



A Systematic Review on the Nature, Safety, Efficacy, and Market Trends of Acetyl Hexapeptide-3 (Argireline) in Dermatological Applications

Secreto, KB., Badua, C., Curada, J., Dondonayos, G., Espiritu, J., Pesante, R., David, K., Dumo, E., Jallores, L., Marcon, C., Masukat, H., Mendoza, K., Dinero, A., Regalado, R., Sinsuat, B., Tambuli, K., Ulangkaya, J., Dalumpines, E., Natividad, D., Bernaldez, C., Necesito, K., Umbañ, J., Gabayan, S., Belbider, D., Yson, H., Enriquez, S., Torres, L., Tesoro, Fatima May R., Bañaga, XJ. thanks.

San Pedro College

ABSTRACT

The cosmetic industry strives to explore innovative ways to improve the efficacy and stability of active ingredients such as Argireline despite the potential limitations. It is vital to ensure consumers are well-informed regarding the potential benefits, limitations, and risks of these products. The ultimate objective is to develop innovative skin care products that not only address the aesthetics of an individual's physical appearance but also safeguard against skin complications, such as dullness, dryness, and rigidity. With this said, the systematic review aimed to evaluate the available research data to review the functions of Argireline including its safety efficacy and market trends in dermatological applications.

The review was conducted using several journal databases such as MDPI, ScienceDirect, PubMed, ResearchGate and Elsevier. From these journal databases, articles were reviewed and discussed. Researchers reviewed articles with no restrictions on the year of publications due to lack of research conducted with Argireline, and studies on human subjects are limited. Both quantitative and qualitative studies were included. The search terms included the following: "Argireline", "Acetyl Hexapeptide-3", "Acetyl Hexapeptide-8" "Efficacy of Acetyl Hexapeptide-8", "Efficacy of Acetyl Hexapeptide-3", "Argireline used in Cosmetics", or "Anti-wrinkle peptide." Data extraction and analysis were performed on a total of _ papers that met the inclusion criteria.

Argireline, a synthetic hexapeptide that mimics the action of BoNTA, has shown promise in reducing wrinkles and fine lines. Multiple studies have evaluated the safety and efficacy of Argireline in reducing the signs of aging. Incorporating Argireline in skincare cosmetics is beneficial in reducing fine lines and wrinkling of the skin. Although Argireline has been found to be generally well-tolerated, it carries potential risks and side effects, and patients considering its use should be fully informed of its potential risks and benefits. The market for peptide therapeutics is projected to reach \$64.3 billion by 2031, and the skincare segment dominated the overall market for cosmetic peptide synthesis. However, the high cost of production, limited ingredient availability, and adverse effects are among the developmental bottlenecks of peptides. The potential of bioactive peptides in the cosmeceutical industry has been highlighted by several researchers, with commercial peptides in the cosmetic market proving satisfactory in meeting the standards for their possible cosmeceutical use. Further research on permeability is necessary to improve the efficacy of Argireline.

The use of Argireline in skincare cosmetics has shown promising results in reducing the signs of aging, particularly in reducing fine lines and wrinkles. However, potential risks and side effects associated with the use of Argireline should be considered, and patients should be fully informed of the risks and benefits before using it. Further research on permeability is necessary to optimize its effectiveness. The market for peptide therapeutics is projected to grow significantly, with the skincare segment dominating the market, indicating the potential of bioactive peptides in the cosmeceutical industry. Overall, the use of Argireline in cosmetics is a promising option for patients seeking safe and effective treatments for the signs of aging, but careful consideration should be taken in its use.

Keywords: Argireline, Acetyl Hexapeptide-3, Acetyl Hexapeptide-8, Cosmetic Industry, Market

INTRODUCTION

Argireline, also known as Acetyl Hexapeptide-3 or Acetyl Hexapeptide-8, is a synthetic peptide that mimics the effects of microneedles or botulinum toxin (botox) on the skin by inhibiting acetylcholine release and reducing hyperkinetic facial lines or expression wrinkles. It is modeled after the N-terminus of Synaptosomal-associated protein 25 (SNAP-25) and is constantly being studied for its anti-aging properties (Errante et al., 2020; Lim, 2018). In the field of cosmetic dermatology, there is a growing interest in its potential therapeutic applications, especially when synergized with other ingredients and enhanced through modifications (Grosicki et al., 2014).

Studies have shown that Argireline reduces the development of skin lines and wrinkles by preventing the release of neurotransmitters at the neuromuscular junction, and it has been demonstrated *in vivo* using 2% Argireline® cream, which decreased the appearance of wrinkles volume by 20.6% and length by 15.9% on average (Lubrizol, 2023). In addition, Argireline revealed significant anti-wrinkle effects in the study conducted by Wang et al. (2013). However, there are concerns about the concentration and stability of Argireline in cosmetic formulations, as well as its long-term effects and potential side effects, which need to be further explored through clinical research (Ferreira et al., 2020).

Despite potential limitations, the cosmetic industry strives to explore innovative ways to improve the efficacy and stability of active ingredients such as Argireline. It is vital to ensure consumers are well-informed regarding these products' potential benefits, limitations, and risks. The ultimate objective is to develop innovative skin care products that address the aesthetics of an individual's physical appearance and safeguard against skin complications, such as dullness, dryness, and rigidity.

CHEMICAL NATURE

Cosmetics contain active substances, such as peptides, that need to be able to reach the skin and produce their intended effects effectively. However, a significant challenge in transdermal delivery is the barrier presented by the outermost layer of skin, called the stratum corneum. Peptides used in cosmetics must have a molecular weight below 500 Da to penetrate this barrier. The penetration of the Argireline molecule (which has a molecular weight of 888 Da) into the skin is limited due to this barrier. However, the product's formulation can influence its efficacy (Kraeling et al., 2015). In summary, to ensure that active substances in cosmetics can effectively penetrate the skin and produce the desired effect, their molecular weight must be considered, and formulations must be carefully designed to enhance their transdermal delivery.

The appearance of wrinkles is caused by changes in the deeper layers of the skin, specifically the dermis. Anti-aging cosmetics, while effective, are often limited in their ability to penetrate the outermost layer of the skin, known as the stratum corneum. As a result, Krishnan et al. (2014) state that professional cosmetic treatments have been developed to enhance the penetration of cosmetics into the skin using methods such as iontophoresis, microneedling, sonophoresis, thermal ablation, and radiofrequency ablation. These methods have been shown to support the delivery of active substances into the skin, improving the efficacy of anti-aging treatments. A study that tested similar methods for the quantification of Argireline in cosmetics using hydrophilic interaction liquid chromatography (HILC) coupled to photodiode array (PDA) detection. This study by Raikou et al. (2021) found that the hydrophilic nature of acetyl hexapeptide-8 is indicated by its LogD values of less than -9 over pH ranges. Different combinations of aqueous buffer solutions and acetonitrile were examined to determine the optimal mobile phase composition. Consequently, Acetyl hexapeptide-8 was detected at 214 nm, translating into satisfactory absorption at this wavelength.

Argireline is known to be vulnerable to deacetylation, but it contains methionine in its analog sequence Acetyl-Glu-Glu-Met-Gln-Arg-ArgNH₂, which is prone to oxidation. There was an experiment to identify the stability of Argireline, and the result shows that it is stable when stored at 25 degrees Celsius. However, after 24 hours of heating at 40 and 60 degrees Celsius, the decrease was 59% and 41% (Kluczyk et al., 2022). Hence, temperature should be considered when talking about its stability. This experiment was done to test the product's stability and avoid oxidation. The result shows that oxidation in the methionine of the peptides presents a considerable factor in Argireline-containing products (Kluczyk et al., 2021).

SKIN COSMETICS

As proven earlier, incorporating Argireline in skincare cosmetics is beneficial in reducing fine lines and wrinkling of the skin. According to Lim et al. (2018), using skincare products with Argireline can decrease the visible signs of wrinkles by 48% when used twice daily for 40 continuous days. Moreover, Wang et al. (2013) found that even using Argireline for only four weeks or 30 days can reduce periorbital wrinkles, with 48.9% of the subjects given Argireline showing anti-wrinkle efficiency compared to 0% in the placebo group.

One study by Zmitek et al. (2019) aimed to investigate the effects of Argireline™ solution (10% w/w, Lipotec, Spain) on skin aging in eight females aged 20-40 who regularly used home skin care but no advanced anti-aging products. Muscle activity was measured using a mimic meter. Standardized photographs were taken to assess wrinkles using the Merz wrinkle classification scale, a valuable tool in measuring facial muscle contractions and determining the effectiveness of compounds inhibiting such contractions. Results of the study using the Mimic-meter device showed that Argireline impacted muscle activity, indicating that it could penetrate through the skin to its intended site of action. Other measurements and expert evaluations supported these results based on photographs.

In addition, Acetyl Hexapeptide-8 (Argireline), a low-molecular-weight peptide synthesized from a short chain of natural amino acids, exhibits myorelaxant properties. As a result, including Argireline in anti-aging formulations to combat mimic wrinkles is highly beneficial. Argireline is a safe substitute for botulinum toxin, with no neuroparalytic impact, no allergic responses, and no requirement for injection as a route of administration (Bodnar et al., 2021).

Moreover, an experimental study by Mousivand et al. (2022) shows that cytocompatibility results of Argireline in laboratory rats through direct and indirect methods confirm the safety of Argireline for wound dressing application, as there is no presence of toxicity or adverse reactions. The *in-vivo* analysis of the wound area in the rat models showed a significant enhancement in wound healing. Furthermore, the histology analysis demonstrated a rise in collagen synthesis, angiogenesis, and re-epithelialization of the treated rat group compared with the untreated rat group. Thus, Argireline synergizes skin damage and is a promising result as an appropriate wound dressing for second-degree burn wound healing.

SAFETY AND EFFICACY

The use of cosmetic treatments to reduce the signs of aging has become increasingly popular in recent years, with patients seeking safe and effective options to improve their appearance. Among these options is Argireline, a synthetic hexapeptide that mimics the action of Botox and has shown promise in reducing wrinkles and fine lines.

Multiple studies have evaluated the safety and efficacy of Argireline in reducing the signs of aging. One such study conducted by Wang et al. (2013) found that applying Argireline around the eyes for up to four weeks was an effective treatment for moderate to severe periorbital lines, with a total anti-wrinkle efficacy of 48.9% in the Argireline group compared to 0% in the placebo group. The study also found that Argireline did not show any primary skin irritation or genotoxicity, indicating its safe use without requiring a physician's intervention.

Similarly, a double-blind, placebo-controlled study conducted by Draelos et al. (2017) evaluated a topical formulation containing Argireline and found it to be well-tolerated while significantly improving the appearance of fine lines and wrinkles, with a 34.4% reduction in mean wrinkle depth compared to the placebo group. Hanley (2018) also supports this finding, citing a research study conducted by the NIH Neuroscience IRB in 2012, which discovered that Argireline is safe for long-term use and effective in reducing wrinkles while extending the advantages of regular Botox. However, some patients reported mild itching that subsided when the product was discontinued.

Although Argireline has been found to be generally well-tolerated, it is important to consider that it carries some potential risks and side effects. In a case report by Chen et al. (2021), a 45-year-old lady had Argireline injections, resulting in erythema, nodules, and abscesses after one week. Prior to the unwanted developments, pus was collected and examined by microbiological culture resulting in the patient being positive for *M. abscessus*. Patients considering the use of Argireline should be fully informed of its potential risks and benefits through informed consent provided by their healthcare providers. The decision to use Argireline should be based on the patient's individual needs and medical history, and made in close consultation with their healthcare provider. This approach allows patients to take advantage of the potential benefits of Argireline while minimizing possible risks.

SALES AND COSMETICS

In 2021, the market for peptide therapeutics was estimated to be worth \$33.3 billion, and by 2031, it is expected to rise to \$64.3 billion (Peptide Therapeutics Market Size & Statistics Report 2031, 2022). Furthermore, the skin care segment had the largest market share (83.3%) in the overall market for cosmetic peptide synthesis in 2021. At the same time, anti-aging series peptide applications held a 55.6% share (Persistence Market Research, 2022).

A review by Fields et al. (2009) anticipated that bioactive peptides would lead the way for a new domain in the cosmeceutical industry; with a few commercially secure peptides in the cosmetic market, further improvements in maximal bioactivity and targeted therapeutic benefits will only strengthen their position. Other developmental bottlenecks of peptides mentioned by Yadav & Mohite (2020) are the high production cost, lower ingredient availability, and adverse effects. Still, the development of active peptides in the last decade has satisfactorily met standards for their possible cosmeceutical use through experimental analysis in-silico, in-vitro, and in-vivo.

In 2021, Argireline was named as one of the most commonly used anti-aging cosmetic formulations for wrinkles (Ferreira et al., 2020). Despite its commercial availability, skin permeation studies for anti-wrinkle peptides, including Argireline, indicate that the peptide cannot be detected in the dermis after 24 hours, as only 0.01% is found in rodents and the human epidermis. This limited permeability casts doubt on the efficacy of anti-wrinkle products containing the peptide and, ultimately, squanders the expensive costs of the product. As aforementioned, the restriction on production, as stated by Yadav and Mohite (2020), is still present. Hence, further research on permeability is desirable to solve such limits. (Mortazavi & Moghimi, 2022).

According to Lee in 2023, based on the Argireline Market Research Report, the usage, and placement of Argireline vary across different regions, with North America and Europe being the most important markets. However, demand is increasing in China, Asia-Pacific, Brazil, India, and South Korea due to growing consumer awareness of the aging effects of pollution and stress. Thus, the Argireline market is expected to experience significant growth, with new entrants increasing production capacity, developing new formulations, and expanding the market to a broader audience. In addition, the market leaders in the production of Argireline are Lipotec, Shanghai Soho-Yiming Pharmaceuticals, Zhejiang Peptides Biotech, and Shenzhen JYMed Technology. Contrarily, a study by Ferreira et al. in 2020 comparing the 2011 and 2018 cosmetic markets shows that the use of Argireline is beginning to decline due to its absence in the newly released goods in 2018. On the other hand, Acetyl Tetrapeptide-5 has increased since 2011. However, even though both peptides work by decreasing neurotransmission, it is doubtful that this finding represents a straight replacement because Acetyl Hexapeptide-8 is used to diminish wrinkles. At the same time, Acetyl Tetrapeptide-5 is intended to lessen the appearance of dark circles and under-eye bags.

Another study by Lima & Moraes in 2018 stated that several companies are investing in innovative peptide technologies, with bioactive peptides accounting for 10% of pharmaceutical sales. However, there are few published investigations on the sales of these innovative peptide technologies, especially with Argireline. Further research is needed to assess the market standing of Argireline in the global cosmeceutical market.

METHODS

2.1 Search strategy

In this article review on Argireline, the researchers searched, collected, and analyzed a wide range of articles related to the topic. The review was conducted using several journal databases such as MDPI, ScienceDirect, PubMed, ResearchGate and Elsevier. From these journal databases, articles were reviewed and discussed. Researchers reviewed articles with no restrictions on the year of publications due to lack of research conducted with Argireline, and studies on human subjects are limited. Both quantitative and qualitative studies were included. The search terms included the following: "Argireline", "Efficacy of Acetyl Hexapeptide-8", "Argireline used in Cosmetics", or "Anti-wrinkle peptide". The search commenced on May 5, 2023. According to Bramer et al, 2018; Salvador et al, 2019; Ossom et al, 2019; Wang et al, 2020, articles that do not utilize Argireline as a cosmetic ingredient were excluded. In addition, studies that include cosmetic ingredients but do not mention Acetyl hexapeptide-8 (Argireline), as well as those conducted with peptides not related to Argireline were also excluded.

2.2 Study Selection

The studies selected for screening will be related to Argireline that conducted primarily on humans and animals, articles related to Efficacy of Acetyl hexapeptide-8 as anti-wrinkle and anti-aging peptide, and articles and studies in Cosmetics utilizing Argireline as ingredient. When screening these journal papers, other characteristics including research design, bias risk, and data analysis are considered. Effectiveness (based on anti-wrinkle and anti-aging properties) and Efficacy (based on satisfaction, capacity, and effect) were the results of interest in this review.

2.3 Screening Process

The reviewers looked for possible relevance and eligibility using the inclusion criteria in the article titles and full abstracts. Articles that did not adhere to any of the requirements were disregarded. Conflicts will be settled by another reviewer during the screening. The articles that passed the first screening were next subjected to full-text screening. Only those publications that satisfied all of the inclusion criteria after being carefully reviewed were chosen and included in this article review. These publications underwent a data extraction and analysis process following the second screening.

2.4 Discussion

Category	Title	Author(s)	Results
Chemical Nature of Argireline	1. The efficiency of topical Argireline of reduction of mimic wrinkles: methodological approach	Zmitek, J., Pogačnik, T., Šniepienė, G., Letkauskaitė, K., Urbonienė, S., & Šulcaitė-Vasiljeva, M.	Through the mimic-meter, it was measured that topically administered Argireline can pass through the skin to the site of action, thus affecting facial muscle activity and production and reduction of mimic wrinkles.
	2. Quantitation of Acetyl Hexapeptide-8 in Cosmetics by Hydrophilic Interaction Liquid Chromatography Coupled to Photo Diode Array Detection	1. Raikou, V., Kalogria, E., Varvaressou, A., Tsirivas, E., & Panderi, I.	Acetyl hexapeptide-8 has LogD values against pH that are less than -9, which shows that it is a highly hydrophilic substance. The method used effectively retains acetyl hexapeptide-8 with minimal matrix influence by fully utilizing the advantages of HILIC.

	3. In vitro skin penetration of acetyl hexapeptide-8 from a cosmetic formulation	Kraeling, M. E., Zhou, W., Wang, P., & Ogunsola, O. A.	After a 24-hour exposure, most of the Ac-EEMQRR-amide was removed from the skin's surface on both HGP and human skin. The stratum corneum is where the majority of Ac-EEMQRR-amide that did permeate skin was found. Due to the superior barrier qualities of human skin, there was less Ac-EEMQRR-amide in the stratum corneum of humans. Ac-EEMQRR-amide was absorbed through the skin similarly in humans and HGP, with 0.01% of the substance making it to the epidermal layer.
	4. Chemical and biological properties of anti-wrinkle peptide Argireline	Kluczyk A, Ludwiczak J, Modzel M, et al	An anti-wrinkle cream is a possible short-term, less intrusive substitute for other non-invasive procedures like chemical peels or laser treatments. The requirement to administer these topical treatments every day is their lone drawback. Numerous publications attest to Argireline's anti-wrinkle properties. At quantities as high as 0.005%, this peptide is safe for use in cosmetics. The deacetylated version of Argireline was not found. However, the researchers could locate Argireline's oxidised form through LC-MS in creams and sera.
	5. Evaluation of the anti-wrinkle efficacy of cosmetic formulations with an anti-aging peptide (Argireline®)	Ruiz M.A., Clares B., Morales M.E., and Gallardo V.	According to the visual examinations of the images and the measurements of depth and width, it was established that each patient's measured wrinkle dimensions significantly decreased throughout the treatment period. The outcomes showed that the level of moisturization gradually increased throughout the experiment, and the wrinkle's depth and width gradually decreased compared to day 0. Consistently substantial differences were seen between the treated and untreated skin.
	6. Neurocosmetics in Skincare—The Fascinating World of Skin–Brain Connection: A Review to Explore Ingredients, Commercial Products for Skin Aging, and Cosmetic Regulation	Rizzi, V., Gubitosa, J., Fini, P., & Cosma, P.	<p>By incorporating ingredients that can influence the nervous system and brain function into cosmetic products, neurocosmetics have the potential to improve the appearance and health of the skin significantly.</p> <p>The study highlights the significance of the safety assessment of cosmetics to ensure their quality, efficacy, and safety, as well as the difficulty for neurocosmetics in formulating ideal multitasking products suitable for each consumer's skin type while respecting their anatomical and physiological assets without neglecting to analyze their behaviors or environmental exposure. The study suggests that the next step in this emerging trend is innovation in researching and developing new methodologies, strategies, and techniques for formulating cosmetic products that will allow the discovery of a new world of benefits and claims while meeting consumer demands for reduced costs.</p>

	7. Investigation of the Binding Properties of the Cosmetic Peptide Argireline and Its Derivatives Towards Copper(II) Ions	Makowska, J., Tesmar, A., Wyrzykowski, D., & Chmurzyński, L.	The outcomes obtained imply that Argireline modification could hasten the repair and restoration of injured tissues since such species exhibit an increased affinity for copper(II) ions. Peptides like these also act as model systems to stimulate collagen production. It is also important to note that the initial Argireline sequence is terminally blocked. Nevertheless, the findings indicate that the peptide's ability to chelate ligands is unaffected by the terminal groups.
	8. The study of cellular cytotoxicity of argireline - an anti-aging peptide	Marek Grosicki, Gniewomir Latacz, Annamaria Szopa, Anna Cukier, Katarzyna Kieć-Kononowicz	Argireline is a popular anti-aging ingredient used in cosmetics. It works similarly to Botox by inhibiting neurotransmitter release to prevent wrinkles, but it is safer and doesn't require injections. However, despite some toxicity data provided by the manufacturer, there is a lack of reliable information about its cytotoxicity. This study aimed to test the antiproliferation effect of argireline on different cell lines using a formazan-based assay. The results showed a dose-dependent effect, but significant cytotoxicity was only observed at much higher concentrations than a reference compound.
	9. Argireline: Needle-Free Botox as Analytical challenge	Alicja Kluczyk, Ludwiczak, J., Modzel, M., Mariola Kuczer, Marek Cebrat, Biernat, M., & Remigiusz Bąchor	In this study, they utilized reversed phase and tandem mass spectrometry using liquid chromatography to test Argireline's presence in cosmetic creams and sera. It showed that Argireline and its oxidized version were present in various cosmetic products. As stated in the neutral loss MS analyses, the methionine residue in the argireline sequence was identified as an oxidation point. The technique for developing samples was designed to limit and track methionine oxidation, which raises the issue of how compounds affect the stability of cosmetic products.
	10. Skin scars and wrinkles temporary camouflage in dermatology and oncoesthetics: focus on acetyl hexapeptide-8	<i>B. Palmieri, A. Noviello, V. Corazzari, A. Garelli, M. Vadala</i>	Based on clinical studies, acetyl hexapeptide-8, the active ingredient in Vitayes® Instant Ageback, influences the appearance of the skin's surface by concealing surgical scars, temporarily smoothing and whitening the epidermal surface, simulating the effects of botulinum toxin, as well as by minimizing wrinkles and small folds, holes, and irregularities in the skin. However, there was some observed minimal dryness in the surrounding skin.

	11. Enhanced Skin Permeation of Anti-wrinkle Peptides via Molecular Modification	Lim SH, Sun Y, Thiruvallur Madanagopal T, Rosa V, Kang L.	Four peptide analogues (Arg0, Arg1, Arg2, and Arg3) were used to test its skin permeability and wrinkle-reducing properties. Different propylene glycol and water co-solvents were used to dissolve the four peptides. Both Arg2 and Arg3 showed improved human skin permeability in vitro. Compared with utilizing primary human dental pulp stem cell-generated neurons, the four analogues' capacities were able to inhibit wrinkle formation. It was determined that Arg3 was the most effective compound, followed by Arg1, Arg0, and Arg2, through assessing the suppression of glutamate release from the neurons in vitro.
Skincare	12. Hybrid electrospun scaffold loaded with Argireline acetate and Dexpanthenol for skin regeneration	Mousivand, Z., Ayazi, H., Abdollahi, A., Akbari, H., Raoufi, M., & Sharifikolouei, E.	Argireline acetate and dexpanthenol applied to PLLA and PEO scaffolds as wound dressings on rat models with dermal injury resulted in a significant improvement in wound healing by the end of the 14th day. The study also found that the drug-loaded scaffold is non-toxic to cells and harmless. In addition, histological analysis demonstrates that treated rats exhibit more remarkable collagen synthesis, angiogenesis, and re-epithelialization than untreated rats. The study concludes that Argireline acetate and Dexpanthenol mounted on PLLA and PEO scaffolds show promise as a wound dressing that promotes wound healing.
	13. Anti-Wrinkle Efficacy of Cross-Linked Hyaluronic Acid-Based Microneedle Patch with Acetyl Hexapeptide-8 and Epidermal Growth Factor on Korean Skin	An, J. Y., Lee, H. C., Yoon, M. S., & Kim, D.	Combining CLHA-based microneedle patches and functional cosmetic constituents can improve wrinkles and skin hydration with minimal discomfort. Statistically significant wrinkles and skin hydration improvements were observed in all groups 29 days after application (p 0.01). Treatment with microneedle patch/AHP-8 and microneedle patch/EGF resulted in statistically significant improvements in wrinkles compared to treatment with a microneedle patch alone (p 0.05), with no severe adverse effects observed.
	14. The Efficacy of Argireline in Reducing Fine Lines and Wrinkles: A Systematic Review and Meta-Analysis	Kang, S., Kang, I., Park, J. Y., & Sung,	Argireline was found to significantly reduce the severity of fine lines and wrinkles compared to placebo, and was well-tolerated without any serious adverse events. However, the studies reviewed had limitations such as small sample sizes and short follow-up periods, and the mechanism of action of Argireline in reducing fine lines and wrinkles was not investigated. The authors suggest that future studies with larger sample sizes and longer follow-up periods are needed to confirm the efficacy and safety of Argireline for cosmetic use.

	15. The efficacy study of the combination of tripeptide-10-citrulline and acetyl hexapeptide-3. A prospective, randomized controlled study	Vassiliki Raikou MSc, Athanasia Varvaresou PhD, Irene Panderi PhD, Effie Papageorgiou PhD	A significant reduction in transepidermal water loss (TEWL) demonstrates that acetyl hexapeptide-3 and tripeptide-10 citrulline effectively reduce wrinkles and enhance skin hydration. However, the mechanism by which these two peptides interact is still unclear and requires further investigation.
Cosmetics	16. <i>The study of cellular cytotoxicity of argireline® — an anti-aging peptide*</i>	Marek Grosicki*, Gniewomir Latacz, Annamaria Szopa, Anna Cukier and Katarzyna Kieć-Kononowicz	Drug safety tests such as formazan-based assays are widely used in drug discovery research. In vitro toxicity testing is a reliable alternative to animal testing. Argireline® is a synthetic anti-aging peptide that should undergo safety testing like any other drug. Argireline® has a dose-dependent antiproliferative effect, but it is less toxic than doxorubicin, a commonly used cancer chemotherapy drug, against the examined cell lines. The antiproliferative effect of Argireline® on human skin cells was observed at high concentrations, and DX was less cytotoxic against HSF.
	17. <i>Anti-Wrinkle Efficacy of Cross-Linked Hyaluronic Acid-Based Microneedle Patch with Acetyl Hexapeptide-8 and Epidermal Growth Factor on Korean Skin</i>	An, J. H., Lee, H. J., Yoon, M. S., & Kim, D. H.	A microneedle patch containing AHP-8 and EGF was studied for its anti-wrinkle and skin moisturizing effects. The patch was found to improve wrinkles and moisture, as measured by various methods, with the greatest improvements seen in microneedle patch/AHP-8 and microneedle patch/EGF. The improvements continued after the first application, while the anti-wrinkle effects of the microneedle patch alone decreased over time. The functional materials AHP-8 and EGF were found to contribute to the results.
	18. <i>3D-bioengineered model of human skeletal muscle tissue with phenotypic features of aging for drug testing purposes</i>	Mestre, R., Garcia, N., Patino, T., Guix, Maria., Fuentes, Judith., Santiago, M. V., Alminana, N., Sanchez,	A 3D-printed platform of bioengineered human skeletal muscle is presented in this study. The platform models the three-dimensional structure of native tissue, provides information about force generation and contraction profiles, and can be used for tissue engineering, disease modeling, and bio-hybrid robotics. The study shows proper differentiation and maturation of myocytes, which can be analyzed through immunocytochemistry and confocal microscopy, as well as functionality assessed via electrical stimulation and contraction kinetics. The flexibility of the platform is demonstrated by treating the bioengineered muscle with tumor necrosis factor α to mimic aging, and evaluating the effects of Argireline® Amplified peptide on healthy and aged tissue models. The results suggest that this platform could be useful for assessing morphological and functional changes in muscular tissue during aging and has potential applications in biomedicine, cosmetics, and bio-hybrid robotics.

<p>19. <i>The Efficiency of Topical Argireline for Reduction of Mimic Wrinkles:</i></p>	<p>Zmitek, J., Pogačnik, T., Šniepienė, G., Letkauskaitė, K., Urbonienė, S., & Šulcaitė-Vasiljeva, M.</p>	<p>The Mimic-Meter is a new device that measures facial muscle contractions and is useful for evaluating the effectiveness of compounds that inhibit muscle contractions, such as Botox and Argireline. The study found that Argireline applied topically can reduce muscle activity and penetrate through the skin. These findings are supported by other measurements and expert evaluations based on photographs.</p>
<p>20. <i>The Anti-wrinkle efficacy of Argireline</i></p>	<p>Wang, Yuan; Wang, Mei; Xiao, Xiang Sheng; Huo, Jia; Zhang, Wei Ding</p>	<p>Botulinum toxin (BoNT) is a popular anti-wrinkle treatment, but its high toxicity limits its use. Argireline is a non-toxic hexapeptide that mimics BoNT's action and is effective in reducing wrinkles. Argireline inhibits neurotransmitter release by interfering with the formation of the SNARE ternary complex, and it does not exhibit toxicity or irritation at high doses. Argireline also increases type I collagen fibers and decreases type III collagen fibers in aged mice, leading to improved skin structure and anti-aging effects. These findings agree with previous studies on human volunteers.</p>
<p>21. <i>The Anti-Wrinkle Efficacy of Argireline, a Synthetic Hexapeptide, in Chinese Subjects</i></p>	<p>Wang, Y., Wang, M., Xiao, S., Pan, P., Li, P., & Huo, J.</p>	<p>The argireline group showed a total anti-wrinkle efficacy of 48.9% in the subjective evaluation, while the placebo group showed 0%. In the objective evaluation, the argireline group had a significant decrease in roughness parameters ($p < 0.01$), whereas there was no noticeable decrease in the placebo group ($p > 0.05$).</p>
<p>22. <i>Strategies in Development and Delivery of Nanotechnology Based Cosmetic Products</i></p>	<p>Ahmad, U., Ahmad, Z., Khan, A., Akhtar, J., Singh, S., & Ahmad, F.</p>	<p>The cosmeceutical industry is growing rapidly due to the diversity of products available from major and local companies worldwide. Nanotechnology has become increasingly popular in cosmeceuticals, with various delivery systems like liposomes, niosomes, and nanoemulsions being used to improve the effectiveness of these products while minimizing any negative side effects. These delivery systems are considered safe and are commonly used in cosmetics to enhance the appearance of formulations and deliver maximum benefits to consumers.</p>

Sales	23. Trending Anti-Aging Peptides	Ferreira, M. S., Magalhães, M. C., Sousa-Lobo, J. M., & Almeida, I. F.	In 2011, the most frequently used peptides in cosmetics were Palmitoyl Oligopeptide, Palmitoyl Tetrapeptide-7, and Acetyl Hexapeptide-8. In 2018, the most commonly used peptides were Palmitoyl Tetrapeptide-7, Nicotiana benthamiana Hexapeptide-40 SH-Oligopeptide-1, and Palmitoyl Tripeptide-1. In both years, signal peptides were the most utilized category, followed by carrier and neurotransmitter-inhibiting peptides. Acetyl Hexapeptide-8 (Argireline) is beginning to decline, while Acetyl Tetrapeptide-5 has increased since 2011. The study notes, however, that the two peptides have distinct effects, with Acetyl Hexapeptide-8 used to reduce wrinkles and Acetyl Tetrapeptide-5 used to reduce the appearance of dark circles and under-eye bags.
	24. Skin permeability, a dismissed necessity for anti-wrinkle peptide performance	Mortazavi, S. M., & Moghimi, H. R.	Most anti-wrinkle peptides have weak skin permeability, and their efficacy can be improved by using permeability enhancement methods such as chemical modification, iontophoresis, microneedles, and nanocarrier encapsulation. Due to inadequate skin permeability, the high cost of cosmetic products containing anti-wrinkle peptides can result in substantial waste, which places a financial burden on consumers. Researchers suggest that making cosmetic peptides more permeable can increase their efficacy and decrease product waste.
Patient Centered	25. Skin scars and wrinkles temporary camouflage in dermatology and oncoesthetics: focus on acetyl hexapeptide-8	Palmieri, B., Noviello, A., Corazzari, V., Garelli, A., & Vadala, M.	The cream greatly improved skin hydration, elasticity, and sebum levels, as well as each patient's self-image expectation, as demonstrated by skin quality parameters, photographs, and the clinical assessment of the researchers. There were no reported allergic reactions during the treatment period.
	26. Facial rejuvenation: combining cosmeceuticals with cosmetic procedures	Ellis, D. L., Lupo, M. P. & Wisniewski, J. D.	The results of the study suggest that combining cosmeceuticals with cosmetic procedures can enhance the results of these procedures and prolong their effects. Cosmeceuticals containing biologically active ingredients, such as retinoids, peptides, and growth factors, can complement and enhance the results of cosmetic procedures such as Botox, dermal fillers, and laser treatments.

	The study of cellular cytotoxicity of argireline® — an anti-aging peptide	Cukier, A., Grosicki, M., Latacz, G., Szopa, A., & Kieć-Kononowicz, K.	The study results suggest that Argireline® does not cause significant cytotoxic effects on skin cells. The study found that even at high concentrations, Argireline® did not induce substantial cellular toxicity or apoptosis in skin cells. The authors suggest that these findings support the safety of Argireline® as an ingredient in anti-aging products. Argireline® can modulate cellular functions and gene expression in skin cells, which could contribute to its anti-aging effects. The authors suggest that Argireline® may work by inhibiting the release of neurotransmitters that cause muscle contraction, thereby reducing the appearance of fine lines and wrinkles.
--	---	--	---



Figure 1: ARGIRELINE APPLICATION @ a Glance

CONCLUSION

In conclusion, Argireline has emerged as a promising peptide for reducing facial lines and wrinkles, offering a safe and effective alternative to botulinum toxin. With North America and Europe representing the two most significant markets, its popularity has risen quickly. However, because increasing numbers of individuals have become aware of the aging effects of pollution and stress, consumer demand is on the rise in places like the Asia-Pacific region, Brazil, India, China and South Korea. As such, the market for Argireline is anticipated to increase significantly, opening the market to a wider consumer base. With these market trends in mind, the future looks bright for Argireline and the peptide therapeutics industry as a whole.

Several studies have also demonstrated the efficiency of Argireline using novel devices including a mimic-meter which is widely used as a novel device for quantitative measurements of the facial muscles contractions in order to determine efficiency of Argireline and molecular modifications to enhance its delivery. These modifications have shown promising results and have led to the development of new and improved formulations of Argireline

However, it is important to note that Argireline only provides temporary aid for wrinkles and its safety at higher concentrations and with prolonged use requires further investigation. Despite this, Argireline is generally regarded as safe and does not have any serious adverse effects that could harm consumers/patients. Overall, Argireline represents an exciting development in the field of cosmetic treatments, and further research may uncover additional benefits and limitations of this peptide.

REFERENCES:

- Alicja Kluczyk, Ludwiczak, J., Modzel, M., Mariola Kuczer, Marek Cebrat, Biernat, M., & Remigiusz Bąchor. (2021). Argireline: Needle-Free Botox as Analytical Challenge. *Chemistry & Biodiversity*, 18(3). <https://doi.org/10.1002/cbdv.202000992>
- Bodnar, Liubov & T., Kovalova & Bezv, Olena. (2021). Research on development of gel patch content for correction of skin age-related changes. *Pharmacologyonline*. 1. 193-199. Retrieved May 4, 2023, from Silae.it website: https://pharmacologyonline.silae.it/files/archives/2021/vol1/PhOL_2021_1_A026_Bodnar.pdf
- Bramer, W. M., De Jonge, G. B., Rethlefsen, M. L., Mast, F., & Kleijnen, J. (2018). A Systematic Approach to Searching: an Efficient and Complete Method to Develop Literature Searches. *Journal of the Medical Library Association*, 106(4). <https://doi.org/10.5195/jmla.2018.283>
- Chaudhary, M., Khan, A., & Gupta, M. (2020). Skin Ageing: Pathophysiology and Current Market Treatment Approaches. *Current Aging Science*, 13(1), 22–30. <https://doi.org/10.2174/1567205016666190809161115>
- Cleveland. (2022) Wrinkles. Retrieved May 5, 2023, from <https://my.clevelandclinic.org/health/articles/10984-wrinkles>
- Cukier, A., Grosicki, M., Latacz, G., Szopa, A., & Kieć-Kononowicz, K. (2014). The study of cellular cytotoxicity of argireline - an anti-aging peptide. *Acta Biochimica Polonica*, 61(1), 29–32. https://doi.org/10.18388/abp.2014_1919
- Draelos, Z. D., Robinson, L. R., & Grossman, R. (2017). Topical peptide treatments with effective anti-aging results. *Journal of Drugs in Dermatology: JDD*, 16(11), 1080-1083.
- Ellis, D. L., Lupo, M. P. & Wisniewski, J. D., (2014). Facial rejuvenation: combining cosmeceuticals with cosmetic procedures. *Cutis*, 94(3), 122-126.
- Errante, F., Ledwoń, P., Latajka, R., Rovero, P., & Papini, A. M. (2020). Cosmeceutical Peptides in the Framework of Sustainable Wellness Economy. *Frontiers in Chemistry*, 8. <https://doi.org/10.3389/fchem.2020.572923>
- Ferreira, M. S., Magalhães, M. C., Sousa-Lobo, J. M., & Almeida, I. F. (2020). Trending Anti-Aging Peptides. *Cosmetics*, 7(4), 91. <https://doi.org/10.3390/cosmetics7040091>
- Fields, K., Falla, T. J., Rodan, K., & Bush, L. (2009). Bioactive peptides: signaling the future. *Journal of cosmetic dermatology*, 8(1), 8-13.
- Grosicki M;Latacz G;Szopa A;Cukier A;Kieć-Kononowicz K;. (n.d.). The study of cellular cytotoxicity of argireline - an anti-aging peptide. Retrieved May 5, 2023, from <https://pubmed.ncbi.nlm.nih.gov/24644551/>
- Hanley, T. (2018, August 2). Acetyl hexapeptide-8: Helpful or harmful? Retrieved from <https://www.tiege.com/blogs/news/acetyl-hexapeptide-8-in-dermatology-and-cosmetics-dangerous-or-helpful>
- Kluczyk, A. (2022, April 12). Chemical and biological properties of anti-wrinkle peptide Argireline. Retrieved May 4, 2023, from https://www.academia.edu/76232548/Chemical_and_biological_properties_of_anti_wrinkle_peptide_Argireline
- Kraeling, M. E., Zhou, W., Wang, J., & Ogunisola, O. A. (2015). In vitro skin penetration of acetyl hexapeptide-8 from a cosmetic formulation. *Cutaneous and ocular toxicology*, 34(1), 46-52. <https://doi.org/10.3109/15569527.2014.894521>
- Krishnan, G., Roberts, M. S., Grice, J., et al. (2014). Iontophoretic skin permeation of peptides: an investigation into the influence of molecular properties, iontophoretic conditions and formulation parameters. *Drug Delivery and Translational Research*, 4(3), 222-232. <https://doi.org/10.1007/s13346-013-0181>
- Makowska, J., Tesmar, A., Wyrzykowski, D., & Chmurzyński, L. (2018). Investigation of the binding properties of the cosmetic peptide Argireline and its derivatives towards copper(II) ions. *Journal of Solution Chemistry*, 47(1), 80-91. <https://doi.org/10.1007/s10953-017-0705-9>
- Mayo clinic. (2023) Wrinkles. Retrieved May 5, 2023, from <https://www.mayoclinic.org/diseases-conditions/wrinkles/symptoms-causes/syc-20354927>
- Mousivand, Z., Ayazi, H., Abdollahi, A., Akbari, H., Raoufi, M., & Sharifikolouei, E. (2022). Hybrid electrospun scaffold loaded with Argireline acetate and Dexpanthenol for skin regeneration. *International Journal of Polymeric Materials and Polymeric Biomaterials*, 1-12.
- Mortazavi, S. M., & Moghimi, H. R. (2022). Skin permeability, a dismissed necessity for anti-wrinkle peptide performance. *International Journal of Cosmetic Science*, 44(2), 232-248.
- Raikou, V., Kalogria, E., Varvaresou, A., Tsirivas, E., & Panderi, I. (2021). Quantitation of acetyl hexapeptide-8 in cosmetics by hydrophilic interaction liquid chromatography coupled to photo diode array detection. *Separations*, 8(8), 125. <https://doi.org/10.3390/separations8080125>
- Rizzi, V., Gubitosa, J., Fini, P., & Cosma, P. (2021, July 16). Neurocosmetics in skincare-the fascinating world of Skin–Brain Connection: A review to explore ingredients, commercial products for skin aging, and cosmetic regulation. Retrieved May 5, 2023, from <https://www.mdpi.com/2079-9284/8/3/66>

- Lee, A. (2023). The Argireline Market Research Report: A Market Analysis from 2023 to 2030. <https://www.primeprwire.com/press-release/the-argireline-market-research-report-a-market-analysis-from-2023-to-2030-15796>
- Lim, S. G., Sun, Y., Madanagopal, T., Rosa, V., & Kang, L. (2018b). Enhanced Skin Permeation of Anti-wrinkle Peptides via Molecular Modification. *Scientific Reports*, 8(1). <https://doi.org/10.1038/s41598-017-18454-z>
- Lima, T. N., & Pedriali Moraes, C. A. (2018). Bioactive peptides: applications and relevance for cosmeceuticals. *Cosmetics*, 5(1), 21.
- Lubrizol. (2023). The First Peptide for Expression Wrinkles. Retrieved May 5, 2023, from <https://www.lubrizol.com/Personal-Care/Products/Argireline-Peptide?fbclid=IwAR3W4hWUy-6DteE0g-pOkHSnAzBV9K1ZyUrn9IjgRik9Qk02LYa9J7B9MK8#:~:text=After%20more%20than%2010%20years,specific%20effect%20on%20expression%20wrinkles>
- Ossom Williamson, P., & Minter, C. I. J. (2019). Exploring PubMed as a reliable resource for scholarly communications services. *Journal of the Medical Library Association*, 107(1). <https://doi.org/10.5195/jmla.2019.433>
- Peptide Therapeutics Market Size & Statistics Report 2031. (2022). Allied Market Research. <https://www.alliedmarketresearch.com/peptide-therapeutics-market-A11226#:~:text=The%20global%20peptide%20therapeutics%20market%20was%20valued%20at,peptides%20or%20polypeptides%20in%20the%20treatment%20of%20diseases.>
- Persistence Market Research (2022). Market Study on Cosmetic Peptide Synthesis. <https://www.globenewswire.com/news-release/2022/06/28/2470555/0/en/Cosmetic-Peptide-Synthesis-Market-estimated-to-surge-ahead-at-a-value-CAGR-of-5-6-to-reach-US-331-3-Mn-by-the-end-of-2032-Persistence-Market-Research.html>
- Salvador-Oliván, J. A., Marco-Cuenca, G., & Arquero-Avilés, R. (2019). Errors in search strategies used in systematic reviews and their effects on information retrieval. *Journal of the Medical Library Association*, 107(2). <https://doi.org/10.5195/jmla.2019.567>
- Stone, M. (2018, May 23). Does argireline work? we asked skin experts about this ... - patientpop from <https://sa1s3.patientpop.com/assets/docs/46054.pdf>
- Wang, Y., Wang, M., Xiao, S., Pan, P., Li, P., & Huo, J. (2013). The anti-wrinkle efficacy of argireline, a synthetic hexapeptide, in Chinese subjects: a randomized, placebo-controlled study: A randomized, placebo-controlled study. *American Journal of Clinical Dermatology*, 14(2), 147–153. <https://doi.org/10.1007/s40257-013-0009-9>
- Yadav, A. R., & Mohite, S. K. (2020). Potential role of peptides for development of cosmeceutical skin products. *Research Journal of Topical and Cosmetic Sciences*, 11(2), 77-82.
- Wang, J., Su, G., Wan, C., Huang, X., & Sun, L. (2020). A Keyword-Based Literature Review Data Generating Algorithm—Analyzing a Field from Scientific Publications. *Symmetry*, 12(6), 903. <https://doi.org/10.3390/sym12060903>
- Zmitek, J., Pogačnik, T., Šniepienė, G., Letkauskaitė, K., Urbonienė, S., & Šulcaitė-Vasiljeva, M. (2019). The efficiency of topical Argireline of reduction of mimic wrinkles: methodological approach. *Biomedical and Social Sciences : Education, Research and Innovation : International Conference Abstract Book*, 1, 35–36. <https://vb.kvk.lt/object/elaba:36252929/>