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Nanostructured Serums and Device-Based Methods for Nanoparticle Delivery: An Innovative Alternative to Injection Therapy for Acne

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Abstract

Acne remains a global dermatological problem, the burden of which continues to grow. Traditional treatment methods for severe forms, in particular intralesional injections (ILK), are associated with significant risks, including irreversible skin atrophy. The aim of this study is a systematic analysis and theoretical justification of protocols that combine nanostructured serums (NSS) and apparatus-based delivery methods (ADM) as an innovative noninvasive alternative. The methodology is based on a systematic review of academic and industry sources, including a comparative analysis of clinical data. The results show that NSS (for example, liposomal tretinoin) demonstrates 1.5-fold higher efficacy in comedone reduction (94.17% vs 62.36%) and significantly better tolerability compared to conventional gels. Device-based methods, including sonophoresis and LADD, show efficacy (80-89% improvement) comparable to injections. Synergistic protocols (LED photobiomodulation + nano-gel) have clinically demonstrated the ability to significantly reduce the number of papules (-61.58%), sebum level, and erythema. In conclusion, it is noted that the integration of NSS and ADM represents a clinically substantiated, safe, and highly effective alternative to invasive therapy. The findings will be of interest to dermatologists, cosmetologist-estheticians, and researchers in the field of pharmaceutical delivery.

Keywords: Acne, nanotechnologies, nanostructured serums, hardware cosmetology, noninvasive delivery, liposomes, sonophoresis, photobiomodulation (LED), laser-assisted delivery (LADD), intralesional injections.

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1. Introduction

Acne is among the most prevalent chronic inflammatory dermatoses and is currently regarded not only as a medical condition but also as a significant socio-economic problem. According to the international Global Burden of Disease (GBD) project, this nosological entity ranks eighth among the most common skin diseases worldwide, affecting approximately 9.4% of the global population [8]. Epidemiological studies covering the period from 1990 to 2021 demonstrate a sustained increase in the burden of acne among adolescents and young adults in almost all countries, regardless of their level of socio-economic development [1]. According to 2024 estimates, the prevalence of acne in the 16–24-year age group is 28.3%, remaining substantial also in the adult population aged 25–39 years (19.3%) [9].

The high incidence of the disease directly translates into a considerable economic burden. The global pharmaceutical market volume of therapeutic agents for the treatment of acne in 2024 was estimated at 11.62

billion US dollars, with a projected increase to 12.19 billion dollars in 2025 [10]. In the United States, according to the American Academy of Dermatology (AAD), the combined direct and indirect costs associated with acne treatment, as well as loss of working capacity and decreased productivity against the background of psychosocial distress, exceed 1.2 billion dollars annually [8].

Despite the availability of an expanded spectrum of therapeutic options, current strategies for managing patients with acne face fundamental limitations. Topical treatment (in particular, classical retinoids and benzoyl peroxide) remains first-line therapy in clinical practice; however, its effectiveness is substantially reduced by low patient adherence. An analysis of real-world clinical practice data including 1160 treatment courses demonstrated that the median duration of topical agent use was only 2 months; at the same time, 52% of patients discontinued therapy due to subjectively perceived insufficient efficacy, and a further 9% due to adverse reactions such as irritative phenomena, xerosis, and erythema [12].

To control severe, nodular, and cystic forms of acne, as well as to achieve rapid resolution of individual acute inflammatory lesions, invasive therapy is widely used, primarily intralesional corticosteroid injections (ILK) [14]. However, this approach is characterized by a high risk of iatrogenic complications. The most frequent and clinically significant adverse effects include pronounced pain during administration, persistent pigmentary alterations (hypo- and hyperpigmentation), the development of telangiectasias and, in particular, local skin atrophy. A study in which 100 dermatologists were surveyed showed that, despite the predominant use of low drug concentrations (for example, 2.5 mg/ml), a unified standardized ILK-therapy protocol is lacking, and in 48.4% of cases the resulting skin atrophy persisted for more than 6 months [3].

Systemic therapy, primarily oral isotretinoin, remains the most effective modality acting on all key links in the pathogenesis of acne. At the same time, its use is strictly regulated due to severe systemic adverse effects, including marked teratogenicity, the risk of drug-induced liver injury, and possible psychoneurological disturbances [15].

Taken together, this forms a pronounced scientific and practical gap in contemporary dermatology and aesthetic medicine: there is a therapeutic dichotomy between highly effective systemic and invasive interventions with a substantial risk profile on the one hand, and relatively safe topical methods with limited efficacy and low compliance on the other [12]. At present, there is no therapeutic strategy that simultaneously provides topical efficacy comparable to invasive methods and is characterized by a high level of safety and sustained patient adherence.

The aim of the study is to conduct a systematic analysis and develop a theoretical rationale for a synergistic protocol combining nanostructured serums (HCC) and hardware methods (AM) of transdermal delivery as a highly effective and safe alternative to injectable acne therapy.

The working hypothesis assumes that the integration of nanotechnologies (providing increased tolerability and targeted delivery of active substances to the pilosebaceous unit) with non-invasive hardware methods (creating conditions for forced overcoming of the epidermal barrier) makes it possible to achieve clinical outcomes in terms of reduction of inflammatory lesions comparable to intralesional injection therapy, while simultaneously reducing the frequency of adverse effects and increasing patient satisfaction.

The scientific novelty of the work lies in the fact that, for the first time, a comprehensive non-invasive paradigm of acne treatment is proposed and theoretically substantiated, integrating nanopharmaceutical formulations, non-aggressive chemical peels, and methods of hardware physiotherapy (sonophoresis, LADD, LED) as an alternative to injection-based interventions.

2. Materials and Methods

The methodological basis of the study was built around a strategy of systematic literature review, integrated with procedures of comparative analysis of therapeutic modalities and content analysis of technical documentation and industry analytical materials.

The analytical corpus included 19 relevant sources, predominantly published in the period 2020–2025, which ensures the contemporary character of the empirical base and reflects the current level of technological development. To ensure comprehensive coverage of the subject area, the sources were typologized by type:

Type 1: Academic articles. The core of the sample was formed by peer-reviewed clinical studies, systematic

reviews, and technical publications from indexed databases Scopus, Web of Science, and PubMed Central (PMC). These materials were used to reconstruct pathogenetic mechanisms, to evaluate the efficacy and safety profile of therapeutic interventions, and to analyze the technological characteristics of the applied solutions.

Type 2: Industry and market reports. Analytical reviews of leading consulting companies (McKinsey & Company, Precedence Research) were used to interpret macro-level trends, to assess consumer demand, and to describe the market context of the implementation of non-invasive technologies.

3. Results and Discussion

The classical model of acne management is based on stepwise escalation of therapy: from topical agents to systemic drugs and subsequently to invasive interventions. However, critical analysis of the data demonstrates that the generally accepted most appropriate options encompass a substantial spectrum of risks and methodological limitations, which call into question their universality and suitability for broad routine use.

The most common strategy for rapid resolution of deep inflammatory lesions (nodules and cysts) remains intralesional corticosteroid injection (ILK) [14]. Although this approach provides pronounced and relatively rapid reduction of local inflammation, it is associated with serious, often irreversible complications. The most clinically significant is the development of local skin atrophy, driven by steroid-induced suppression of collagen synthesis by fibroblasts [2]. According to a survey of 100 practicing dermatologists in the USA, even with awareness of this risk, atrophy remains a frequent outcome; 48.4% of respondents reported that in their practice atrophic changes in patients persisted for more than 6 months [3]. In addition, the spectrum of adverse effects includes pain, telangiectasias, and pigmentary disorders (hypo- and hyperpigmentation) [2].

The situation is further complicated by the complete absence of standardized protocols and consensus recommendations for ILK administration [25]. In the aforementioned study [3], pronounced inter-practice variability was demonstrated in the concentrations used (from 2.5 mg/mL to 10 mg/mL), the injected volumes, and the depth of injection. Thus, the reproducibility and predictability of the outcome largely depend on the subjective experience of the operator, which makes ILK methodologically vulnerable and a potentially unsafe option for routine aesthetic practice aimed at minimizing iatrogenic risks.

Oral isotretinoin, which retains the status of a highly effective systemic agent, is characterized by such an adverse event profile that its use is objectively limited mainly to severe forms of acne that are resistant to other therapies. The systemic nature of the drug's action predetermines the development of mucocutaneous adverse effects (cheilitis, xerosis) and is also associated with serious risks, including pronounced teratogenicity and possible psychoneurological disturbances [16].

Even first-line therapy based on topical agents proves to be inadequate at the level of real-world clinical practice, primarily in terms of adherence. Analysis of real-life use data [12] showed that the median duration of topical treatment (adapalene, BPO) is only about 2 months. The main reason for premature discontinuation in 52% of cases was reported by patients as lack of effect, and in another 9% as the development of adverse reactions in the form of irritation. This indicates that conventional topical formulations do not provide an optimal balance between clinical efficacy and tolerability, as a result of which patients tend to discontinue treatment before achieving a stable therapeutic outcome.

A summary comparative analysis of the risk profiles of the main therapeutic modalities for acne is presented in Table 1.

Table 1. Comparative analysis of adverse effect profiles: invasive/systemic methods vs. non-invasive topical approaches [2, 4, 11, 12, 15]).

Therapeutic modality	Primary mechanism	Key adverse effects (Frequency/Severity)	Limitations
Systemic (Isotretinoin)	Oral retinoid, systemic action	High frequency: cheilitis, xerosis, mucocutaneous dryness. Severe: teratogenicity, depression, hepatotoxicity.	Requires strict monitoring (blood tests, pregnancy).
Invasive (ILK injections)	Intralesional corticosteroid	Frequent: pain during injection. Clinically significant: local atrophy (in up to 48.4% of cases persisting >6 months), hypo/hyperpigmentation, telangiectasias.	Risk of irreversible changes, lack of standardization.
Topical (conventional)	Topical retinoids, BPO	High frequency: erythema, dryness, burning, peeling.	Low adherence; 52% discontinue due to inefficacy.
Topical (nanostructured)	Encapsulated retinoid (liposomes)	Low frequency: markedly reduced erythema and burning compared with conventional gels.	Higher manufacturing cost; regulatory barriers.

The solution to the problem of low efficacy and poor tolerability of topical therapy lies in the field of pharmaceutical nanotechnology. Nanostructured delivery systems (NDS), including liposomes, solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC), have been developed to overcome the limitations of conventional formulations [18, 26].

The mechanism of action of NDS in acne has a dual function. First, they encapsulate volatile or irritating active substances (such as retinoids or benzoyl peroxide) within a lipid or polymeric shell [13]. This provides controlled, prolonged release of the active agent, minimizing its contact with the superficial layers of the epidermis. As a consequence, the irritant potential (dryness, erythema) is significantly reduced, which directly addresses the problem of poor compliance [4].

Second, nanocarriers provide targeted delivery to the epicenter of acne pathogenesis, the pilosebaceous unit (hair follicle and sebaceous gland). Owing to their physicochemical properties (lipophilicity, small size), nanoparticles predominantly penetrate the skin not transepidermally, but transfollicularly, using the so-called follicular shunt [17]. They accumulate in the follicle, creating a high local drug depot while minimizing its systemic absorption [4]. This mechanism is illustrated in Fig. 1.

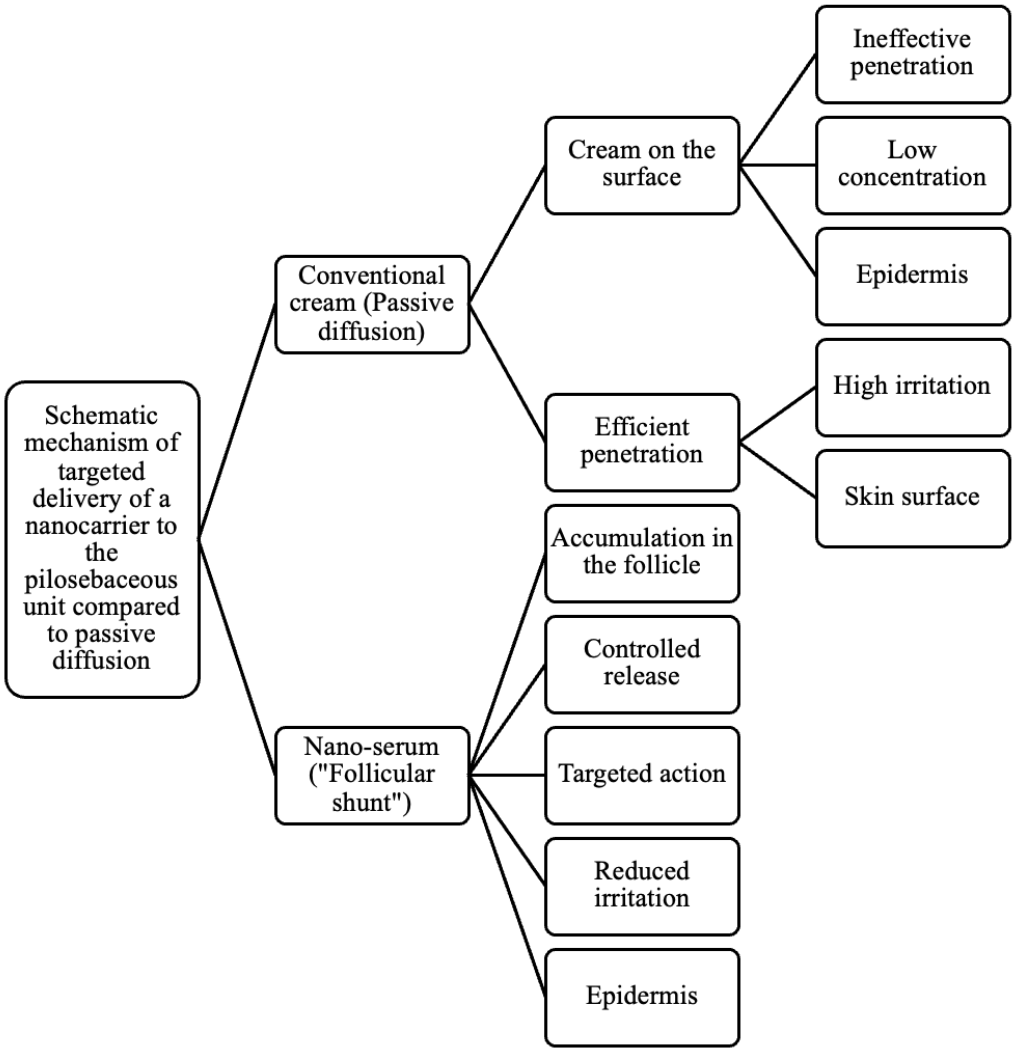

Fig. 1. Schematic mechanism of targeted delivery of a nanocarrier to the pilosebaceous unit compared to passive diffusion (compiled by the author based on [4]).

The effectiveness of this approach is convincingly demonstrated by a body of clinical studies. The most representative is a systematic review [4] devoted to the use of liposomal tretinoin. Analysis of double-blind clinical trials showed the following:

– Advantage in efficacy. The liposomal tretinoin gel provided an approximately 1.5-fold more pronounced therapeutic effect compared with a conventional gel of identical concentration.

– Quantifiable reduction in comedones. In a 3-month study, the mean percentage reduction in comedones reached 94.17% in the group using the liposomal gel, whereas in the standard gel group this value was 62.36% (see Fig. 2).

– Improved tolerability profile. In all studies included in the review, patients and physicians reported that the liposomal formulation was associated with substantially less pronounced erythema, burning and irritation compared with commercially available gels [4].

Taken together, these results demonstrate that nanostructuring addresses the first part of the key task: topical therapy becomes simultaneously more effective and safer, which fundamentally improves patient compliance.

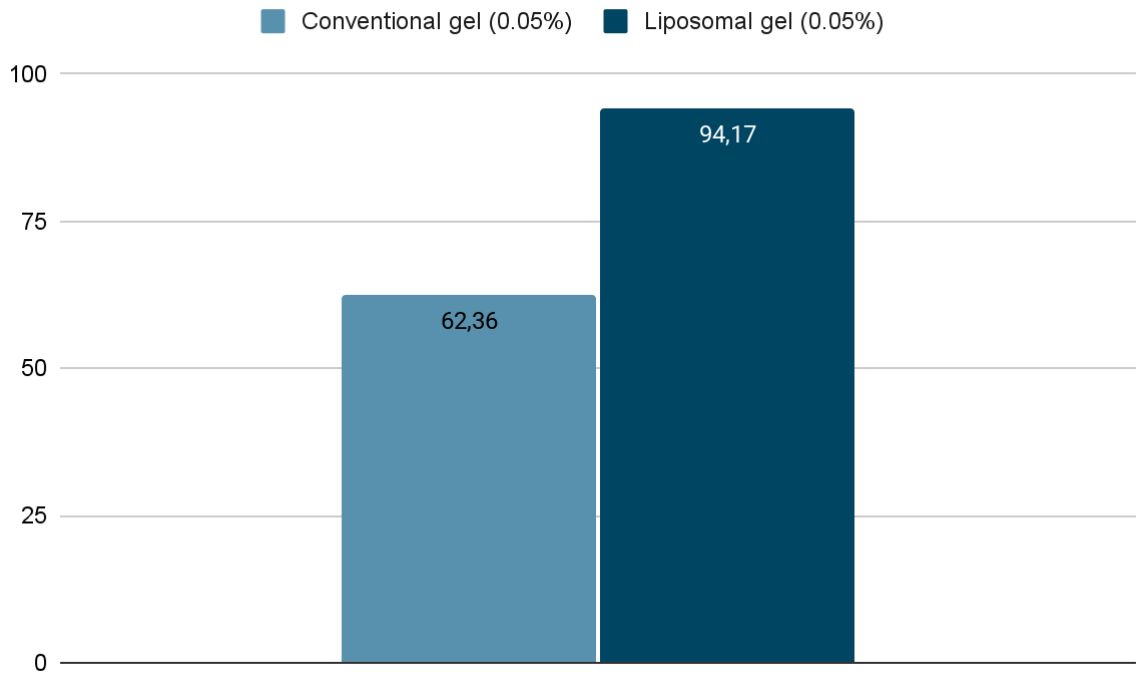

Fig. 2. Comparative clinical efficacy: Reduction of comedones using liposomal tretinoin and conventional gel (3 months) (compiled by the author based on [4]).

If nanocapsulation to a significant extent addresses the tasks of increasing tolerability and selective targeting, device-based methods focus on overcoming the key limiting factor, the penetration barrier. In essence, they act as a noninvasive analog of a needle, forcibly overcoming the epidermal barrier and ensuring the delivery of nanostructured serums into the deeper layers of the skin.

Sonophoresis achieves this effect through the action of ultrasound waves that transiently increase the permeability of the skin barrier. High-frequency ultrasound (HFS, 0.7 MHz) exerts its effect predominantly through thermal mechanisms, whereas for the purposes of transdermal drug delivery low-frequency sonophoresis (LFS, 20–100 kHz) is considered the most clinically relevant and safe.

The key mechanism of action of LFS is acoustic cavitation [5]. Low-frequency ultrasound waves induce the formation, growth, and subsequent rapid collapse of gas microbubbles in a bound medium (for example, within a topical gel). The collapse is accompanied by the generation of local shock waves and mechanical stresses that transiently disorganize the ordered lipid bilayers in the stratum corneum [5]. As a result, reversible micropores are formed, through which large molecules and nanoparticles are able to penetrate [5]. It is fundamentally important that this process is predominantly mechanical rather than thermal in nature, which ensures its atraumatic profile and makes the method suitable for patients with sensitive skin and active inflammation.

LADD (Laser-Assisted Drug Delivery) is a more intensive technology based on the use of fractional lasers (both ablative, for example CO_2, and non-ablative, for example Er:Glass) to create microscopic channels in the skin [20]. These microchannels function as direct transport pathways for drugs, allowing them to reach the dermis while bypassing the epidermal barrier.

The efficacy of LADD has been confirmed in the treatment of conditions that require deep delivery of active substances, in particular atrophic scars (including post-acne scars) and melasma. According to a systematic review, in the treatment of melasma the side of the face treated with LADD showed a statistically significant reduction in the MASI (Melasma Area and Severity Index) score compared with the control side. Similarly, in scar correction a significant improvement on the GAIS (Global Aesthetic Improvement Scale) was observed [19].

The mechanisms of action of sonophoresis and LADD differ fundamentally (see Fig. 3), which makes it possible to differentiate the choice of method depending on the clinical task: sonophoresis is appropriate for atraumatic delivery of active agents in active acne, whereas LADD is optimal for the combined management of patients with acne and post-acne scars.

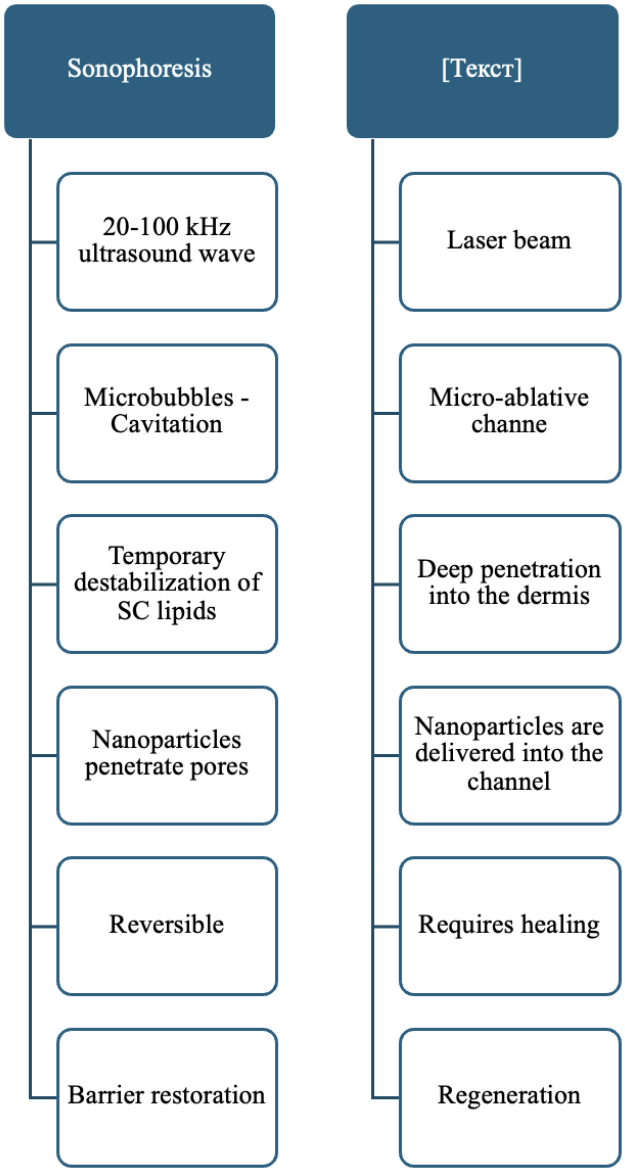

Fig. 3. Comparative mechanisms of hardware delivery of nanoparticles (compiled by the author based on [5])

The key empirical basis for the viability of the concept of the noninvasive needle is provided by the study [6], in which a direct comparison was performed between traditional intralesional injection of triamcinolone (TMC) and its noninvasive delivery using a photothermal method (LID). It was shown that the degree of reduction in the height of inflammatory elements was practically identical between the groups: 82–93% reduction in the injection group and 80–89% with the use of the noninvasive protocol. These data demonstrate that device-based delivery of TMC can provide a clinical effect equivalent to that of injection while eliminating the risks associated with disruption of skin integrity, incorrect selection of injection depth, and subsequent steroid-induced atrophy.

The optimal therapeutic protocol for managing patients with active acne, especially in the presence of sensitive skin (which corresponds to the profile of the author's patients), should simultaneously ensure atraumaticity, a pronounced anti-inflammatory effect, and stimulation of regenerative processes. Under these conditions, integration of three mutually complementary components appears most rational:

– a preparatory chemical peel with a low damaging potential;

– targeted delivery of a nanostructured serum;

– therapeutic exposure in the mode of LED photobiomodulation.

The initial phase is preparation (Non-aggressive peels). Within this phase, to enhance the efficacy of subsequent device-based delivery and light therapy, it is necessary to purposefully modify the properties of the stratum corneum. Superficial chemical peels represent the most convenient and controllable tool for this purpose. In the context of acne, salicylic acid (SA) is considered the most successful option. Its clinical relevance is determined by its high lipophilicity: unlike water-soluble AHA acids, SA readily diffuses into the lipid-rich environment of the hair follicle, providing a pronounced comedolytic and keratolytic effect directly in the area of the inflammatory focus. In patients with sensitive skin, which often accompanies acne, the use of acids with a relatively high molecular weight, characterized by slower and more controlled penetration, such as mandelic acid, is justified, as well as lactic acid, which additionally possesses a pronounced moisturizing effect.

The second phase, which includes delivery and therapy, follows (LED photobiomodulation). Light-emitting diode (LED) therapy is the central element of the protocol, functioning simultaneously as an independent therapeutic modality and as a factor that potentiates the penetration and biological activity of topical agents. The mechanism of action of LED in acne is bidirectional and is determined by the wavelength used:

– Blue light (~465 nm): exerts a direct bactericidal effect. The radiation energy is selectively absorbed by endogenous porphyrins (coproporphyrin III and protoporphyrin IX), which are synthesized in increased amounts by Cutibacterium acnes. Absorption of a light quantum initiates photochemical reactions with the generation of singlet oxygen and free radicals, which possess cytotoxic activity against C. acnes [21].

– Red light (~640 nm): is characterized by deeper penetration into the dermis and exerts predominantly anti-inflammatory and regenerative effects. It is absorbed by mitochondrial cytochrome c oxidase in fibroblasts and macrophages, leading to enhanced ATP synthesis and modification of intracellular signaling cascades. As a result, the production of proinflammatory cytokines decreases, while collagen synthesis is simultaneously activated, which promotes accelerated healing and a reduced risk of atrophic scar formation [21].

The clinical efficacy of the combined use of LED and topical preparations (including nanostructured gels that often contain photoacceptors or chromophores) has been convincingly confirmed. In a study [7] involving 15 patients with moderate to severe acne, a course of six procedures that included combined LED exposure in the 465–880 nm range and application of a photoacceptor gel provided statistically significant improvement in all key clinical parameters.

Not only pronounced visual changes were observed, but also objective shifts documented using 3D imaging, sebumetry, and corneometry. The combined protocol (LED + Gel) resulted in a 61,58% reduction in the number of papules and a 63,15% reduction in comedones, whereas on control skin areas the reduction was only 43,33% and 43,30%, respectively [7].

Fundamentally important is that this protocol demonstrated a statistically significant ($p < 0,05$) decrease in the secretory activity of the sebaceous glands (sebum level) with a simultaneous increase in the hydration of the stratum corneum. This indicates restoration and normalization of the skin barrier function, in contrast to traditional therapeutic regimens, which often lead to excessive overdrying [12]. Additionally, a significant reduction in the volume of atrophic scars was recorded, confirming the pronounced regenerative potential of the red spectrum of LED irradiation.

Detailed quantitative indicators of the efficacy of the described synergistic protocol are summarized in Table 2.

Table 2. Quantified efficacy of combined therapy (LED + photoacceptor gel) (N=15) (compiled by the author based on [7])

Clinical parameter	Assessment method	Time point	Result
Inflammatory lesions (papules)	Counting (split-face)	10 weeks	-61.58% (LED+gel) -43.33% (control)
Comedones	Counting (split-face)	10 weeks	-63.15% (LED+gel) -43.30% (control)
Erythema intensity	3D visualization	6 weeks after 6 sessions	Statistically significant reduction ($p < 0.05$)
Sebum level	Sebumetry	6 weeks after 6 sessions	Statistically significant reduction ($p < 0.05$)
Skin hydration	Corneometry	6 weeks after 6 sessions	Statistically significant increase ($p < 0.05$)
Volume of atrophic scars	3D visualization	6 weeks after 6 sessions	Statistically significant reduction ($p < 0.05$)

The shift of emphasis from invasive interventions to high-tech non-invasive protocols is based not only on clinical arguments, but also on pronounced market and behavioral trends on the part of consumers.

First, a rapid expansion of the non-invasive aesthetic medicine segment is being observed. According to industry analytics [22], the global aggregate market for the corresponding procedures was estimated at 21.01 billion US dollars in 2024, and by 2034 it is projected to increase to 41.55 billion, which corresponds to a compound annual growth rate (CAGR) of 7.0% (see Fig. 4). This dynamic is directly related both to the rapid implementation of technological innovations and to the transformation of the expectations and demands of the patients themselves.

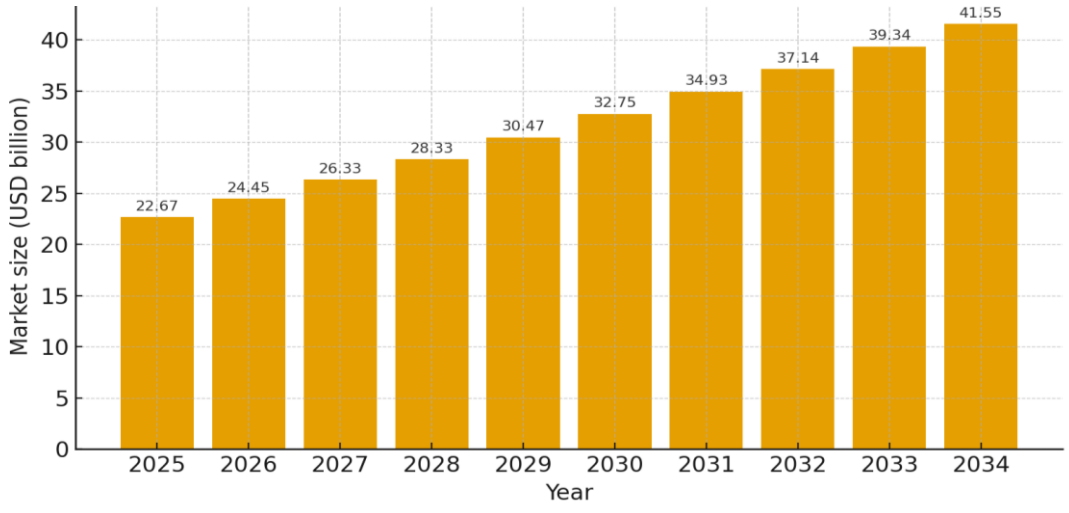

Fig. 4. Forecast of growth of the global market for non-invasive aesthetic procedures (2024-2034) (compiled by the author based on [22]).

Secondly, the analysis of consumer behavior presented by McKinsey [23] demonstrates a high level of adherence and satisfaction of patients with non-invasive techniques. The digital environment and social media have contributed to the normalization of aesthetic interventions, making them socially acceptable and accessible to a significantly broader audience. Patients deliberately prefer procedures with a minimal recovery period while maintaining high clinical effectiveness, which fully correlates with the logic of the protocols under consideration. Studies evaluating patient satisfaction in the treatment of acne with laser and light-based technologies consistently demonstrate a high level of approval of the obtained outcomes.

Despite the obvious clinical and market-related advantages, the large-scale implementation of protocols based on nanotechnologies encounters a number of substantial limitations. The key among them is the complexity of regulatory approval. Nanotechnology-based medical products (NHPs) pose a fundamentally new challenge for EU and US regulators [24]. The absence of unified, harmonized assessment standards and the insufficient maturity of approaches to the analysis of nanotoxicology, that is, the long-term interactions of nanostructures with biological systems, lead to the prolongation of registration procedures and substantially slow down the market introduction of a number of innovative nanostructured serums [24].

Additional limiting factors include the relatively high cost of high-tech device-based systems (laser complexes, LED platforms, ultrasound equipment), as well as the need for advanced training of specialists. The effectiveness of device-based techniques, especially LADD, is critically dependent on the proper adjustment of exposure parameters and strict adherence to the procedural protocol, which imposes increased requirements on the operator's level of qualification [19].

4. Conclusion

The conducted systematic analysis shows that traditional approaches to acne therapy, particularly invasive (intralesional injections) and systemic (isotretinoin) modalities, currently do not meet contemporary safety criteria. The risks associated with ILK, including cutaneous atrophy of unpredictable severity and duration, as well as the systemic toxicity of isotretinoin, create a pronounced demand for the search for and implementation of alternative therapeutic strategies.

The objective formulated in this study was fully achieved: the theoretical and clinical-analytical review performed made it possible to substantiate the synergistic protocol as a highly effective and at the same time safe alternative to existing methods.

It has been shown that the use of nanostructured serums makes it possible to overcome the key limitation of classical topical therapy – low compliance. Owing to the encapsulation of active substances (for example, liposomal tretinoin), not only an increase in therapeutic efficacy is achieved (approximately 1.5-fold; reduction of comedones up to 94.17%), but also a significant improvement in tolerability, manifested by a decrease in the severity of erythema and burning.

Device-based technologies in this context perform the function of a noninvasive needle, ensuring targeted delivery of these serums. Clinical direct-comparison data indicate that device-based delivery (LID) provides improvement in the range of 80–89%, which is comparable to the results of intralesional injections (82–93%), but is not accompanied by the risks associated with skin puncture.

The author's hypothesis was confirmed. The integration of nanotechnologies with device-based methods, in particular the synergistic protocol SA peeling + nano serum + LED photobiomodulation, constitutes an innovative therapeutic approach. Clinical studies of this synergy demonstrate not only a pronounced reduction of inflammatory lesions (a decrease in the number of papules by 61.58%), but also an objective improvement in the qualitative characteristics of the skin: reduced sebum production, increased hydration, and a decrease in the volume of atrophic scars.

Thus, the present work provides a theoretical and clinical basis for aestheticians, dermatologists, and cosmetologists that is necessary for the implementation in practice of comprehensive device-based protocols for acne treatment. These protocols make it possible to abandon invasive interventions in favor of safer, yet technologically advanced noninvasive solutions, which is particularly important for patients with sensitive skin who are focused on maximizing efficacy while minimizing risks.

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