

Review

Sustainable Dynamic Wrinkle Efficacy: Non-Invasive Peptides as the Future of Botox Alternatives

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Abstract: Dynamic wrinkle reduction continues to challenge aesthetic dermatology, predominantly addressed through Botulinumtoxin (Botox) injections. Despite Botox's robust efficacy with up to an 80% reduction in wrinkle visibility within just one week, its invasive administration and specific mechanism of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex inhibition prompt the exploration of safer, non-invasive alternatives. This review critically assesses recent innovations in non-invasive effects, with a focus on peptides and botanical extracts that exhibit a diverse array of mechanisms including SNARE complex inhibition, modulation of calcium and sodium channels, and interactions with acetylcholine receptors, contributing to their effectiveness in muscle relaxation on dynamic wrinkle approaches. Noteworthy peptides such as Argireline and SYN-Ake replicate the neuromodulatory effects of Botox, achieving up to a 52% reduction in wrinkles within four weeks without injections. Moreover, botanical extracts meet the rising demand for clean beauty solutions by enhancing skin elasticity and health through gentle yet potent mechanisms. However, the main concern with peptides is their low absorption rate, with only six clinical validations regarding Botox-like peptide anti-wrinkle efficacy available. These advancements not only deepen our understanding of cosmetic dermatology but also significantly influence market dynamics and consumer behavior, underscoring their pivotal role in redefining the future landscape of anti-aging effects.

Keywords: alternative; botulinum toxins; cosmetic; dynamic wrinkle; peptide; skin aging; topical



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1. Introduction

Dynamic wrinkles, a prevalent concern in dermatological practice, result from repetitive facial expressions such as smiling, frowning, and squinting [1,2]. Affecting mostly individuals over the age of 35 [3], these specific wrinkles include glabellar lines (frown lines), nasolabial folds, periorbital wrinkles, and forehead lines. These differ from static wrinkles, which arise due to age-related declines in skin elasticity and collagen degradation [4]. The significant impact of dynamic wrinkles on aesthetic appearance and psychological well-being highlights the urgent need for effective applications within cosmetic dermatology.

Botulinum toxin, commonly known as Botox, has long been a cornerstone in the treatment of dynamic wrinkles [5,6]. Its primary mechanism involves the temporary paralysis of underlying muscle activity, which significantly reduces wrinkle formation [6–8]. Despite its efficacy, Botox injections are invasive and associated with potential adverse effects, including pain, swelling, ptosis, and facial asymmetry, occurring in up to 5% of cases [9]. These limitations underscore the increasing demand for safer, non-invasive alternatives in clinical practice to Botox usage.

In response to these challenges, the field has seen significant advancements in topical applications that are emerging as promising alternatives. Among those researches, peptides [10–12] and botanical extracts [13] represent a significant shift in cosmetic dermatology, aiming to provide effective anti-dynamic wrinkle benefits without the need for invasive procedures like injections. These topical formulations are designed to mimic the neuromodulatory effects of Botox while enhancing safety and accessibility [10–13]. These topical agents align with the growing consumer preference for ‘clean beauty’ products that utilize non-toxic ingredients [14].

This review aims to comprehensively summarize the reported efficacy, mechanisms of action, safety profiles, and patient-oriented outcomes of peptide topical alternatives to traditional Botox injections. By critically assessing current research within the framework of evidence-based cosmetic science, this paper seeks to elucidate the potential of these novel ingredients to redefine anti-aging practices, specifically in expression lines. Additionally, this review will explore the socio-economic and psychological implications of more accessible anti-aging effects, providing a comprehensive understanding of their impact on the cosmetic industry and societal beauty standards.

2. The Pathophysiology of Dynamic Wrinkles

2.1. Mechanisms of Wrinkle Formation

Dynamic wrinkles, a prominent indicator of aging skin, result from the intricate interplay of neuromuscular activities [15] and skin biomechanics [16]. These wrinkles are distinct from static wrinkles as they are primarily formed by the repeated contraction of facial muscles in response to various expressions [1,2]. The formation of dynamic wrinkles begins deep at the neuromuscular junctions [15], triggered by the depolarization of the muscle cell membrane, swiftly propagates along the sarcolemma, and extends into the T-tubules [16], setting the stage for further muscular activity. Understanding this progression provides valuable insights into both the natural aging process and opportunities for intervention (Figure 1).

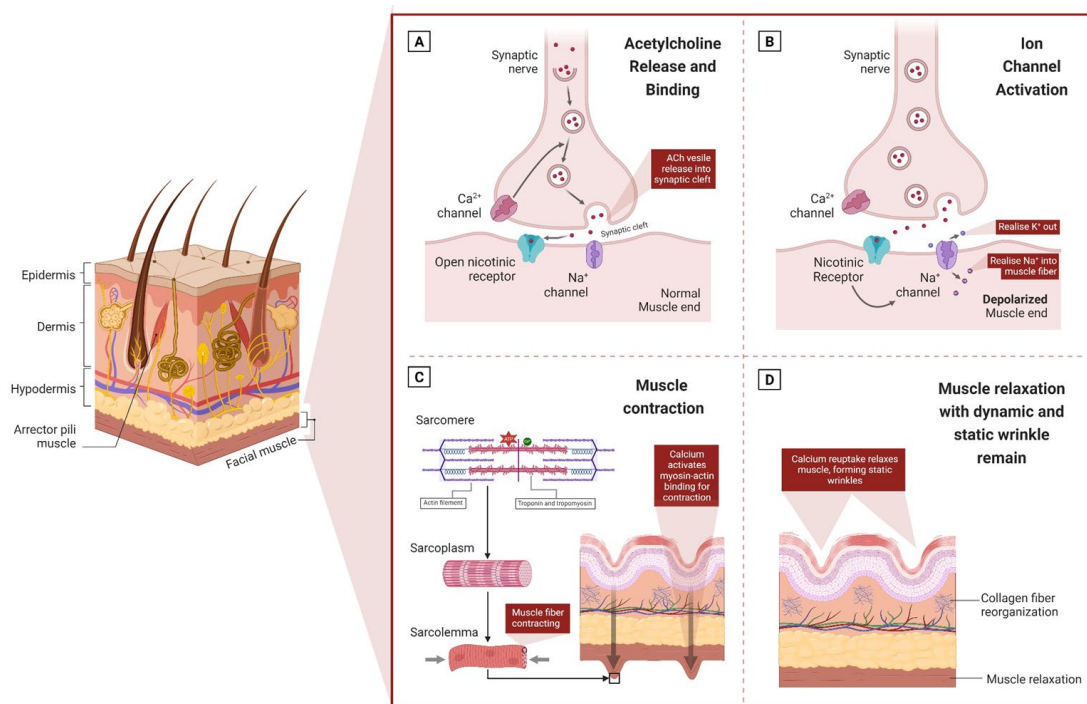


Figure 1. Sequential neuromuscular activation and its role in wrinkle development. Acetylcholine release triggers muscle contraction (A); calcium-mediated muscle contraction leads to skin deformation (B); persistent muscle contractions (C); and static wrinkle formation as the muscle relaxes and calcium is reabsorbed into the sarcoplasmic reticulum (D).

2.1.1. Acetylcholine Release and Neuromuscular Activation

The process of dynamic wrinkle formation initiates at the neuromuscular junction where the release of acetylcholine, a critical neurotransmitter, is catalyzed by an action potential [17,18]. This event triggers the opening of voltage-gated calcium channels, facilitating a calcium influx that prompts the exocytosis of acetylcholine into the synaptic cleft [15,17,19]. In the synaptic cleft, the binding of acetylcholine to the nicotinic receptors on the muscle cell membrane is pivotal as it induces muscle contraction [16,17,20] and sets the foundation for the next phase, where the depolarization of the muscle membrane, enhanced by sodium influx [19,21] through the nicotinic receptors, facilitates the significant release of calcium from the sarcoplasmic reticulum [22,23].

2.1.2. Calcium Ion Release and Muscle Preparation

Subsequent to acetylcholine engagement, the muscle membrane undergoes further depolarization due to sodium ions entering the muscle fiber and potassium ions exiting into the synaptic cleft [19,21,24]. This depolarization at the nicotinic receptors enhances calcium release from the sarcoplasmic reticulum within the muscle fiber [23]. The released calcium binds to troponin, causing tropomyosin to shift and expose myosin-binding sites on actin filaments [15], an essential step in the contraction cycle. This phase is critical as it prepares the muscle for precise activity, presenting opportunities for targeted interventions to modulate muscle contractions and mitigate dynamic wrinkle formation.

2.1.3. Muscle Contraction and Initial Skin Folding

The theory of sliding filaments describes muscle contraction, where myosin heads, energized by the hydrolysis of adenosine triphosphate, pull actin filaments inward to effectuate contraction [25]. Muscle contractions pull on connective tissue fibers in the skin, forming temporary folds that, over time, are subjected to mechanical stress, leading to a reorganization of collagen fibers [26,27]. This continuous stress can cause the collagen to become misaligned or degrade, while fibroblasts may deposit new, disordered collagen, permanently deepening these folds. Understanding this process is crucial for developing effective interventions, such as topical application to enhance collagen alignment or injections to reduce muscle activity, aimed at reducing the formation and permanence of wrinkles.

2.1.4. Development of Dynamic and Static Wrinkles

Facial expressions, characterized by repeated muscle contractions, impose mechanical stress on the skin, initiating the formation of dynamic wrinkles [4]. As the skin ages, its resilience decreases due to diminished collagen and elastin production [18,26,28], reducing its capacity to repair micro-damage from continuous contractions. This leads to the transformation of dynamic wrinkles into permanent static lines. Exacerbating this process, environmental factors like ultraviolet A and B exposure accelerate structural protein degradation [29]. To counteract these effects, strategies including reducing muscle activity through botulinum toxin injections [8] and enhancing structural protein levels [26,28] in the skin are employed to preserve skin elasticity and appearance.

2.2. Current Treatment of Dynamic Wrinkles

The psychological perceptions of aging, especially regarding the presence of dynamic wrinkles, significantly impact individuals, with many seeking treatments to mitigate visible signs of aging [30]. Traditional treatments, such as botulinum toxin injections, have demonstrated high efficacy, with 100% of users observing significant dynamic wrinkle improvements in clinical trials [31], lasting from two to six months [32]. However, the invasive nature of these treatments and the potential for complications, which can affect up to 2 to 16% of patients according to clinical reports and the United States Food and Drug Administration (FDA) database [33–36], highlight the necessity for developing non-

invasive alternatives. This widespread concern underscores the urgent need for effective and safer alternative options.

In response to this demand, emerging research is being developed that aims to reduce the appearance of dynamic wrinkles by enhancing skin health and elasticity, without the risks associated with invasive procedures. These innovations focus on advanced peptide technologies that mimic or inhibit neurotransmitter effects at the neuromuscular junction, directly targeting the underlying causes of wrinkle formation. Offering a promising and safer alternative, these ingredients not only address aesthetic concerns but also support the structural integrity of the skin. By improving methods of delivering active ingredients, these novel ingredients seek to effectively and safely mitigate the signs of aging, catering to the growing demand for non-invasive solutions in cosmetic dermatology.

3. Current Standard Care: Botulinum Toxin

3.1. Botulinum Toxin Injection

Botox was determined to originate from an anaerobic bacterium known as *Clostridium botulinum*, and researchers identified seven distinct subtypes of this bacterium, labeled A through G [37,38]. Botulinum toxin type A, notably Botox cosmetic (onabotulinumtoxinA) [36], Dysport (abobotulinumtoxinA) [39], and Xeomin (incobotulinumtoxinA) [40], is FDA-approved for cosmetic use in specific facial applications with a detailed history summarized in Figure 2 [38,41,42]. Botox was first approved by the FDA in 2002 for glabellar lines [43], with clinical studies demonstrating its high efficacy, reporting that about 80% of recipients observe a noticeable reduction in wrinkle appearance within one week of application [44]. Subsequent approvals extended its use to periorbital wrinkles in 2013 [45] and forehead lines in 2017 [37], employing precise dosages such as 24 units for periorbital wrinkles and 20 units for forehead lines, which are effective for approximately 3 to 4 months according to FDA guidelines [37,45]. Dysport and Xeomin followed, targeting glabellar lines with distinct properties and dosage recommendations, achieving similar efficacies [39,40]. Clinical trials indicate that Dysport, administered via injection, begins to manifest effects within one week, achieving an approximate 25% enhancement in wrinkle reduction compared to the baseline measurements obtained with Botox cosmetics. Furthermore, the longevity of Dysport effects extends up to 20 weeks, underscoring its superior duration of action in clinical settings [46]. In a comparative study, Botox demonstrated a more significant reduction in dynamic wrinkles than Xeomin, with noticeable improvements from as early as three days and continuing up to four months [47]. By day three post-application, 65.2% of subjects showed at least a 1-point improvement from baseline, increasing to 100% by day eight, and remaining significant through weeks 20–21. Moreover, response rates were higher under maximum muscle tension, with over 68% of subjects reporting improved or markedly improved platysmal bands at later visits, without any serious adverse events noted [48]. FDA guidelines ensure targeted and age-specific use (under 65 years) to maximize safety and effectiveness, emphasizing the precision required in these treatments [36,37,39,40,45]. Despite the proven effectiveness of botulinum toxin type A in reducing dynamic wrinkles, the demand for non-invasive alternatives continues to grow, driven by procedural invasiveness and stringent controls over application and dosing.

Botox functions by impeding motor and parasympathetic nerve function via diminished acetylcholine release (Figure 3A) and evades neutralizing antibodies swiftly, although the onset of muscle paralysis is delayed [49]. This process is mediated by the toxin binding to nerve terminals, internalization, and subsequent disruption of SNAP-25 (Synaptosomal Associated Protein, 25 kDa), a crucial protein in the SNARE (soluble N-ethylmaleimide-sensitive factor attachment protein receptor) complex that is essential for synaptic vesicle fusion and docking with other proteins including Syntaxin (a t-SNARE protein involved in vesicle docking) and VAMP/synaptobrevin (Vesicle-Associated Membrane Protein, v-SNARE critical for vesicle fusion) [50,51]. Clinically, Botox cosmetic is utilized to decrease muscle contractions by inhibiting acetylcholine release at motor nerve terminals. This

mechanism has been effectively applied in dermatology to smooth facial wrinkles by relaxing the underlying muscles. The relaxation of these muscles reduces the appearance of wrinkles and prevents the formation of new ones, making Botox a staple in cosmetic applications for facial rejuvenation [36,37,49]. This approach not only enhances aesthetic outcomes but also contributes to the understanding of neuromuscular interactions at the dermatological level.

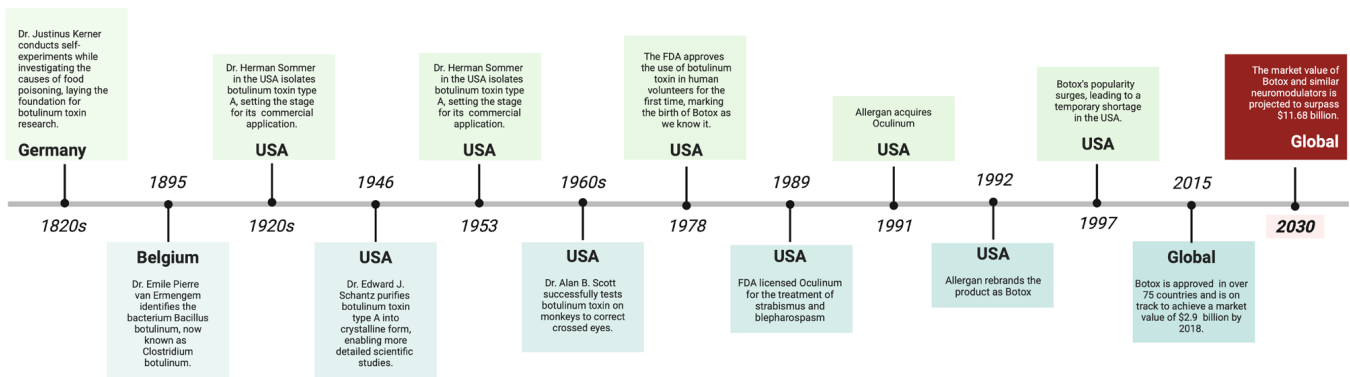


Figure 2. Timeline of key developments in Botox: inventions, approvals, and global market impact (1820–2030).

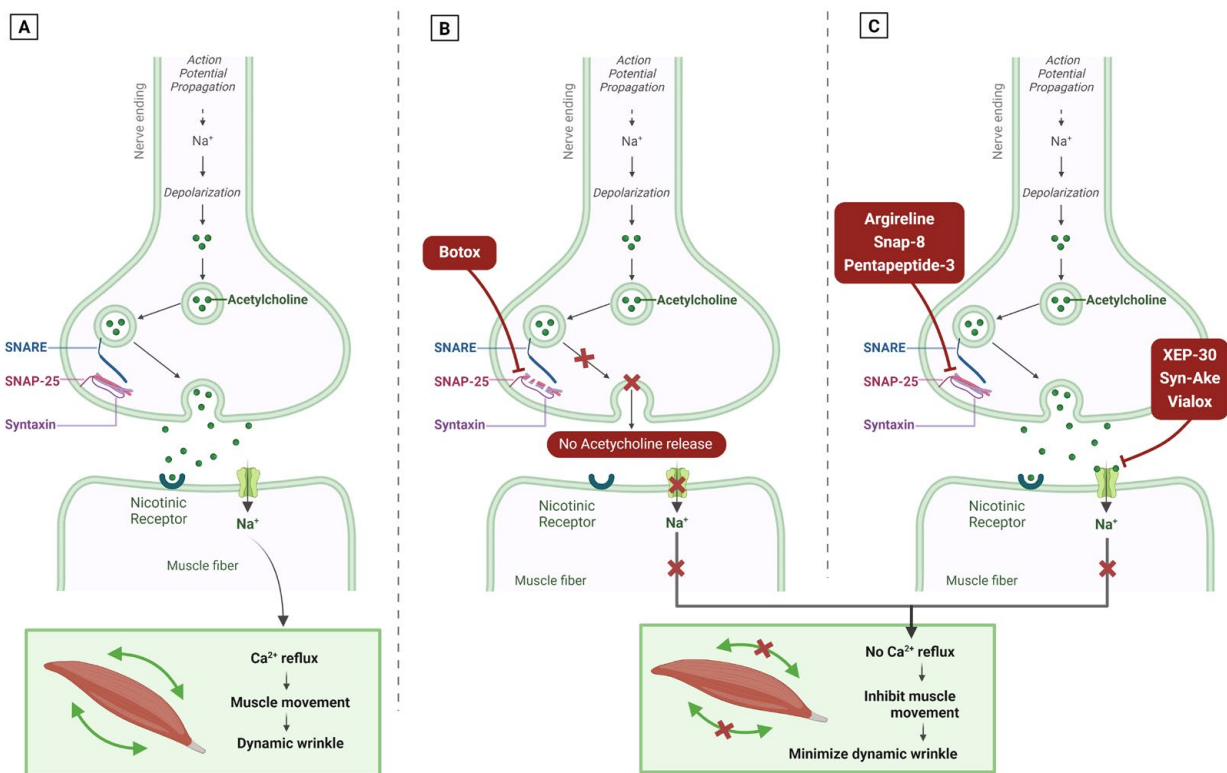


Figure 3. Mechanisms of neurotransmitter inhibitor action in dynamic wrinkle treatment. Normal neuromuscular activity leading to wrinkle formation (A); botulinum toxin inhibiting acetylcholine release by cleaving SNAP-25 (B); and topical alternatives (peptides and extracts) interfering with acetylcholine signaling and enhancing skin structure (C).

According to FDA guidelines, while Botox is generally safe when administered by qualified professionals, it carries a risk of side effects [36]. Common adverse effects, occurring in approximately 1 to 10% of cases, include localized pain, infection, inflammation, tenderness, swelling, redness, and bruising at the injection site. More serious but less

common risks, affecting around 1 to 5% of patients, involve ptosis, asymmetry of facial expressions, and dry eyes due to the spread of the toxin to adjacent muscles. In rare instances (less than 1%), patients might experience systemic effects such as difficulty swallowing, difficulty breathing, or muscle weakness if the botulinum toxin spreads beyond the intended injection area [36,37,45,52]. The global botulinum toxin market is forecasted to expand from 6.6 billion US dollars in 2023 to 11.68 billion US dollars by 2030, showing strong growth. Leading contributors include Allergan, known for Botox, and Merz Pharma, known for Xeomin, alongside emerging Asian brands like Revance and Daewoong. North America leads in demand due to a high rate of cosmetic surgeries, while the Asia-Pacific region is rapidly growing due to increasing aesthetic and therapeutic uses of botulinum toxin products [42,53]. Botox treatments in 2024, which typically cost between USD 100 and USD 2800 per session, can be particularly expensive for comprehensive treatments that cover multiple facial areas, with costs potentially rising to USD 5000 or more for extensive applications [54]. These treatments must be administered by professional practitioners, highlighting the need for more accessible and safer alternatives.

3.2. Botulinum Toxin Topical Gel

The introduction of botulinum toxin in topical formulations marks a significant development in cosmetic dermatology, expanding beyond traditional injectable methods. Injectable botulinum toxin, which typically shows up to an 80% reduction [44,55] in wrinkle depth within 3 to 7 days and maintains efficacy for 3 to 4 months [55], has long been established as an effective treatment for dynamic facial lines. In contrast, topical formulations aim to provide a non-invasive alternative for patients seeking cosmetic improvement without the use of needles [55–60].

Current research indicates that topical botulinum toxin can deliver modest improvements in wrinkle appearance with a considerably lower efficacy compared to injectable forms. Studies have documented various outcomes based on the formulation and delivery system used:

- Nanoparticle-based formulations: Demonstrated a 25% reduction in wrinkle depth after four weeks of daily application, significantly higher than the 5% reduction observed in the placebo group [55].
- Liposomal delivery systems: Reported a 30% improvement in wrinkle severity over an eight-week period [57].
- Peptide-based carriers: Achieved a 20% reduction in periorbital wrinkles after six weeks of treatment [60].

These gradual and less pronounced outcomes cater to users desiring subtle aesthetic enhancements. Such characteristics are likely to foster greater adherence among those who prioritize convenience and minimal discomfort, contrasting sharply with the rapid but sometimes overly pronounced effects of injectable treatments. Commonly reported disadvantages of injectable botulinum toxin, such as procedural pain, the need for professional administration, substantial costs averaging several hundred dollars per session, and potential adverse effects including the ‘frozen’ look, are significantly mitigated by topical formulations. This approach not only aligns with current trends towards more conservative cosmetic procedures but also expands the accessibility and acceptability of botulinum toxin treatments.

Most topical botulinum toxin formulations are still in experimental or early commercial stages and still require medical practitioner application. Noteworthy developments include Revance Therapeutics RT001 [57], a topical gel formulation of Botox cosmetic, and Allergan Botox Topical Gel, both of which are undergoing further research and clinical trials to evaluate their safety and efficacy [55]. These characteristics evoked the studies of peptide topical alternatives and addressed these concerns by offering a non-invasive application method that can be administered at home, leading to reduced side effects and overall lower healthcare expenditure.

4. Emerging Peptide Topical Alternatives

4.1. Synthetic Peptide

Peptides are at the forefront of non-invasive anti-aging effects, particularly those that inhibit neurotransmitter release, offering effects similar to Botox (Table 1 and Figure 3B,C). These short chains of amino acids can relax facial muscles and reduce wrinkles without the need for injections.

Table 1. Efficacy, time to visible results, duration of effects, common side effects, and mechanisms of action of Botox and peptide topical alternative.

Name	Brand Name	Source/Origin	Mechanism of Action	Duration of Effect	Clinical Study Findings
Botulinum Toxin Injection	Botox, Dysport, Xeomin	Clostridium botulinum	Inhibits ACh ¹ release by cleaving SNAP-25 ² , blocking muscle contractions	3–4 months	80% reduction in wrinkle appearance within one week; effects last 3–4 months
Botulinum Toxin Topical Formulations	Topical Botox Gel	Botulinum toxin type A	Inhibits ACh release by targeting SNAP-25, blocking muscle contractions	Continuous use	Nanoparticle-based formulations: 25% reduction after 4 weeks; Liposomal delivery: 30% improvement after 8 weeks
Argireline	Acetyl Hexapeptide-8	Synthetic peptide	Inhibits SNARE ³ complex assembly, blocking neurotransmitter release	Continuous use	Reduced wrinkle depth by up to 30% after 30 days
Snap-8	Acetyl Octapeptide-3	Synthetic peptide	Extends Argireline action, inhibiting SNARE complex	Continuous use	Reduced wrinkle depth by up to 38% after 28 days
Leupharyl	Pentapeptide-18	Synthetic peptide	Modulates muscle contraction by blocking calcium channels, reducing ACh release	Continuous use	Reduced wrinkle depth by up to 24% after 28 days
Vialox	Pentapeptide-3	Synthetic peptide	Acts as a competitive antagonist at ACh postsynaptic membrane receptors, inhibiting muscle contraction	Continuous use	Reduced skin roughness by 47% and wrinkle depth by 49% after 28 days
XEP-30 and XEP-018	μ-conotoxin CnIIIC	Synthetic peptide derived from marine cone snail venom	Blocks ACh release by targeting NaV1.4 ⁴ sodium channels, mimicking botulinum toxin	Continuous use	Reduced wrinkle depth by up to 48% after 30 days
Syn-Ake	Dipeptide Diaminobutyryl Benzylamide Diacetate	Synthetic (Snake venom mimic)	Antagonizes muscle nAChRs ⁵ and modulates GABA _A ⁶ receptors	Continuous use	Reduced wrinkle size by up to 52% after 28 days
Myoxinol	Hibiscus esculentus extract	Natural extract	Inhibits muscle contractions via interaction with GABA ⁷ receptors, enhancing GABAergic transmission	Continuous use	Reduced wrinkle depth by up to 26% after 3 weeks

¹ ACh (Acetylcholine), ² SNAP-25 (Synaptosomal Associated Protein, 25 kDa), ³ SNARE (Soluble N-ethylmaleimide-sensitive factor attachment protein receptor), ⁴ NaV1.4 (Voltage-gated sodium channel 1.4), ⁵ nAChRs (Nicotinic Acetylcholine Receptors), ⁶ GABA_A (Gamma-Aminobutyric Acid type A), ⁷ GABA (Gamma-Aminobutyric Acid).

4.1.1. Argireline (Acetyl Hexapeptide-8)

Peptides such as Argireline represent the vanguard of non-invasive anti-aging ingredients, offering an alternative to the neuromodulatory effects of botulinum toxin without requiring injections. Argireline, a synthetic hexapeptide developed by Lipotec in 2002 [61], mimics the natural mechanisms of botulinum toxin. Structurally, it is a synthetic peptide derived from the N-terminal end of the SNAP-25 substrate in the SNARE complex, crucial for neurotransmitter release [61–63]. The Argireline mechanism of action is remarkably akin to that of Botox.

Argireline has been clinically validated to reduce the appearance of wrinkles, albeit with less immediate or dramatic effects compared to Botox. A seminal study by Blanes-Mira

et al. (2002) demonstrated a 30% reduction in wrinkle depth after a 30-day application of a 10% Argireline solution [61]. Another study showed a 48.9% anti-wrinkle efficacy in subjects after four weeks of use [62]. This peptide offers a less invasive application, suitable for individuals seeking subtle cosmetic improvements without the risks associated with injections. Its efficacy, combined with a favorable safety profile, underscores its utility as a viable cosmetic peptide for reducing signs of aging.

The non-toxic nature of Argireline makes it an appealing alternative for topical use [61,64]. Unlike Botox, which involves precise injection and carries risks such as potential 'frozen' looks or other minor side effects, Argireline can be applied topically and absorbed through the skin, minimizing systemic effects and enhancing user compliance due to its ease of application. This has led to its increased popularity in formulations targeted at consumers who prefer non-invasive options.

4.1.2. Snap-8 (Acetyl Octapeptide-3)

Snap-8, developed by Lipotec in the late 2000s, enhances the peptide sequence by extending Argireline eight amino acids (Ac-Glu-Glu-Met-Gln-Arg-Arg-Ala-Asp-NH₂) [65]. Such a strategic augmentation enhances its ability to disrupt the assembly of the SNARE complex, critical for neurotransmitter release at neuromuscular junctions, similar to Argireline.

The effectiveness of Snap-8 in reducing wrinkle depth, particularly in areas with frequent dynamic muscle activity such as around the eyes, is significant. Clinical studies have indicated that Snap-8 can achieve up to a 38% reduction in wrinkle depth within 28 days of application, presenting it as a potent neuromodulatory peptide [65]. This result supports its utility as a non-invasive alternative to traditional treatments like Botox, targeting similar mechanisms of action but without the need for injections.

In terms of delivery and formulation, products containing Snap-8, such as patches, face challenges with permeability through the stratum corneum. However, Dissolving Microneedle technology effectively delivers Snap-8 to target areas, enhancing wrinkle reduction and maintaining peptide stability more significantly than Botox [12,65,66]. Clinical studies confirm Snap-8's excellent tolerability over 12 weeks and highlight the synergistic effects of formulations combining Snap-8 with other bioactive compounds [66], collectively boosting anti-wrinkle efficacy [65].

4.1.3. Leuphasyl (Pentapeptide-18)

Leuphasyl is developed by Lipotec to mimic the effects of enkephalins, targeting the neuromuscular junction to modulate acetylcholine release, which is crucial for muscle contraction. This results in muscle relaxation, reducing dynamic wrinkles. Leuphasyl acts by lowering calcium influx at nerve endings, decreasing acetylcholine release and muscular contractions, and shares similarities with the Botox mechanism but via different biochemical pathways [67]. Combining Leuphasyl with Argireline, targeting different mechanisms within the SNARE complex, enhances anti-wrinkle efficacy [68]. Using Leuphasyl at a 2% concentration targeting the SNARE complex results in significant wrinkle depth reductions, 34.7% in the frontal region and 28.4% in the periorbital area, thus, enhancing the efficacy against dynamic wrinkles [67].

4.1.4. Vialox (Pentapeptide-3)

Pentapeptide-3, marketed as Vialox, is an oligopeptide developed by DSM that mimics the neuromuscular blocking effect of snake venom peptides, notably from the temple viper. It acts as a competitive antagonist at the acetylcholine postsynaptic membrane receptor, preventing sodium ion channels from opening and inhibiting muscle contraction. In vitro studies show a significant reduction in muscle cell contraction, while in vivo studies indicate a 49% decrease in wrinkle size and a 47% decrease in skin roughness after 28 days. Vialox effectively smooths periorbital, forehead, and nasolabial fold wrinkles, providing an immediate tightening effect with a recommended concentration of 0.05 to

0.3% [69,70]. However, Vialox required further clinical trials to prove its effects on a larger patient demographic.

4.2. Animal-Derived Synthesis Peptide

4.2.1. XEP-30 and XEP-018 (μ -Conotoxin CnIIIC)

XEP-30 and XEP-018, also known as μ -conotoxin CnIIIC, are conopeptides derived from the venom of the marine cone snail *Conus consors* [71,72]. This synthetic peptide is renowned for its Botox-like effects and belongs to a class of peptides that have garnered significant attention for their potential in aesthetic dermatology due to their ability to modulate neuromuscular activity. Similar to Botox, XEP-30 and XEP-018 function by inhibiting the release of neurotransmitters that signal muscle contraction. This action results in a temporary relaxation of facial muscles, thereby reducing the appearance of dynamic wrinkles and fine lines. The peptide targets the voltage-gated sodium channels, particularly the NaV1.4 channel [71], which plays a critical role in neuromuscular transmission.

According to data published on the Erasa Skincare website, the application of their XEP-30 serum resulted in an average wrinkle reduction of 64% across the sample over a 14-day period. Additionally, 42% of participants experienced a wrinkle reduction of 70% or better, with the top quartile seeing reductions of 90% or more [73]. These effects are comparable to those achieved with Botox, but a randomized clinical trial would need to be published to reconfirm this number.

4.2.2. SYN-Ake (Dipeptide Diaminobutyryl Benzylamide Diacetate)

SYN-Ake, an analog of the peptide Waglerin-1 derived from the venom of the Southeast Asian Temple Viper (*Tropidolaemus wagleri*), functions by antagonizing muscle nAChRs and modulating GABA_A receptors [74,75]. The tripeptide links to a receptor subunit, blocking the attachment of nAChR. As a result, the ionic channel remains closed, preventing the uptake of sodium ions and keeping the muscles relaxed. This action reduces muscle contraction and, consequently, the appearance of expression wrinkles [68]. This pharmacological action inhibits the neuromuscular transmission responsible for muscle contractions that lead to the formation of dynamic expression lines, particularly in the periorbital and forehead regions. By blocking these receptors, SYN-Ake induces localized muscle relaxation, resulting in a smoother and more refined dermal surface. This targeted neuromodulation decreases the visibility of fine lines and wrinkles without affecting other cellular processes, thereby ensuring a high safety profile for topical application. Clinical investigations have substantiated the efficacy of SYN-Ake 4%, with one study demonstrating that a topical formulation containing SYN-Ake resulted in a reduction of wrinkle size by up to 52% over a 28-day period. Subjects reported significant improvements in skin texture and a reduction in wrinkle depth, with visible effects observable as early as one week into the regimen [76,77].

4.3. Plant-Based Extract

Myoxinol, derived from *Hibiscus esculentus*, also known as okra, is a plant-based extract celebrated for its natural muscle-relaxing properties [78]. The primary action of Myoxinol involves inhibiting the mechanical factors that contribute to expression lines and wrinkles. The effectiveness of Myoxinol can be attributed to its interaction with GABA receptors, similar to other flavonoids, saponins, and terpenoids found in plants. These phytoconstituents enhance GABA transmission, which results in the hyperpolarization of neuronal membranes and a subsequent decrease in neuronal firing rates, and reduces the contraction frequency of muscle fibers [79].

Several studies support the effectiveness of Myoxinol in cosmetic applications. Research indicates that regular application of Myoxinol leads to visible reductions in fine lines and wrinkles. A notable clinical trial observed that products containing Myoxinol reduced wrinkle depth by up to 26% after just three weeks of use [80]. These results highlight its potential as a natural alternative to more invasive procedures. Myoxinol's potential is

further enhanced by its origin from a well-known edible plant, which aligns with the trend towards cleaner, safer cosmetic ingredients.

5. Market Insights and Consumer Trends

The global market for anti-aging products, particularly those targeting dynamic wrinkles, is experiencing robust growth, driven by increasing consumer awareness and demand for non-invasive alternatives to traditional treatments like botulinum toxin. According to a report by Grand View Research, the global anti-aging market is projected to reach approximately 120 billion USD by 2030, expanding at a compound annual growth rate (CAGR) of 7.5% [81]. This surge is primarily fueled by the aging population and a significant shift in consumer preferences towards safer, non-toxic, and sustainable skincare solutions.

In recent years, there has been a discernible trend towards ‘clean beauty’ products, with consumers increasingly opting for skincare items that are free from harsh chemicals, which can be overly aggressive or cause dermal irritation and are made with environmentally friendly ingredients. Market analysis from Transparency Market Research highlights that over 60% of consumers aged 18 to 35 prefer to purchase products labeled as “natural” or “organic,” a trend that is reshaping the landscape of the dermatological cosmetics market. This demographic is particularly interested in preventative skincare regimes that integrate seamlessly into their daily routines, further driving the demand for topical alternatives that can mimic the effects of procedures like Botox without the associated risks [82].

The market for peptide topical alternatives (Table 2) to botulinum toxin has been growing, with several key brands and products leading the charge. Argireline, developed by Lipotec (a subsidiary of Lubrizol), is sold under various brand names like Sederma’s Matrixyl and is featured in many high-end skincare products, contributing significantly to the anti-aging segment. Leuphasyl, marketed by Lipotec, is often combined with other peptides in anti-aging products, capturing a significant market share in premium skincare lines. The global cosmetic peptide market is expected to grow from 244.2 million USD in 2024 to 411.9 million USD by 2034, driven by increased demand for effective, non-invasive skincare solutions, particularly in the U.S. and Europe [83]. Syn-Ake is highly sought after in Asian, European, and North American markets for its innovative anti-aging properties [84]. Myoxinol, from *Hibiscus esculentus*, is gaining traction in the natural and organic skincare segment [85], driven by a growing consumer preference for clean beauty products in Asia Pacific and Europe [86].

Table 2. Representative peptide topical alternatives commercial names and companies.

Peptide/Extract	Brand/Company	City, Country
Argireline® Amplified peptide solution Argireline® peptide solution C Argireline® YOUth peptide Argirelox™ peptide solution Inyline® peptide solution SNAP-8™ peptide solution C Leuphasyl Argirelox Inyline	Lipotec	Barcelona, Spain
Vialox SYN-Ake	DSM-Firmenich	Heerlen, Netherlands
XEP-30 XEP-018	Erasa XEP-30	New York, United States
Myoxinol	BASF	Monheim, Germany

6. Challenges and Future Perspectives

While non-invasive options for dynamic wrinkles are becoming increasingly popular, they face significant challenges and limitations that must be addressed to improve their

efficacy and consumer acceptance. A primary limitation of topical agents is their inability to penetrate deeply enough into the skin to significantly affect the muscles. This barrier often results in these ingredients being less effective, achieving a maximum of 52% wrinkle reduction [77] compared to Botox injections, which can achieve up to 80% wrinkle reduction [46] by directly targeting neuromuscular junctions.

Moreover, the long-term clinical effects and safety of many new peptides and botanical extracts used in these ingredients are not well-documented. While initial results are promising, comprehensive studies over longer periods are necessary to establish their safety, potential side effects, and sustained efficacy. This uncertainty can deter consumers who are seeking reliable and proven solutions to their aging concerns.

The market for dynamic wrinkle ingredients also lacks stringent regulatory oversight for topical anti-aging products compared to invasive procedures. This can lead to the proliferation of products with unsubstantiated claims, potentially misleading consumers and eroding trust in non-invasive ingredients.

Future trends in addressing dynamic wrinkles non-invasively involve enhancing penetration technologies such as microencapsulation, nanotechnology, and skin permeation enhancers to improve the delivery of active ingredients to deeper skin layers. There is also growing advocacy for stricter regulations and clearer labeling to ensure product efficacy and safety, which could help standardize the market and build consumer trust. Additionally, advancements in dermatological research are steering towards personalized skincare ingredients tailored to individual skin types, conditions, and genetic profiles, potentially increasing the effectiveness of topical options for dynamic wrinkles [87].

Research needs to expand to include diverse demographic groups to ensure that application efficacy is broad and inclusive. More research is required on how these topical agents can be effectively combined with other ingredients, such as light therapy or mechanical stimulation, to enhance their anti-wrinkle effects. Evaluating the cost-effectiveness of these non-invasive ingredients compared to traditional methods is crucial, especially since many are not covered by health insurance.

By addressing these challenges and leveraging innovative technologies and regulatory improvements, the future of treating dynamic wrinkles can shift towards more effective, safer, and accessible non-invasive options. This shift promises to revolutionize the approach to anti-aging ingredients and aligns with the increasing consumer demand for non-toxic, sustainable, and gentle skincare solutions.

7. Conclusions

The revolution in dermatological care is driven by non-invasive alternatives to Botox for dynamic wrinkle treatment. Although peptides encounter distinct scientific challenges, such as a low absorption rate that significantly varies depending on the method of application, these topical agents continue to lead the charge by offering:

- **Effective, safer solutions:** These ingredients meet the growing consumer demand for 'clean beauty' products, aligning with preferences for non-toxic and sustainable skincare.
- **Technological advancements:** Innovations in delivery technologies are overcoming challenges like skin penetration, ensuring these ingredients are not only effective but also reliable.
- **Market expansion:** The booming market, fueled by consumers seeking seamless and risk-free skincare routines, highlights the transformative potential of these alternatives.

This paradigm shift promises to set new standards in cosmetic dermatology, making anti-aging solutions more accessible and delivering profound socio-economic and psychological benefits.

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