced distribution. Both formulations were identical in appearance, texture, and odor to maintain blinding. Participants were instructed to apply the assigned serum twice daily for 12 weeks, using separate applicators and techniques to avoid cross-contamination. A patch test was conducted prior to treatment initiation to ensure safety, and individuals with adverse reactions were excluded. The placebo serum contained the same base formulation without the active ingredient to allow accurate comparison of treatment effects. Participants were closely monitored throughout the study for any adverse reactions, and ethical safeguards were implemented, including confidentiality measures such as anonymized photographic data. Outcome measures included both objective and subjective assessments, including changes in eyebrow hair count and diameter, global photographic assessment scores, participant satisfaction, and safety evaluation for side effects.

RESEARCH RESULTS



Figure 2 Photos of subject showing before and after 12th week result on 2% copper peptide (GHK-Cu) serum treated side

Table 1 Statistical comparison of eyebrow hair count, eyebrow hair diameter, and Global Photographic Assessment Scores (GPAS) between the active serum-treated side and the placebo-treated side at baseline and at weeks 4, 8, and 12 (n = 18).

Number of eyebrow hair	(GHK-Cu) active serum side	Placebo side	Paired differences ± SE	p-value ^(a)
	Mean ± SD	Mean ± SD		
Baseline	28.89 ± 5.910	28.78 ± 4.545	0.111 ± 0.804	0.892
Week 4	28.78 ± 5.976	28.67 ± 4.728	0.111 ± 0.867	0.899
Week 8	29.28 ± 5.899	28.11 ± 4.549	1.167 ± 0.715	0.121
Week 12	30.50 ± 5.773	28.67 ± 4.102	1.833 ± 0.864	0.049
p-value ^(b)	p = 0.001	p = 0.075		
Diameter of eyebrow hair				
Baseline	1.83 ± 0.28	1.77 ± 0.21	0.054 ± 0.04	0.213
Week 4	1.83 ± 0.29	1.77 ± 0.21	0.062 ± 0.043	0.175
Week 8	1.85 ± 0.31	1.76 ± 0.21	0.083 ± 0.041	0.055
Week 12	1.88 ± 0.30	1.78 ± 0.22	0.10 ± 0.044	0.036

p-value ^(b)	p = 0.005	p = 0.236		
GPAS score				
Week 4	0.83 ± 0.514	0.33 ± 0.485	0.5 ± 0.146	0.003
Week 8	1.11 ± 0.417	0.56 ± 0.511	0.556 ± 0.166	0.004
Week 12	1.44 ± 0.705	0.78 ± 0.548	0.667 ± 0.229	0.010
p-value ^(b)	P < 0.001	P = 0.028		

Statistical analysis was performed using a paired t-test and repeated measures ANOVA.

^(a)Paired Samples Test, ^(b)Repeated measurement ANOVA

Table 2 Post-hoc multiple comparison analysis of eyebrow hair count, diameter, and GPAS.

Number of eyebrow hair	Compare to	(GHK-Cu) active serum side	Placebo side
		p - value	p - value
Baseline	Week 4	1	1
Baseline	Week 8	1	0.058
Baseline	Week 12	0.005	1
Week 4	Week 8	0.645	0.278
Week 4	Week 12	0.003	1
Week 8	Week 12	0.03	0.456
Diameter of eyebrow hair			
Baseline	Week 4	1	1
Baseline	Week 8	1	1
Baseline	Week 12	0.04	1
Week 4	Week 8	1	1
Week 4	Week 12	0.077	1
Week 8	Week 12	0.089	0.67
GPAS score			
Week 4	Week 8	0.288	0.021
Week 4	Week 12	0.005	0.001
Week 8	Week 12	0.147	0.104

Post-hoc comparisons were conducted using the Wilcoxon signed-rank test with Bonferroni correction.

Prior to statistical analysis, data normality was assessed using the Shapiro–Wilk test due to the relatively small sample size, and all variables showed approximately normal distribution ($p > 0.05$). Therefore, parametric tests, including paired t-tests and repeated measures ANOVA, were applied, while post-hoc comparisons were analyzed using the Wilcoxon signed-rank test with Bonferroni correction.

Number of eyebrow hairs

The mean number of eyebrow hairs on the active serum–treated side increased significantly from 28.89 ± 5.910 at baseline to 30.50 ± 5.773 at week 12 ($p = 0.001$), whereas the placebo-treated side showed no significant change over time ($p = 0.075$). No significant differences between the two sides were observed at baseline, week 4, or week 8; however, by week 12, the active serum side demonstrated a significantly higher eyebrow hair count than the placebo side (mean difference = 1.833 ± 0.864 , $p = 0.049$). Post-hoc analysis showed significant increases on the active serum side at week 12 compared with baseline, week 4, and week 8 ($p < 0.05$), while no significant differences were found on the placebo side throughout the study period.

Diameter of eyebrow hair

The mean diameter of eyebrow hairs on the active serum–treated side increased significantly from 1.83 ± 0.28 at baseline to 1.88 ± 0.30 at week 12 ($p = 0.005$), whereas the placebo-treated side

showed no significant changes throughout the study period ($p = 0.236$). No significant differences between the two sides were observed at baseline, week 4, or week 8; however, by week 12, the active serum side demonstrated a significantly greater eyebrow hair diameter than the placebo side (mean difference = 0.10 ± 0.044 , $p = 0.036$). Post-hoc analysis showed a significant increase in hair diameter on the active serum side at week 12 compared with baseline ($p = 0.040$), while no significant differences were observed between earlier time points or on the placebo side. These findings suggest that meaningful improvement in eyebrow hair thickness became evident only after 12 weeks of active serum application.

Global Photographic Assessment Score (GPAS score)

The mean GPAS scores on the active serum side increased progressively from week 4 to week 12, demonstrating a statistically significant improvement over time ($p < 0.001$), while the placebo side showed only mild improvement ($p = 0.028$). Comparisons between the two sides revealed significantly higher GPAS scores on the active serum side at week 4 ($p = 0.003$), week 8 ($p = 0.004$), and week 12 ($p = 0.010$), indicating superior clinical outcomes with the active serum. Post-hoc analysis showed a significant improvement on the active serum side between week 4 and week 12 ($p = 0.005$), reflecting a gradual and sustained effect over time. In contrast, the placebo side demonstrated improvement mainly during the early phase of the study, with no significant difference observed between week 8 and week 12, suggesting that the effect stabilized after the midpoint of the study.

Research Participants' Satisfaction Score

At the 12-week follow-up assessment, the mean patient satisfaction score for the GHK-Cu active serum-treated side was 1.83 ± 0.86 , whereas the placebo-treated side showed a lower mean score of 0.67 ± 0.49 . Statistical analysis revealed that patient satisfaction was significantly higher on the active serum side compared with the placebo side, with a mean paired difference of 1.167 ± 0.218 ($p = 0.001$). These findings suggest that participants were considerably more satisfied with the effects of the active serum than with the placebo treatment at the conclusion of the 12-week study period.

Safety Evaluation

Safety assessment was conducted at each follow-up visit by evaluating the presence of local cutaneous reactions and participant-reported symptoms on both the active serum side and the placebo side. The parameters assessed included burning sensation, erythema, itching, dryness, scaling, vesicle formation, edema, flaking, abnormal hair growth, and any other treatment-related adverse effects. Throughout the 12-week study period, no adverse events or local skin reactions were observed in any participant on either the copper peptide (GHK-Cu) serum side or the placebo side. Clinical examination revealed no evidence of irritation, inflammation, or hypersensitivity reactions at any evaluation time point. Participants also did not report discomfort, intolerance, or complications associated with the application of the study products.

DISCUSSION & CONCLUSION

This study evaluated the efficacy of 2% copper peptide (GHK-Cu) serum compared with placebo for eyebrow enhancement in a population primarily composed of young, healthy adults. Most participants were female, with a mean age of 28.94 years. Standardized photographic and clinical assessment tools, including the VISIA® Skin Analysis System and Visioscan® VC 20plus, were used to evaluate eyebrow hair count, diameter, global photographic assessment scores (GPAS), and patient satisfaction. The findings demonstrated that the GHK-Cu serum-treated side showed significantly greater improvements compared with the placebo side, particularly by week 12. The results showed that eyebrow hair count and diameter increased significantly on the GHK-Cu-treated side, with meaningful changes becoming evident after prolonged application. In contrast, the placebo side showed no significant changes in these parameters. Although GPAS scores improved on both sides, the active serum consistently demonstrated significantly higher scores at

all follow-up visits, indicating superior clinical outcomes. Patient satisfaction scores followed a similar trend, with significantly higher ratings observed on the active serum side at the final follow-up. The delayed significant improvement in eyebrow hair diameter observed at week 12 may be related to the relatively short anagen phase of eyebrow hair compared with scalp hair. Therefore, prolonged and consistent application of GHK-Cu serum may be required before measurable changes in hair thickness become clinically evident. Importantly, the 2% GHK-Cu serum was found to be safe and well tolerated. No allergic reactions were observed during patch testing, and no adverse events such as irritation, redness, or itching were reported throughout the study period, supporting its safety for topical cosmetic use in the eyebrow area. The observed improvements may be explained by the biological mechanisms of GHK-Cu, including stimulation of dermal fibroblasts, increased collagen synthesis, promotion of dermal papilla cell proliferation, and upregulation of growth factors such as VEGF, which enhance angiogenesis and follicular support. These mechanisms contribute to increased hair thickness and density. Consistent with previous experimental and clinical findings, the results of this study indicate that 2% GHK-Cu serum is a safe, well-tolerated, and effective topical option for enhancing eyebrow hair growth and density.

Limitations

This study was limited by its small sample size of 18 participants, which may reduce statistical power and limit the generalizability of the findings. In addition, the study included only healthy participants aged 18–40 years with idiopathic eyebrow hypotrichosis and had a relatively short follow-up period of 12 weeks, limiting applicability to other populations and long-term outcomes. Nevertheless, the split-face, double-blind, placebo-controlled design strengthened the internal validity of the study by minimizing inter-individual variability and treatment bias.

Conflict of Interest

The author declare no conflict of interest.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Conflicts of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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