doi:10.36849/JDD.8760e

 BRIEF COMMUNICATION Journal of Drugs in Dermatology

Acetyl Hexapeptide-8 as a Topical Alternative to Botulinum Toxin: A Review of the Literature

Kalisa Lum BS,[a*] Milan M. Hirpara BA,[b*] Christine Pham MD,[b]
Megan Nguyen BS,[b] Natasha Mesinkovska MD PhD[b]

[a]School of Medicine, Loma Linda University Health, Loma Linda, CA
[b]Department of Dermatology, University of California, Irvine, CA

*Equal Contributors

INTRODUCTION

Acetyl hexapeptide-8, marketed as Argireline® (Lipotec, Barcelona, Spain), is a six-amino-acid biomimetic of botulinum toxin promoted as a wrinkle-reducing compound. It entered the market in 2001 and has grown in popularity, as evidenced by a progressively increasing volume of Google searches from 2013 to 2023.[1]

Acetyl hexapeptide-8 is applied topically as a cream or serum and is marketed as a less invasive and less expensive alternative to botulinum toxin. Compared to botulinum toxin, acetyl hexapeptide-8 is both less potent (12 vs 0.003 AAUs) and less toxic (2000 mg/kg vs 20 ng/kg).[2] Additionally, consumers may pay from $10 to $30 per ounce for drugstore products to $100 to $300 per ounce for premium formulations containing acetyl hexapeptide-8.[3] Comparatively, full-face applications of botulinum toxin can cost $1000 to 3000.[3] Our objective was to review the current literature on acetyl hexapeptide-8 and its efficacy in wrinkle minimization.

MATERIALS AND METHODS

A literature search was conducted in August 2024 utilizing PRISMA guidelines using the PubMed, Cochrane Library, and Embase databases with search terms, '"acetyl hexapeptide-8" OR "acetyl hexapeptide-3" OR "argireline"'. Inclusion criteria included human studies evaluating cutaneous effects of acetyl hexapeptide-8. Exclusion criteria included non-human studies, non-English studies, studies not analyzing the cutaneous effects of acetyl hexapeptide-8, and articles without available full text.

RESULTS

Ten studies (302 females, and 10 males) met our inclusion criteria (Table 1).[4-12] Four studies[4-7] analyzed the isolated effect of acetyl hexapeptide-8. Five studies[8-12] explored the efficacy of multi-ingredient formulations, and 1 study[13] assessed both its isolated effects and in combination with other compounds. All 10 studies reported decreases in wrinkle and scar prominence although significance varied. No significant adverse effects were reported in any trial.

All 4 studies describing the isolated effects of acetyl hexapeptide-8 reported significant changes in wrinkle appearance. Blanes-Mira et al[4] used Confocal Microscopy and 3D analyses to measure topography. Ruiz et al[5] measured skin hydration and wrinkle size using Clinipro Antiaging SD with the IMAGE DB system. Wang et al[6] measured topography with Skin-Visioline VL 650® and SPSS 17.0 software. Tadini et al[7] used the Corneometer® CM for skin hydration, and the CutometerSEM 575 and ReviscometerRV600 for anisotropy.

Four of 5 studies that utilized multi-ingredient formulations showed statistically significant changes in wrinkle and scar appearance. An et al[8] utilized Antera 3D® (Miravex, Ireland). Henseler[9] created wrinkle scores and biologic age comparisons with the Visia® Complexion Analysis camera. Palmieri et al[10] measured scar hydration (DermaLabR USB), skin elasticity (ElastiMeter R), sebum levels (Sebumeter SM 815), and used photos and SF-36 quality of life questionnaires. Li et al[11] used the Corneometer CM825, Skin Elastometer MPA580, PRIMOS CR technique, and self-assessment questionnaires. Draelos et al[12] used investigator evaluations, subject evaluations, and facial photographs. Raikou et al[13] measured both the isolated and adjunctive effects of acetyl hexapeptide-8 on microtopography (Skin Visioscan VC98) and transepidermal water loss (tewameter).

doi:10.36849/JDD.8760e

TABLE 1.

Summary of Clinical Studies Describing the Cutaneous Effects of Topical Acetyl Hexapeptide-8

Study	Demographics			Study Characteristics				Outcomes	Severe Adverse Effects
	n	Sex (% F)	Age Range; Mean (y)	Type	Active Ingredients	Location	Follow-up (d)		
Blanes-Mira et al[4±]	10	100	NA	Prospective	10% AH-8 (O/W emulsion)	Periorbital	30	30% decrease in wrinkle depth and texture*	None reported
Ruiz et al[5±]	20	100	40-57	RCT	AH-8 O/W gel and cream	Full face	30	Decreased wrinkle depth*; Decreased wrinkle width	None reported
Wang et al[6±]	60	83.3	25-60	RCT	10% AH-8 (O/W emulsion)	Periorbital	28	Decreased wrinkle height*; Subjective wrinkle improvement in 48.9% patients	None
Tadini et al[7±]	40	100	33-55	RCT	10% AH-8 (W/W)	Ventral forearm, full face	28	Decreased anisotropy of facial skin*; Increased facial stratum corneum water content*	None reported
An et al[8]	52	100	37-57; 45.02±4.85	RCT; split-face	0.005% AH-8 (W/W) and hyaluronic acid-based microneedle patch	Perioral, periorbital	29	Deceased wrinkle severity*	None
Henseler[9]	19	100	24-68; 51.1±10.4	RCT; split-face	10% AH-8 in triple hyaluronic acid serum	Hemiface	28	Decreased wrinkle score	None
Palmieri et al[10]	26	100	23-63	Retrospective	10% AH-8, magnesium aluminum silicate, and sodium silicate	Chin, neck, forehead, malar area	NA	Increased scar elasticity*; Reduced sebum levels*; Decreased hydration of affected area*; Increased QOL*	None
Li et al[11]	32	100	20-45; 28.5	Prospective	10% AH-8, 4% combination of palmitoyltetrapeptide-7 and palmitoyl tripeptide-1, and 2% combination of dipeptide-2, palmitoyl tetrapeptide-7, and hesperidin methyl chalcone	Periorbital	28	Decreased wrinkle number, depth, and volume*; Subjective wrinkle improvement in 75% patients	None
Draelos et al[12]	29	100	35-60; 47±6.6	Prospective	Serum containing gamma-aminobutyric acid and 7 peptides including AH-8, acetyl octapeptide-3, dipeptide diaminobutyroyl benzylamide diacetate, trifluoroacetyl tripeptide-2, and palmitoyl tetrapeptide-7	Crow's feet, glabella, forehead	98	Decreased severity of facial lines, facial wrinkles, eye lines, eye wrinkles*	None
Raikou et al[13±]	24	100	30-60; 45±5	RCT	10% AH-8 (W/W); 10% AH-8 (W/W) and 5% tripeptide-10 citrulline (W/W)	Forehead, periorbital	60	Decreased cR2 & cR3 in both formulations; Decreased TEWL in isolated formulation*; Increased TEWL in multi-serum formulation	None

* = statistically significant
± = included isolated acetyl hexapeptide-8 formulation
AH-8 = acetyl hexapeptide-8, cR2 = measure of maximal roughness of skin, cR3 = measure of average roughness of skin F = Female, NA = not applicable, RCT = randomized control trial, O/W = oil-in-water, TEWL = transepidermal water loss, W/W = weight-by-weight

DISCUSSION

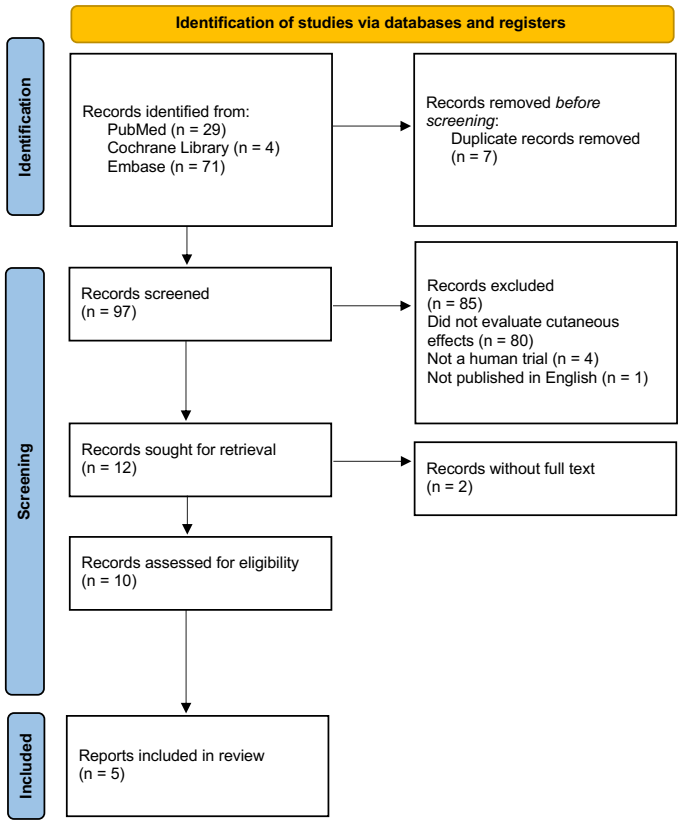
Acetyl hexapeptide-8 is marketed as a milder, non-invasive option for anti-aging treatment because its proposed mechanism of action mimics botulinum toxin. All 10 studies showed improvements in wrinkle appearance with acetyl hexapeptide-8 though statistical significance was inconsistent. Six showed significant improvement in wrinkle parameters.[4-6,8,11,12] Tadini et al showed significant changes in anisotropy, and Palmieri et al reported significant reductions in scar severity. Studies suggest acetyl hexapeptide-8 may be more effective as an adjunct.[9-13] However, only Raikou et al tested acetyl hexapeptide-8 in isolation and combination, making it unclear if improvements are due to synergistic effects or other ingredients.

No standardized acetyl hexapeptide-8 serum formulas were used in these studies, highlighting the need to consider its cutaneous absorption. Kraeling et al analyzed percutaneous penetration of acetyl hexapeptide-8 using hairless guinea pigs and cadaver human skin.[14] After applying the emulsion of 2 mg/cm^2 and washing the skin, 99.4% of the metabolite was removed. Only a small proportion reached the epidermis: 0.54% in the stratum corneum and 0.01% in the epidermis, indicating minimal absorption. Acetyl hexapeptide-8's large molecular weight (889 Dalton) and hydrophilic nature likely cause its poor transdermal permeability. Several recent studies have investigated various methods to enhance skin penetration of acetyl hexapeptide-8 and have shown promising results.[15-17]

Limitations of this review included study design and an inability to direct comparisons. Study design limitations include small sample sizes, short follow-up, and predominance of female participants (97%). Comparing results was challenging due to varying methodologies and the absence of standardized wrinkle analysis methods. Furthermore, no study directly compared acetyl hexapeptide-8 to botulinum toxin, raising questions about the required concentration for comparable efficacy.

doi:10.36849/JDD.8760e

FIGURE 1. PRISMA diagram showing articles identified for inclusion in the review.



CONCLUSION

Current data suggests that acetyl hexapeptide-8 may improve wrinkle appearance, but the significance is unclear due to varying quantification methods. Utilization of acetyl hexapeptide-8 in a multi-ingredient topical shows more consistent and promising results, but formulations vary widely. Compared to botulinum toxin, acetyl hexapeptide-8 has lower potency and toxicity with no serious adverse effects reported. Given the poor intrinsic cutaneous absorption of acetyl hexapeptide-8, further investigation and development of vehicles of application for acetyl hexapeptide-8 are necessary. Larger studies with broader subject populations comparing the effects of acetyl hexapeptide-8 with botulinum toxin using standardized methodology are also needed.

DISCLOSURES

No funding was received for this work. None of the authors disclose conflict of interest related to this work.

REFERENCES

1. Olsson SE, Sreepad B, Lee T, et al. Public interest in acetyl hexapeptide-8: Longitudinal analysis. *JMIR Dermatology.* 2024;7. doi:10.2196/5421.
2. Wang Y, Wang M, Xiao XS, et al. The anti-wrinkle efficacy of Argireline. *J Cosmet Laser Ther.* 2013;15(4):237-241. doi:10.3109/14764172.2013.769273.
3. Grand View Research. *Anti-Aging Market Size & Share Report, 2022-2030.* Grand View Research, Inc. Available from: https://www.grandviewresearch.com/industry-analysis/anti-aging-market. Accessed August 18, 2024.
4. Blanes-Mira C, Clemente J, Jodas G, et al. A synthetic hexapeptide (Argireline) with antiwrinkle activity. *Int J Cosmet Sci.* 2002;24(5):303-310. doi:10.1046/j.1467-2494.2002.00153.x.
5. Ruiz Martínez MA, Clares Naveros B, Morales Hernández ME, et al. Evaluation of the anti-wrinkle efficacy of cosmetic formulations with an anti-aging peptide (Argireline®). *Digibug.* 2010;50(4). http://hdl.handle.net/10481/27392.
6. Wang Y, Wang M, Xiao S, et al. The anti-wrinkle efficacy of Argireline, a synthetic hexapeptide, in Chinese subjects. *Am J Clin Dermatol.* 2013;14(2):147-153. doi:10.1007/s40257-013-0009-9.
7. Tadini K, Mercurio D, & Campos P. Acetyl hexapeptide-3 in a cosmetic formulation acts on skin mechanical properties-clinical study. *Brazilian Journal of Pharmaceutical Sciences.* 2015;51(4). doi:10.1590/S1984-82502015000400016
8. An JH, Lee HJ, Yoon MS, Kim DH. Anti-Wrinkle Efficacy of Cross-Linked Hyaluronic Acid-Based Microneedle Patch with Acetyl Hexapeptide-8 and Epidermal Growth Factor on Korean Skin. *Ann Dermatol.* 2019;31(3):263-271. doi:10.5021/ad.2019.31.3.263
9. Henseler H. Investigating the effects of Argireline in a skin serum containing hyaluronic acids on skin surface wrinkles using the Visia® Complexion Analysis camera system for objective skin analysis. *PubMed.* 2023;12(9). doi:10.3205/iprs000179
10. Palmieri B, Noviello A, V Corazzari, et al. Skin scars and wrinkles temporary camouflage in dermatology and oncoesthetics: Focus on acetyl hexapeptide-8. *Clin Ter.* 2020;171(6). doi:10.7417/ct.2020.2270.
11. Li F, Chen H, Chen D, et al. Clinical evidence of the efficacy and safety of a new multi-peptide anti-aging topical eye serum. *J Cosmet Dermatol.* 2023;22(12):3340-3346.
12. Draelos ZD, Kononov T, Fox T. An open label clinical trial of a peptide treatment serum and supporting regimen designed to improve the appearance of aging facial skin. *J Drugs Dermatol.* 2016;15(9):1100-1106.
13. Raikou V, Varvaresou A, Panderi I, Papageorgiou E. The efficacy study of the combination of tripeptide-10-citrulline and acetyl hexapeptide-3. A prospective, randomized controlled study. *J Cosmet Dermatol.* 2017;16(2):271-278. doi:10.1111/jocd.12314.
14. Kraeling MEK, Zhou W, Wang P, Ogunsola OA. In vitro skin penetration of acetyl hexapeptide-8 from a cosmetic formulation. *Cutaneous Ocular Toxicol.* 2014;34(1):46-52. doi:10.3109/15569527.2014.894521.
15. Hou J, Wei W, Geng Z, et al. Developing Plant Exosomes as an Advanced Delivery System for Cosmetic Peptide. *ACS Applied Bio Materials.* 2024;7(5):3050-3060. doi:https://doi.org/10.1021/acsabm.4c00096
16. Peng, C.-L., Lee, P.-C., Liu, H.-T., & Lai, P.-S. (2024). Advancing transdermal delivery by Zn/Ag-electrode-printed iontophoretic patch with self-generating microcurrents. *Scientia Pharmaceutica, 92*(2), 26. https://doi.org/10.3390/scipharm92020026
17. Lim, S. H., Kathuria, H., Amir, M. H. B., Zhang, X., Duong, H. T. T., Ho, P. C.-L., & Kang, L. (2021). High resolution photopolymer for 3D printing of personalised microneedle for transdermal delivery of anti-wrinkle small peptide. Journal of Controlled Release: Official *Journal of the Controlled Release Society, 329,* 907–918. https://doi.org/10.1016/j.jconrel.2020.10.021 .

AUTHOR CORRESPONDENCE

Natasha Mesinkovska MD PhD
E-mail:..... natashadermatology@gmail.com