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Section 1. Clinical Medicine

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CLINICAL AND PHYSIOLOGICAL DETERMINANTS OF RESTORATIVE DERMOPIGMENTATION: DERMAL RETENTION, AGE-RELATED VARIABLES, AND LONG-TERM PIGMENT STABILITY

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Abstract

Restorative dermopigmentation represents an evolving clinical direction within aesthetic and reconstructive skin procedures. The discipline addresses aesthetic and structural dermal deficits resulting from alopecia, hormonal transitions, post-traumatic tissue remodeling, and age-related pigment loss. Unlike conventional decorative micropigmentation, restorative protocols require a detailed understanding of the interaction between implanted pigment particles and dermal physiology.

This article examines the influence of dermal density, vascular reactivity, and environmental factors such as ultraviolet exposure and humidity on pigment integration and long-term chromatic stability. Observational analysis of clinical cases indicates that long-term retention is influenced by the balance between pigment particle aggregation, dermal encapsulation processes, and macrophage-mediated immune response.

The findings support a staged and adaptive implantation strategy aimed at improving morphological stability and chromatic predictability over extended time intervals. Restorative dermopigmentation therefore represents a hybrid discipline positioned between aesthetic micropigmentation and clinically informed dermal reconstruction.

Keywords: *dermopigmentation; permanent makeup; pigment retention; skin physiology; restorative aesthetics; dermal remodeling, dermatology*

1. Introduction

Permanent makeup has historically been associated with elective aesthetic enhancement, including eyebrow definition, eyeliner application, and lip color intensification. Over the past decade, dermopigmentation practice

has expanded beyond decorative aesthetics toward restorative applications designed to address structural changes in facial features.

Restorative dermopigmentation focuses on the visual reconstruction of facial balance in individuals affected by hair loss, age-related thinning of soft tissues, or pigment depletion. Clinical indications frequently include androgenetic alopecia, telogen effluvium, chemotherapy-related hair loss, and gradual loss of vermilion border definition.

The clinical complexity of restorative dermopigmentation arises from the biological variability of the recipient tissue. Unlike the relatively stable dermal structure typically encountered in younger cosmetic clients, restorative procedures are frequently performed on tissue characterized by altered collagen organization, reduced elasticity, and variable vascular response.

These biological variables influence pigment integration, healing dynamics, and long-term chromatic stability. As a result, successful restorative dermopigmentation requires procedural strategies informed by skin physiology rather than purely aesthetic technique.

2. Dermal Pathophysiology and Pigment Integration

Pigment implantation into the skin represents a biologically active event rather than a purely mechanical process. During dermopigmentation procedures, pigment particles are introduced into the papillary dermis at an approximate depth of 0.5–1.5 mm. This intervention initiates a localized inflammatory response that contributes to stabilization of the pigment within the dermal matrix.

Following implantation, immune cells such as macrophages and fibroblasts interact with the introduced pigment particles. Macrophages attempt to phagocytose foreign material, while fibroblasts participate in tissue remodeling and collagen synthesis during the healing process.

Long-term pigment stability appears to depend on several interrelated mechanisms:

Macrophage response

Macrophages interact with pigment particles during the early inflammatory phase. Larger pigment aggregates demonstrate lower probability of lymphatic clearance and therefore tend to remain within the dermal matrix.

Collagen encapsulation

During dermal healing, fibroblast activity leads to formation of a collagen network surrounding pigment deposits. This structural encapsulation contributes to long-term pigment stabilization.

Vascular influence

The vascular characteristics of the treated region may influence the perceived color of the implanted pigment. In areas with increased vascularity, such as the lips, hemoglobin-related optical signals may interact with pigment spectral reflectance and modify perceived undertones.

These physiological processes determine the long-term visual and structural stability of dermopigmentation outcomes.

3. Age-Related Dermal Remodeling

Age-related changes in dermal structure represent one of the most important variables affecting dermopigmentation outcomes. With increasing age, collagen organization gradually becomes less dense and more fragmented, while glycosaminoglycan concentration decreases.

Table 1.

Variable	Young Dermis (20–35 yrs)	Mature Dermis (55+ yrs)	Clinical Impact
Collagen density	High, organized	Fragmented, reduced	Increased probability of pigment diffusion
Transepidermal water loss (TEWL)	Stable	Elevated	Slower barrier recovery
Vascular stability	Robust	Capillary fragility	Higher risk of microbruising

These changes influence the physical properties of the dermis and therefore affect pigment distribution and retention.

Reduced dermal density and elasticity may increase the likelihood of pigment migration in mature tissue. For this reason, restorative procedures performed on mature skin often require modified procedural parameters.

Lower mechanical pressure, reduced pigment concentration, and gradual layering techniques may improve stability and minimize unintended pigment diffusion.

4. Materials and Methods

An observational review of restorative dermopigmentation procedures was conducted over an 18-month period. The monitored group included 45 individuals between the ages of 35 and 72 who underwent eyebrow reconstruction or lip margin definition procedures.

Clinical follow-up focused on three principal parameters:

- pigment retention stability
- chromatic evolution over time
- dermal healing response

The pigment retention coefficient was estimated using the following relation:

$$R = (D_{12} / D_1) \times 100\%$$

where

D_1 – optical density of the pigment approximately 30 days after the procedure

D_{12} – optical density observed after 12 months

Retention was evaluated using comparative photographic documentation and visual density assessment.

5. Environmental Factors

Environmental conditions can significantly influence dermopigmentation outcomes. Ultraviolet radiation may gradually affect pigment stability through photochemical degradation processes.

Organic pigments demonstrate increased susceptibility to photobleaching, while inorganic pigments such as iron oxides typically show greater stability but may exhibit subtle undertone shifts over time.

Humidity may also influence epidermal recovery during early healing phases. In regions where relative humidity frequently exceeds 70%, the stratum corneum may remain more hydrated, which may affect barrier restoration and healing dynamics.

Controlled post-procedural care and moisture management during the early recovery phase may therefore contribute to improved long-term pigment stability.

6. Discussion

Restorative dermopigmentation differs fundamentally from decorative cosmetic procedures because it aims to reconstruct anatomical balance rather than simply enhance existing features.

In cases of complete eyebrow loss, practitioners must recreate facial proportions and directional hair patterns without natural structural references. Achieving natural visual balance therefore requires an architectural approach to pigment placement and facial mapping.

Clinical observations indicate that staged implantation protocols frequently produce more stable outcomes than high-density single-session procedures. Gradual layering allows dermal tissue to recover between sessions and reduces mechanical trauma.

The commonly used six-week interval between sessions corresponds approximately to the dermal remodeling cycle and allows stabilization of pigment–macrophage interaction within healing tissue.

7. Conclusion

Restorative dermopigmentation represents a developing intersection between aesthetic micropigmentation and clinically informed skin treatment. Long-term pigment stability depends on a complex interaction between dermal structure, immune response, environmental exposure, and implantation technique.

Careful control of implantation depth, adaptation to age-related dermal changes, and awareness of climatic conditions may significantly improve the predictability and safety of restorative procedures.

Further research focusing on pigment composition, dermal biocompatibility, and long-term observational data will help refine dermopigmentation protocols and improve clinical predictability.

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COMPARATIVE ANALYSIS OF MATERNAL AND PERINATAL OUTCOMES IN PREGNANT WOMEN WITH DELTA AND OMICRON SARS-COV-2 VARIANTS

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Abstract

COVID-19 remains a significant global health concern, particularly in pregnant women, who are at increased risk of adverse outcomes. This retrospective single-center cohort study included 9,288 pregnant women with confirmed SARS-CoV-2 infection and compared clinical characteristics and maternal–perinatal outcomes between Delta (n=3,200) and Omicron (n=6,088) variants. The Delta variant was associated with a significantly higher incidence of complications, including uteroplacental insufficiency, acute respiratory distress syndrome, multiple organ dysfunction, preterm birth, and maternal mortality. It also required more frequent intensive care, mechanical ventilation, and cesarean delivery. In contrast, the Omicron variant demonstrated a milder clinical course with significantly higher 30-day survival and lower perinatal mortality. These findings indicate substantial differences in disease severity and outcomes between SARS-CoV-2 variants in pregnancy.

Keywords: *pregnancy, COVID-19, SARS-CoV-2 variants, Delta variant, Omicron variant, perinatal outcomes*

Introduction

COVID-19, caused by the SARS-CoV-2 virus, was declared a global pandemic in March 2020, resulting in more than 500 million infections and over 6 million deaths worldwide (World Health Organization. 2020). The pandemic substantially disrupted healthcare systems, limiting access to medical services, which particularly affected pregnant women who are considered a high-risk group due to potential complications for both mother and fetus (Rasmussen-Torvik L. J., 2022). Clinical management protocols for pregnancy were consequently modified, including restrictions on invasive interventions (Carbone L., Raffone A., Sarno L., Travaglino A., et al., 2022). Although evidence on vertical transmission remains limited, COVID-19 has been associated with an increased risk of adverse outcomes, including preterm birth and neonatal intensive care unit admission (Ferrazzi E., Frigerio L., Savasi V., Vergani P., et al., 2020; Cennamo M., La Civita E., Sarno L., Carbone G., et al., 2023). The increased

vulnerability of pregnant women is largely attributed to physiological changes that may predispose them to a more severe disease course (Vasilescu D. I., Rosoga A. M., Vasilescu S., Dragomir I., et al., 2023; Dobrokhotova Yu.E., Gumenyuk L. N., Puchkina G. A., Mikhailichenko V.Yu., 2022).

The emergence of the Omicron variant in 2021 was associated with a reduction in disease severity compared with the Delta variant, which had been linked to more adverse pregnancy outcomes (Dashraath P., Wong J. L.J., Lim M. X.K., Lim L. M., et al., 2020).

Materials and Methods

This retrospective single-center study included 9,288 pregnant women with confirmed COVID-19 admitted to the maternity complex of the Republican Specialized Hospital "Zangiota-1" (Tashkent, Uzbekistan) between December 2020 and December 2023. Diagnosis was established using antigen rapid diagnostic testing and PCR when indicated. Patients were divided into two groups: Delta variant (n=3,200) and Omicron variant (n=6,088). Statistical analysis was performed using SPSS v24. Continuous variables were compared using Student's t-test, categorical variables using Pearson's χ^2 test, and survival was assessed by the Kaplan–Meier method. Statistical significance was defined as $p < 0.05$.

Results

A total of 9,288 pregnant women with confirmed COVID-19 were included in the analysis. The mean maternal age was 31.5± ± 4.9 years, with the highest proportion observed in the 25–29-year age group (47.7%). The mean time from symptom onset to hospital admission was 11.6±3.8 days, with 41.6% of patients presenting within the first 7 days and 58.4% after 7 days.

At initial assessment, most patients demonstrated moderate disease severity (52%), while mild and severe forms accounted for 30% and 17%, respectively. Critical illness was relatively rare (2%). Lung involvement ≤50% was observed in 65.9% of cases, whereas 34.1% of patients had more extensive pulmonary damage requiring intensive management. The majority of women were multiparous (93%), and most pregnancies were full-term (93.8%).

Table 1. *Frequency of complications and delivery methods*

Parameter	Delta variant (n=3,200)	Omicron variant (n=6,088)	p-value
Uteroplacental insufficiency	512(16.0%)	670(11.0%)	< 0.001
ICU admission	682(21.3%)	774(12.7%)	< 0.001
Mechanical ventilation	314(9.8%)	267(4.4%)	< 0.001
Pregnancy completion	495(15.5%)	597(9.8%)	< 0.001
Term delivery	271(54.7%)	414(69.3%)	< 0.001
Preterm delivery	215(43.4%)	176(29.5%)	< 0.001
Miscarriage	7(1.8%)	7(1.2%)	–
Total deliveries	486(15.2%)	590(9.7%)	< 0.001
Spontaneous delivery	67(13.8%)	165(28.0%)	< 0.001
Labor induction	64(13.2%)	63(10.7%)	0.244
Cesarean section	355(73.0%)	362(61.4%)	< 0.001

Comparative analysis between SARS-CoV-2 variants (table 1) revealed significant differences in demographic and clinical characteristics. The mean age of women in the Delta group was lower compared to the Omicron group (30.7±6.1 vs 31.9±4.2 years, p < < 0.001). The Delta variant was more prevalent among younger women aged 18– – 24 years (31.2% vs 28.0%, p = 0.001).

The interval between symptom onset and hospital admission was longer in the Delta group (12.6 ± 4.2 vs 11.1 ± 3.7 days, p < 0.001), indicating delayed presentation. Moreover, more severe pulmonary involve-

ment was observed in patients with Delta infection, with a higher proportion of lung damage >50% compared to the Omicron group (40.0% vs 31.0%, p < 0.001).

Maternal complications were significantly more frequent in the Delta group. Uteroplacental insufficiency occurred in 16.0% of cases compared to 11.0% in the Omicron group (p < 0.001). The need for intensive care unit (ICU) admission was markedly higher in patients with Delta infection (21.3% vs 12.7%, p < 0.001). Similarly, the requirement for invasive mechanical ventilation was significantly increased (9.8% vs 4.4%, p < 0.001).

Pregnancy outcomes also differed substantially between groups. Completion of pregnancy during infection occurred more frequently in the Delta group (15.5% vs 9.8%, p < 0.001). Among those who delivered, full-term births were significantly less common in the Delta group (54.7% vs 69.3%, p < 0.001), whereas preterm delivery was more frequent (43.4% vs 29.5%, p < 0.001).

Mode of delivery analysis demonstrated a significantly higher rate of cesarean section in the Delta group (73.0% vs 61.4%, p < < 0.001), while spontaneous vaginal delivery was more frequent in the Omicron group (28.0% vs 13.8%, p < 0.001). No significant differences were observed in labor induction rates (p = 0.244).

Relative risk analysis confirmed that Delta variant infection was associated with significantly increased risks of major complications, including uteroplacental insufficiency (RR=1.45), ARDS (RR=2.14), multiple organ dysfunction (RR=2.17), preterm birth (RR=2.32), and maternal mortality (RR=30.92), all p < 0.001. The risks of ICU admission, mechanical ventilation, and cesarean delivery were also significantly elevated.

Maternal mortality was markedly higher in the Delta group (2.0% vs 0.1%, p < 0.001). Survival analysis demonstrated significantly improved 30-day survival in the Omicron group (99.7% vs 95.6%), including among ICU patients (98.2% vs 88.2%) and women with uteroplacental insufficiency (98.9% vs 86.1%).

Neonatal outcomes further confirmed the more severe impact of the Delta variant. Perinatal mortality was significantly higher in the Delta group (6.3% vs 3.0%, p=0.014). Additionally, antenatal fetal death was more frequent (3.4% vs 1.8%). Mean birth weight was lower in neonates born to mothers with Delta infection (3545 ± 625 g vs 3672 ± ± 594 g, p < 0.001), and large-for-gestational-age infants were more common in the Omicron group (32.2% vs 26.5%, p=0.014).

Discussion

When analyzing clinical factors influencing pregnancy outcomes in women with COVID-19, particular attention has been paid to risk determinants such as comorbidities and maternal health status, which may aggravate disease severity and increase complication rates (Huntley B. J.F., Huntley E. S., Di Mascio D., Chen T., et al., 2020). Previous studies have emphasized the importance of tailored management strategies for pregnant women with COVID-19 to minimize complications and improve outcomes (Di Mascio D., Khalil A., Saccone G., Rizzo G., et al., 2020). Consistent with published data, the Delta variant has been linked to higher ICU admission rates, preterm birth, and fetal growth restriction, whereas the Omicron variant is associated with reduced severity, potentially due to increased population immunity (Ellington S., Strid P., Tong V. T., Woodworth K., et al., 2020). Despite the relatively milder course of Omicron infection, continuous monitoring and appropriate management during pregnancy remain essential, particularly in high-risk and unvaccinated populations (Allotey J., Stallings E., Bonet M., Yap M., et al., 2020).

Conclusion

The Delta variant of SARS-CoV-2 is associated with a significantly more severe clinical course in pregnant women, characterized by higher rates of maternal complications, preterm birth, and increased need for intensive care, including mechanical ventilation and cesarean delivery. In contrast, the Omicron variant demonstrates a comparatively milder course with improved maternal and perinatal outcomes. These findings highlight the importance of variant-specific risk assessment and individualized management strategies to optimize outcomes in pregnant women with COVID-19.

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Section 2. Life Sciences

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PATIENT ROUTING SYSTEM AS A TOOL FOR MANAGING HOSPITAL RESILIENCE DURING THE COVID-19 PANDEMIC

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Abstract

During the COVID-19 pandemic, patient routing became a key mechanism for maintaining hospital resilience. This study evaluated a multi-level dynamic routing model implemented at the Republican Specialized Hospital "Zangiota No. 1" for managing hospitalization flows. A retrospective–prospective analysis of admission and discharge data (2020–2025) assessed disease severity distribution, ICU transfer rates, and bed management efficiency. Formalized admission criteria, multi-stage triage, and regular clinical reassessment reduced inappropriate hospitalizations, optimized resource use, and improved timely access to intensive care. Predictive flow management helped prevent critical overload during peak epidemiological periods. The model demonstrated high adaptability, controllability, and scalability, supporting its use as an effective crisis-management tool and a foundation for sustainable multidisciplinary hospital operations.

Keywords: *patient routing, hospital resilience, flow management, COVID-19, organizational management, crisis response*

Introduction

The COVID-19 pandemic exposed structural limitations in healthcare systems and emphasized the need for adaptive organizational mechanisms to maintain hospital resilience under surge conditions (Zhong L., Pei S., et al., 2024). Patient routing became a key crisis-management tool, enabling optimization of hospitalization flows, resource redistribution, and reduction of institutional overload, replacing traditional linear referral models with flexible, multi-level flow management systems (Litvak E., Keshavjee S., et al., 2021). Evidence indicates that effective routing improves resilience through better coordination, optimized admissions, and more efficient resource use (Adelaja I., Sayma M., et al., 2020). Digital routing tools and flexible planning approaches further supported rapid decision-making during epidemiological surges (Carrié A., Penmasta V., et al., 2024). However, large-scale

implementation remains limited by infrastructural disparities, variable digitalization, and inconsistent triage standards, highlighting the need to integrate routing systems into unified organizational management frameworks (Knight E., 2021).

Materials and Methods

This retrospective–prospective analytical study at RSH "Zangiota No. 1" (Tashkent, Uzbekistan) evaluated the patient routing system implemented during the COVID-19 pandemic (2020–2025). The analysis included admission and discharge data, bed capacity dynamics, disease severity, hospitalization flows, and ICU transfer rates, assessed annually to identify epidemiological peaks and workload. The methodology combined organizational and clinical-statistical analysis with comparative evaluation of routing effectiveness, including admission criteria, multi-stage triage, intra-hospital redistribution, and de-escalation mechanisms. Key outcomes were bed management efficiency, timeliness of ICU transfer, and admission-to-discharge balance as indicators of institutional stability.

Results

At the RSH "Zangiota-1," patient routing was organized as a continuous and controlled process covering pre-hospital triage, admission, intra-hospital distribution, and subsequent de-escalation of care, consistent with contemporary hospital flow management concepts. A key managerial decision was strengthening the pre-hospital stage as a filtering mechanism to reduce inappropriate admissions and prevent hospital overload. Hospitalization was based on clearly defined organizational and clinical criteria considering disease severity, required level of care, and treatment priority. These criteria enabled rational patient routing, reduced pressure on the admission department and ICU, and improved bed management efficiency during peak epidemiological periods (Table 1).

Table 1. *Organizational Criteria for Patient Admission at the RSH"Zangiota-1" During the Pandemic*

Admission criterion	Severity level	Admission profile	Priority
Confirmed COVID-19-associated pneumonia without respiratory failure	Moderate	Infectious (therapeutic) ward	Planned
Pneumonia with progressive hypoxemia requiring oxygen support	Severe	Therapy unit with possible ICU transfer	High
Acute respiratory failure with hemodynamic instability	Critical	ICU	Emergency
Pneumonia in patients with impaired immune status (oncologic/hematologic disease, immunosuppression, HIV, etc.)	Moderate	Therapy / ICU	High
Pneumonia associated with hematologic pathology	Severe	Therapy with enhanced monitoring / ICU	High
Pregnant women with COVID-19-associated pneumonia	Moderate	Maternity complex ("Zangiota-1")	High
Acute kidney injury or decompensated CKD requiring renal replacement therapy	Severe	Hemodialysis unit / ICU	Emergency
Patients requiring emergency surgery with concurrent COVID-19	Severe / Critical	Surgical unit with ICU support	Emergency
Combined infectious and somatic pathology with high risk of deterioration	Moderate	Specialized ward with possible ICU transfer	High

Unlike traditional inpatient models, intra-hospital routing at "Zangiota-1" was dynamic, with patients managed as a continuously reassessed flow according to clinical evolution and current bed occupancy. The transition toward a 1,000-bed multidisciplinary republican center required integrated evaluation of manageability, development stages, and potential risks. Key challenges included staffing shortages, workforce burnout, dependence on stable infrastructure and resource supply, epidemiological uncertainty, and increased logistical complexity. However, centralized governance, modular bed structure, resource reserve systems, and prior crisis-management experience allowed these risks to be considered controllable. The transformation project was designed as a phased process, beginning with deployment of core specialized departments and workforce stabilization (Table 2).

Table 2. *Key Transformation Risks and Mitigation Strategies*

Risk group	Risk description	Mitigation mechanism
Human resources	Staff shortage, professional burnout	Rotation, training, staff reserve
Resource-related	Dependence on oxygen, energy, and medications	Backup capacity, centralized reserves
Epidemiological	Re-emergence of infectious threats	Modular re-profiling, dedicated infection units
Managerial	Scaling up to 1,000 beds	Centralized governance, digital monitoring

The mid-term phase is focused on expansion of high-technology services, development of dialysis and intensive care capacity, and implementation of digital tools for monitoring bed utilization and resource allocation.

Table 3. *Expected Social and Medical Outcomes*

Domain	Expected effect
Access to care	Reduction in inter-hospital transfers
Clinical outcomes	Decreased mortality and disability
Public health	Improved quality and continuity of care
Healthcare system	Development of a sustainable response model

The social and medical impact of the transformation is expected to include improved access to specialized care, reduced mortality and disability, fewer inter-hospital transfers, and strengthening of public health outcomes (Table 3).

Discussion

The data obtained confirm that patient routing systems and predictive capacity management tools play a central role in maintaining hospital resilience during epidemiological crises (Parker F., Ganjkhanloo F., et al., 2024). International experience demonstrates that mixed-integer linear programming approaches improve bed allocation and patient flow optimization, reducing the need for reserve capacity and enhancing resource efficiency (Karakra A., Lamine E., et al., 2020). Decision-support dashboards integrating real-time data with predictive analytics enable rapid managerial adjustments, increase process transparency, and support timely resource redistribution without compromising quality of care (Shi P., 2022). Further development is associated with digital twin technologies that allow real-time monitoring of patient pathways and departmental workload, strengthening operational stability under uncertainty (Parker F., Mart'inez D. A., et al., 2024). Hybrid simulation models for forecasting COVID-19 cases and optimizing bed capacity have shown significant potential in reducing mortality and preventing hospital overload (Lu Y., Guan Y., et al., 2021).

Conclusion

Implementation of a multi-level dynamic patient routing system at the Republican Specialized Hospital "Zangiota No. 1" demonstrated high organizational effectiveness during the COVID-19 pandemic. Formalized admission criteria strengthened pre-hospital triage, multi-stage sorting, and regular clinical reassessment improved bed utilization, reduced ICU overload, and minimized delays in specialized care. A systems-based approach to hospitalization flow management proved essential for maintaining hospital resilience during peak epidemiological periods.

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DISCOVERY OF SMALL MOLECULE INHIBITORS OF PCSK9 USING VIRTUAL SCREENING AS POTENTIAL THERAPEUTICS FOR ATHEROSCLEROSIS

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Abstract

High LDL cholesterol can cause heart disease. Current treatments like statins are not always effective, so new therapies are needed. PCSK9 is a protein that reduces the number of LDL receptors in the liver, which keeps cholesterol in the blood, making it a strong target for new drugs. Blocking PCSK9 with small molecules could be a better alternative to current treatments. To find potential inhibitors, I first analyzed the PCSK9 protein to locate possible binding sites using computational methods, which revealed multiple sites that small molecules could target. Then, I created two pharmacophore maps and screened two chemical libraries to find molecules that fit the key interactions. I used molecular docking simulations to estimate how strongly these molecules bind to PCSK9, identifying several with strong predicted binding. Using SwissADME to check drug likeness and absorption properties, we narrowed down the candidates to seven molecules suitable for oral use. Finally, predicted toxicity was analyzed which helped identify the safest and most effective compounds. After comparing binding strength, drug likeness, and toxicity, Z73447142 and Z52103291 are the two most promising drug candidates for PCSK9. These molecules could be further tested using biophysical binding assays and cell-based experiments to confirm their effects, with the goal of eventually developing new oral treatments to lower cholesterol and reduce cardiovascular risk.

Keywords: *PCSK9, cholesterol, virtual screening, molecular docking, drug discovery*

Introduction

Cholesterol is a type of fat that your body needs to build cells and make hormones, but having too much in your blood can be bad and lead to cardiovascular disease (Cui et al., 2025; Guo et al., 2024). It travels through the blood inside particles called lipoproteins. Low density lipoprotein (LDL) carries cholesterol to the body's tissues while high density lipoprotein (HDL) takes extra cholesterol back to the liver to get rid of it (Cui et al., 2025; Guo et al., 2024). The liver controls cholesterol by making it, absorbing it from food, and removing LDL through LDL receptors (Cui et al., 2025; Guo et al., 2024). If this balance is disrupted, LDL can build up in artery walls and cause atherosclerosis, which is when arteries get clogged and can lead to

heart attacks or strokes. Understanding these processes is important before learning about PCSK9 because this protein affects how the liver handles LDL.

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) is a protein made mostly in the liver that controls cholesterol levels by deciding how many LDL receptors are on liver cells (Ajoolabady et al., 2025; Blanchard et al., 2019). It sticks to LDL receptors and makes the liver break them down instead of recycling them to the surface to catch more LDL (Ajoolabady et al., 2025; Blanchard et al., 2019). So when there's too much PCSK9, there aren't enough receptors, and LDL cholesterol stays in the blood. If there's less PCSK9, more LDL gets cleared out (Ajoolabady et al., 2025; Blanchard et al., 2019). Some research also suggests that PCSK9 might influence other parts of metabolism, like blood sugar and inflammation, which could also affect heart health (Ajoolabady et al., 2025). Because of all this, PCSK9 plays a critical role in cholesterol control, and that's why scientists are focusing on it when making new cholesterol lowering drugs.

When PCSK9 is hyperactive, LDL cholesterol levels increase, which raises the risk of cardiovascular events like heart attacks and strokes (Bodapati et al., 2023; Katzmann & Laufs, 2024; Jeswani et al., 2024). Drugs that block PCSK9, like monoclonal antibodies and newer therapeutic approaches, can lower LDL cholesterol and reduce cardiovascular risk significantly (Bodapati et al., 2023; Katzmann & Laufs, 2024; Jeswani et al., 2024; Coppinger et al., 2022). Studies have shown that PCSK9 inhibitors can reduce LDL cholesterol by approximately 50–60% more than what is achieved with statins, which are commonly prescribed drugs that are used to lower LDL cholesterol and triglycerides, which is known to reduce heart attacks and strokes (Bodapati et al., 2023; Katzmann & Laufs, 2024; Jeswani et al., 2024; Coppinger et al., 2022; Chen et al., 2019; Monami et al., 2019). For example, monoclonal antibody drugs like Evolocumab and Alirocumab, which were approved in 2015, were tested in large human outcome trials and showed significant reductions in LDL cholesterol and major cardiovascular events in high risk patients who were already using statin therapy (Rajtar-Salwa et al., 2024). These drugs have been effective in a wide range of patients, including ones who continue to have high LDL levels despite statin use (Bodapati et al., 2023; Katzmann & Laufs, 2024; Jeswani et al., 2024; Coppinger et al., 2022; Chen et al., 2019; Monami et al., 2019). Researchers are also investigating whether PCSK9 inhibitors may benefit patients with diabetes or other metabolic conditions, since PCSK9 appears to influence processes beyond cholesterol metabolism (Monami et al., 2019; Ruhela et al., 2025). Overall, blocking PCSK9 has become one of the most effective strategies for lowering LDL cholesterol and preventing serious cardiovascular disease (Bodapati et al., 2023; Katzmann & Laufs, 2024; Jeswani et al., 2024; Coppinger et al., 2022; Ruhela et al., 2025).

Currently, the main way doctors lower LDL cholesterol is still with statins, which work by reducing how much cholesterol the liver makes. Statins are effective for a lot of people, but there are still patients who either don't reach their LDL goals or can't tolerate higher doses because of side effects like muscle pain (Santulli et al., 2025; Li et al., 2025). Because of this, other drugs such as ezetimibe are sometimes added, which lowers cholesterol absorption in the intestine and gives an extra drop in LDL when statins don't work good enough on their own (Santulli et al., 2025; Liu et al., 2024). Recently, PCSK9 inhibitors have become a major option for patients at high cardiovascular risk, especially those with very high LDL or heart disease (Kao et al., 2025; Garwood et al., 2025). These therapies can lower LDL much more than the traditional treatments, which is why guidelines are starting to recommend them earlier for select high risk patients (Li et al., 2025; Garwood et al., 2025; Nicholls & Nelson, 2025). Even with all these options, managing cholesterol can still be difficult, and many patients need a combination of treatments to successfully get their LDL to safe levels.

PCSK9 is influenced a lot by genetics, which is very important in people with hypercholesterolemia (FH). FH is usually caused by mutations that affect how LDL receptors work, and PCSK9 mutations can make the condition even worse by increasing LDL levels even more (Grejtakova et al., 2025; Kuang et al., 2025). Some genetic variants cause PCSK9 to be overactive, which leads

to very high cholesterol starting at a young age, which increases the risk of early heart disease (Grejtakova et al., 2025; Huh & Kim, 2025). People with a loss of function PCSK9 mutations tend to have much lower LDL levels and a lower risk of cardiovascular events, which helped inspire the development of PCSK9 targeted drugs (Kuang et al., 2025; Huh & Kim, 2025). Because FH is inherited, understanding the genetic role of PCSK9 is important for more than just treatment, but also for screening family members who may be at risk (Grejtakova et al., 2025; Maştaleru et al., 2025). This genetic connection explains why PCSK9 inhibitors work even better in FH patients who do not respond enough to statins alone.

While most PCSK9 inhibitors that are used today are injectable antibodies, researchers are now making small molecule and oral PCSK9 inhibitors, which could make the treatment process easier for patients. The new drugs will block PCSK9 inside cells or interfere with how it is made or functions, instead of neutralizing it in the bloodstream (Ferri & Marodin, 2024; Ho et al., 2025). Early studies show that some of these small molecule approaches can significantly lower LDL cholesterol, although a lot are still in clinical trials and not available globally (Ferri & Marodin, 2024; Ho et al., 2025). An advantage of small molecule inhibitors is that they could be taken as pills, which might improve patient compliance compared to injections (Farhan et al., 2025). However, researchers are still working through challenges like making sure these drugs are specific, safe, and effective in the long term (Ferri & Marodin, 2024; Abdulla et al., 2024). Even so, this area is moving at a fast pace, and if it works, small molecule PCSK9 inhibitors could become a big part of future cholesterol treatment alongside existing therapies (Farhan et al., 2025; Abdulla et al., 2024).

Materials and methods

Analysis of binding sites

Geometric method

First I went to the protein plus website (https://proteins.plus/), I entered the PDB code 6U26, I clicked go, and then I clicked DoGSiteScorer twice, and then I kept all of the settings unchanged and clicked calculate.

PrankWeb

First I went to the PrankWeb website (https://prankweb.cz/). I entered the PDB code 6U26, and then clicked submit.

Identifying Small Molecules

Pharmacophore Map A Using MolPort

First I went to the Pharmit website (https://pharmit.csb.pitt.edu/) and entered the PDB code 6U26 in the "start from PDB" box, and left everything else unchanged and pressed submit. I went into the "Visualization" settings and changed ligand to none, kept results as stick, and changed receptor to none. I put the receptor surface opacity at the minimum and changed the background color to black, which did not have an effect on the results; it was solely for preference. In the Pharmacophore box, I turned on the HydrogenDonors, the first HydrogenAcceptor, and the first Hydrophobic and turned everything else off. I then clicked "Search MolPort" at the top.

Pharmacophore Map A Using Enamine

To use the Enamine library with Map A, I followed all of the steps as in 2.2.1, but instead of clicking "Search MolPort", I clicked the downwards arrow, and selected "Enamine" and then clicked "Search Enamine".

Pharmacophore Map B Using MolPort

Map B has all of the steps as 2.2.1 except for what is turned on and off in the "Pharmacophore" section. For Map B, the HydrogenDonors, the first HydrogenAcceptor, the first Hydrophobic, and the fourth Aromatic were turned on and everything else was off. I clicked "Search MolPort"

Pharmacophore Map B Using Enamine

To use the Enamine library with Map B, I followed the same steps as in 2.2.1 except I clicked the downwards arrow next to "Search MolPort" and selected Enamine in the dropdown menu. Then, I clicked "Search Enamine".

SwissDock Molecular Docking Methods

First I went to the SwissDock website (https://www.swissdock.ch/) to test how the different molecules bind to the PCSK9 protein. I used molecules from the Enamine (https://enaminestore.com/) and Molport (https://www.molport.com/shop/index) websites, and the SMILES codes were also copied from these websites. Once the SMILES was put into the SwissDock website and the green checkmark was showing, then

I clicked "Prepare Ligand". After preparing the ligand, the target protein was set up using the Protein Data Bank (PDB) code 6U26. Only chain A of the protein was used, and all heteroatoms were removed. I selected "Prepare Target" and it was confirmed once the green checkmark appeared. Next, I defined the search space. The search box center was set to 31, 24, 48, and the search box size was set to 31, 34, 47. These values were kept the same for all of the compounds. After setting the search space I selected "Check Parameters". Finally, the docking simulation was started by clicking "Start Docking".

Evaluation of Drug Likeness Using SwissADME

First I went to the SwissADME website (https://www.swissadme.ch/) and I inserted the SMILES of my top 7 compounds from the previous experiment. Once all the SMILES were in, I clicked run. For each compound, I recorded the molecular weight, number of hydrogen bond donors, number of hydrogen bond acceptors, and the consensus Log P. In addition to those, ESOL solubility and predicted gastrointestinal (GI) absorption were collected.

Identifying Drug Toxicity Using Protox 3

First I went to the Protox 3 website (https://tox.charite.de/protox3/index.php?site=home) and I went to Tox Prediction at the top and clicked it. Then, I put in the SMILES code for the compound I was using and clicked the blue smiles button afterwards. Then I went down to the bottom and clicked the all button to select all pathways. Finally, I clicked Start Tox-Prediction and recorded my results.

Results and discussion

Identifying Potential Binding Sites

Protein Plus/DoGSiteScorer

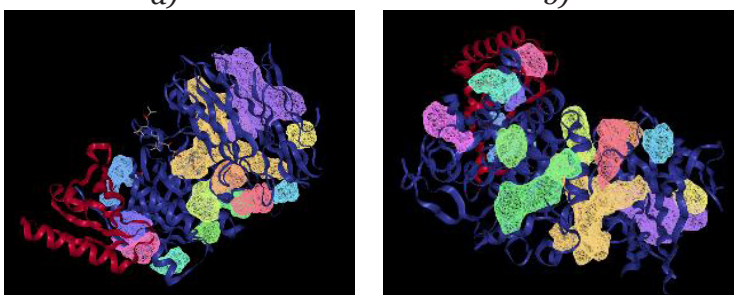
The goal of this experiment was to identify potential binding sites on PCSK9 that could be targeted by small molecule inhibitors. Using DoGSiteScorer, a lot of surface pockets were discovered on the PCSK9 protein (Figure 1). Out of all of them, pockets P_0, P_1, and P_2 showed the most promising characteristics based on size and drug score (Table 1). Pocked P_1 had the highest drug score, .83, and a large pocket volume, 944.38 Å^3, showing that it is a strong option for binding small molecules. Pocket P_0 had the largest volume overall, 1340.9 Å^3, with a high drug score of 0.80, while P_2 also showed a good drug score of 0.90 but had a smaller volume. Smaller pockets like P_10 – P_13 had low drug scores which indicates that they are worse than the others for small molecule binding. Overall, DoGSiteScorer identified multiple binding sites, with P_1 as the best candidate due to its balance of size, surface area, and drug score.

Table 1. *Results from DoGSiteScorer showing the Name, Pocket Volume, Surface Area, Drug Score, and corresponding color in figure 1*

Name	Color	Pocket Volume (Å^3)	Surface Area (Å^2)	Drug Score
P_0	Khaki	1340.9	1533.29	0.8
P_1	Light Purple	944.38	1010.19	0.83
P_10	Lime Green	131.82	298.94	0.3
P_11	Pink	127.54	171.07	0.28
P_12	Cyan	111.72	183.33	0.25
P_13	Yellow	107.87	204.79	0.21
P_2	Light Green	437.89	684.43	0.8
P_3	Red	284.17	612.05	0.49
P_4	Dark Cyan	217.87	233.32	0.48
P_5	Bright Yellow	215.05	414.08	0.49
P_6	Teal	181.6	279.15	0.43
P_7	Orange	146.53	305.24	0.38

Figure 1. *Images from Do G Site Scorer showing potential binding sites in PCSK9 using the geometric method. The blue ribbon represents the structure of the protein and the colored spheres represent the binding sites*

a) *b)*



PrankWeb

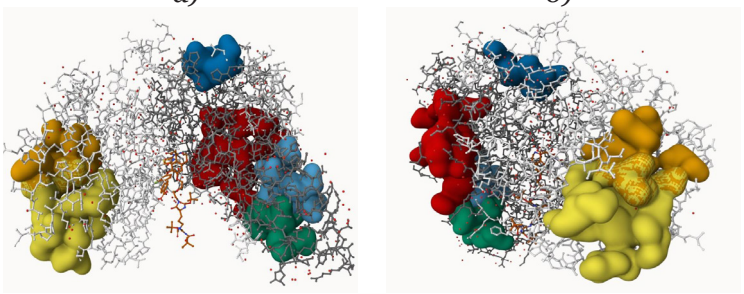
PrankWeb was used to identify and rank potential binding pockets on the PCSK9 protein and to look at the amino acids in each site (Figure 2, Table 2). The highest ranked pocket that PrankWeb identified was pocket 1, which included Gln226, Trp42, and Leu318 residues, all located in the same binding site. The other pockets were ranked lower and were in different areas of the protein's surface. For example, Pocket 2 included Val614, His561, and Gly560, while Pocket 3 included Glu582, Pro609, and Gln557. Other lower ranked pockets involved residues like Pro179, Leu82, Asn177, and Gly46. Overall, PrankWeb found multiple potential binding pockets on PCSK9, with Pocket 1 as the highest ranked.

Table 2. *Results from PrankWeb showing potential pockets in PCSK9 using the machine learning method including the ranking, the score, and the number of residues*

Color	Pocket Ranking	Pocket Score	No. of Residues
Red	1	13.67	19
Yellow	2	7.20	25
Orange	3	3.84	13
Cyan	4	3.10	10
Light Green	5	2.18	8
Blue	6	1.36	8

Figure 2. *Images from PrankWeb showing binding spots on PCSK9. The colored shapes represent the binding sites and the white and gray residues represent the structure of the protein*

a) *b)*



Pharmacophore Based Virtual Screening of PCSK9

Two pharmacophore maps were generated from the predicted PCSK9 binding site and used to identify small molecules with similar interactions (Figure 3). A pharmacophore represents a three dimensional map of interactions that are required for a molecule to bind to a protein, including the type of key interactions such as hydrogen bonding and

hydrophobic contacts. Each pharmacophore map was screened independently against two compound libraries, MolPort and Enamine, using the Pharmit server. These virtual screens evaluated millions of candidate molecules per library and ranked them based on how well they matched the pharmacophore features, measured by RMSD, which measures how closely a compound aligns with the pharmacophore in a three dimensional space. From these screening results, the highest ranking compounds from all four searches (Map A-MolPort, Map A-Enamine, Map B-MolPort, Map B-Enamine) were selected with a total of 17 small molecules. These compounds represent the best overall matches across both pharmacophore maps and both libraries. The final set of 17 compounds included molecules identified using both Map A and Map B, as well as compounds from both MolPort and Enamine. Of the 17 selected compounds, 15 were from the Enamine library while the remaining two were from MolPort. As shown in Table 3, the RMSD values of the selected compounds ranged from 0.019 to 0.034 Å, which means that there is excellent alignment between the compounds and their pharmacophore features. The lowest RMSD value, 0.019 Å, was from MolPort-051–895–715, which was found using pharmacophore map B, which suggests a very strong match.

Figure 3. *Pharmacophore maps A and B. The white spheres represent hydrogen donors, the pink sphere represents aromatic, the green spheres represent hydrophobic, and the orange spheres represent hydrogen acceptors*

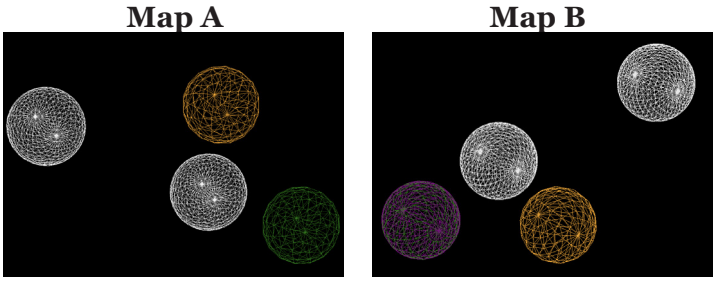
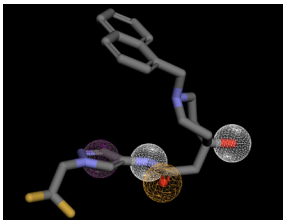
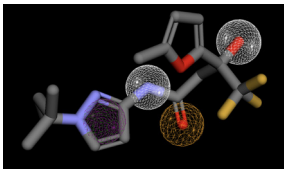
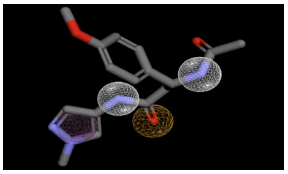
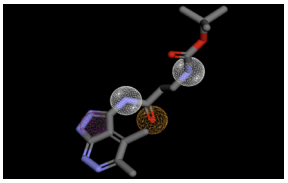
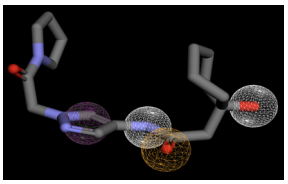
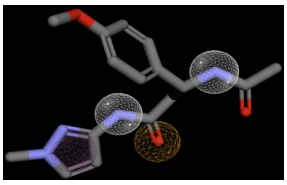
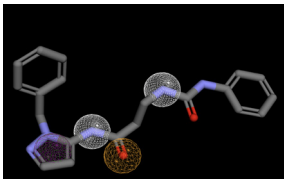
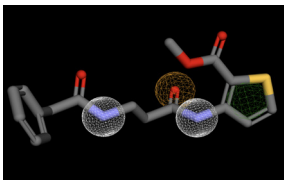
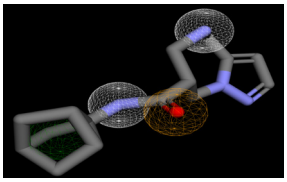
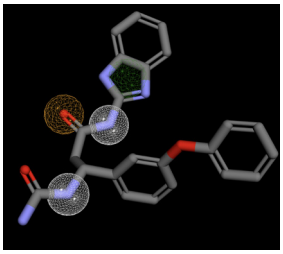
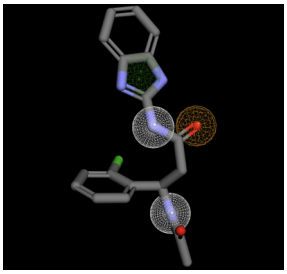
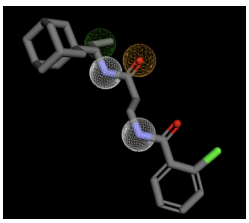
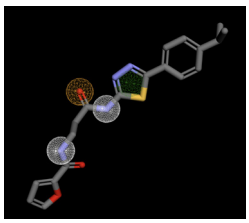
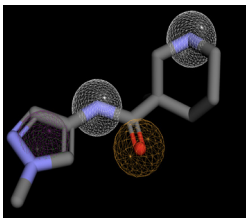
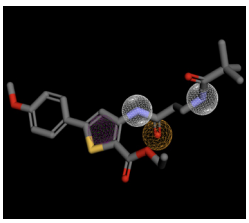
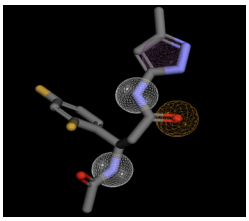
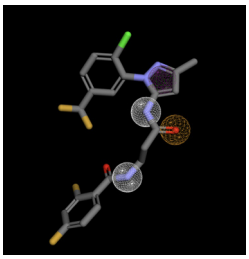


Table 3. *Top 17 potential compounds identified through pharmacophore based virtual screening of PCSK9 using the Pharmit server. Compounds are ranked by RMSD, where lower values indicate better alignment with the pharmacophore features. Two pharmacophore maps (A and B) were used for the screening*

Name	RMSD	Pharmacophore Map	Library	Figure
Molport-051-895-715	0.019	B	Molport	
Z1584010628	0.022	A	Enamine	
Z373772438	0.029	B	Enamine	

Name	RMSD	Pharmacoph-ore Map	Library	Figure
Z1171598708	0.029	B	Enamine	
Molport-020-269-245	0.031	B	Molport	
Z225654462	0.032	B	Enamine	
Z52103291	0.032	B	Enamine	
Z225520308	0.033	A	Enamine	
Z4422192504	0.033	A	Enamine	
Z27664946	0.034	A	Enamine	
Z440626236	0.034	A	Enamine	

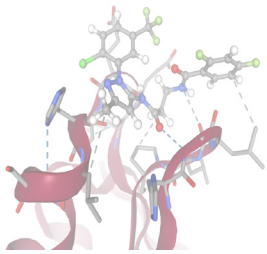
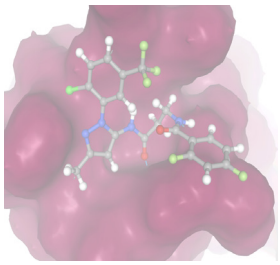
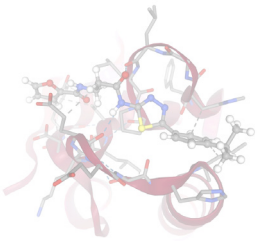
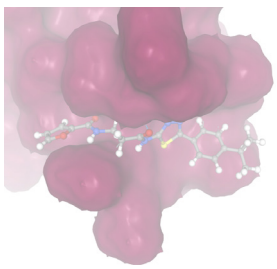
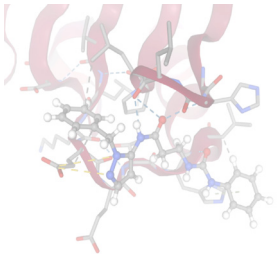
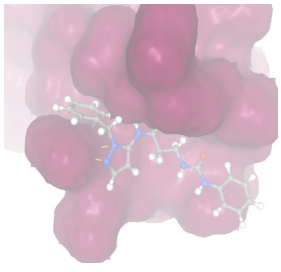
Name	RMSD	Pharmacophore Map	Library	Figure
Z28609494	0.034	A	Enamine	
Z73447142	0.034	A	Enamine	
Z1095263098	0.034	B	Enamine	
Z280289292	0.034	B	Enamine	
Z1279873071	0.034	B	Enamine	
Z764690862	0.034	B	Enamine	

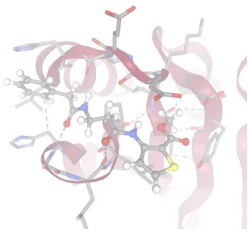
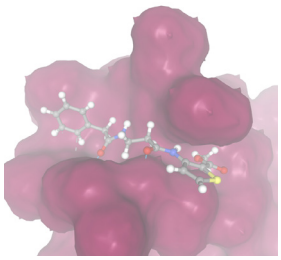
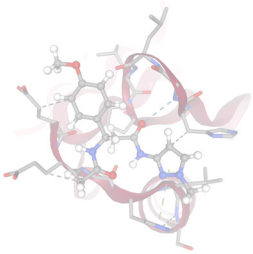
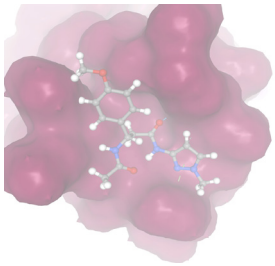
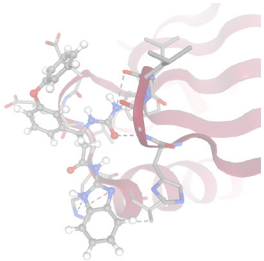
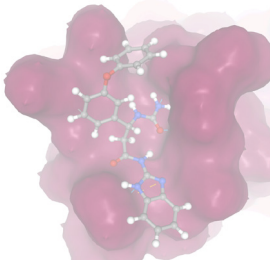
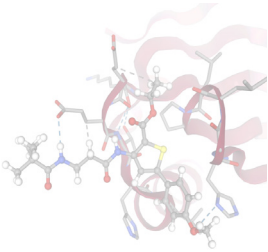
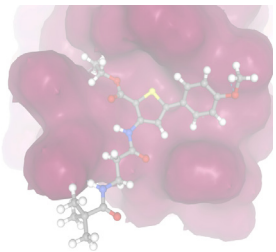
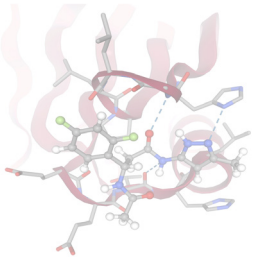
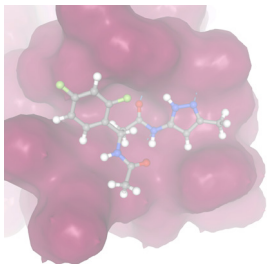
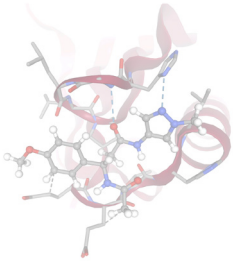
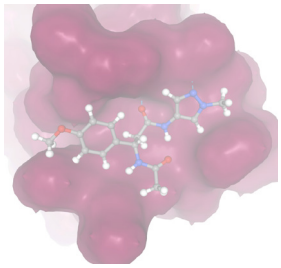
Swiss Dock Virtual Screening Results

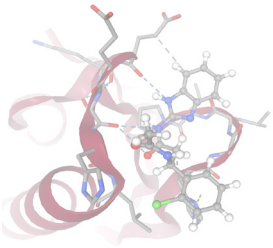
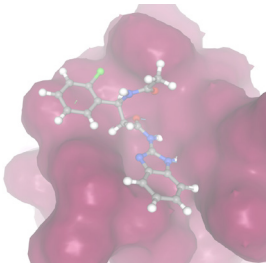
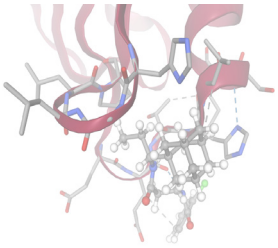
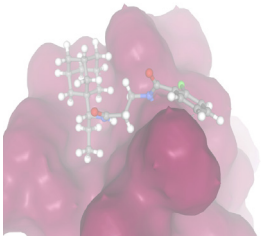
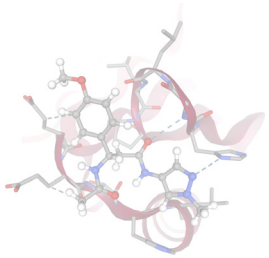
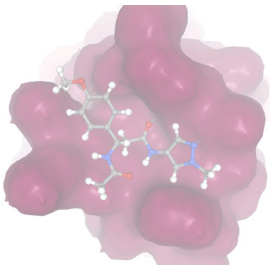
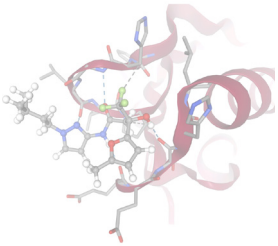
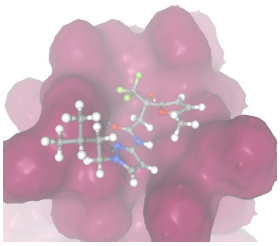
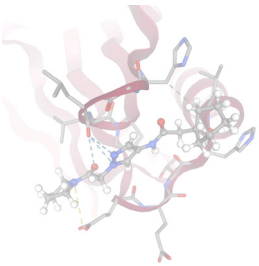
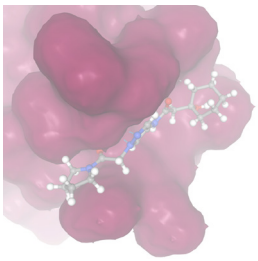
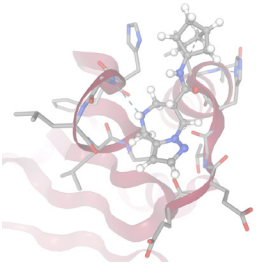
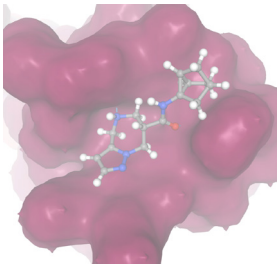
SwissDock was used to test how well each compound might bind to the PCSK9 protein, and SwissParam scores were used to compare their predicted binding strength. Molecular docking is a computational method that predicts how a small molecule, like a lipid, fits into a protein's binding site and estimates the strength of that interaction. The SwissDock scoring provides an estimate of the Gibbs free energy of binding (ΔG), in kilocalories per mol (kcal/mol). Gibbs free energy represents how energetically favorable the interaction is, and more negative ΔG values indicate stronger and more stable binding. Overall,

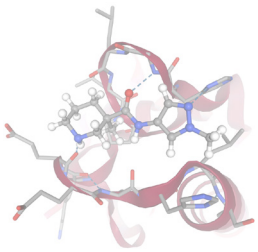
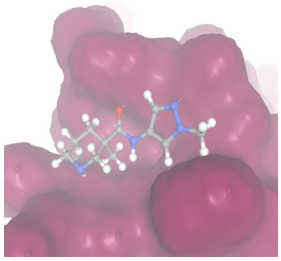
the compounds showed SwissParam scores ranging from around –6.22 kcal/mole to –7.20 kcal/mol, which means that all of the molecules showed at least decent predicted binding to the PCSK9 protein. Most of the compounds had scores between –6.7 kcal/mole and –7.1 kcal/mol, which shows that many of them behaved similarly in the docking simulation. The strongest predicted binder was Z764690862 from the Enamine library, which had the most negative SwissParam score of –7.2042 kcal/mol (Table 4). Two other molecules, Z73447142 and Z52103291, also showed strong predicted binding with SwissParam scores of –7.1420 kcal/mol and –7.1030 kcal/mol respectively. In total, three compounds had SwissParam scores below –7.10 kcal/mol, which indicates that these are the top three molecules for binding. Surprisingly, the molecule with the best SwissParam score also had the worst RMSD value. The fact that the top ΔG scorer had a high RMSD suggests that binding strength and structural stability do not perfectly correlate. Overall, the RMSD and SwissParam scores do not fully agree on which molecule would bind the best.

Table 4. *SwissParam scores obtained from SwissDock virtual screening of selected compounds docked to the target protein. More negative SwissParam scores indicate stronger predicted binding interactions. Compounds are listed with their corresponding chemical library sources. The top figures in each row show the interactions in the molecule and the bottom figure shows the molecule on the protein's surface. Blue represents hydrogen bonds, yellow represents ionic interactions, orange represents Cation-π interactions, the black represents hydrophobic contacts, and the green represents the π-stacking interactions. The red ribbon and blob represent the protein's structure*

Molecule ID	SwissParam Score (Kcal/mol)	Residue Interaction Pose	Protein Surface
Z764690862	–7.2042		
Z73447142	–7.1420		
Z52103291	–7.1030		

Molecule ID	SwissParam Score (Kcal/mol)	Residue Interaction Pose	Protein Surface
Z225520308	–6.9003		
Z225654462	–6.8825		
Z27664946	–6.8772		
Z280289292	–6.8420		
Z1279873071	–6.8089		
Z373772438	–6.8059		

Molecule ID	SwissParam Score (Kcal/mol)	Residue Interaction Pose	Protein Surface
Z440626236	–6.7975		
Z28609494	–6.7942		
Z1171598708	–6.7447		
Z1584010628	–6.5722		
Mol-port-020–269–245	–6.4930		
Z4422192504	–6.3860		

Molecule ID	SwissParam Score (Kcal/mol)	Residue Interaction Pose	Protein Surface
Z1095263098	–6.2196		

Evaluating Drug Likeness with SwissAdme Server

To determine whether the compounds that we have found could function as oral drug candidates, we analyzed the physicochemical and pharmacokinetic properties of the top seven compounds using the SwissADME server. In this experiment, Lipinski's Rule of Five, predicted solubility, and gastrointestinal absorption were analyzed.

Lipinski's Rule of Five is used to estimate whether a compound is likely to be a good oral drug. According to this rule, a molecule should have no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, a molecular weight under 500 daltons, and a consensus LogP value under five. If a compound does not meet all of these rules, it is less likely to be absorbed effectively and was not allowed to continue in this study.

As shown in Table 5, all seven molecules met Lipinski's rules with zero violations. Molecular weights ranged from 316.36 Da to 486.82 Daltons, and none exceeded the 500 Da limit (Table 5). The number of hydrogen bond donors ranged from 2 to 4, and hydrogen bond acceptors ranged from 3 to 8, which all meet the criteria (Table 5). Consensus LogP values ranged from 1.18 to 4.68, which means all of the compounds were below the maximum of 5 (Table 5).

Predicted solubility using the ESOL model was different among all of the compounds (Table 5). Molecule 5 was classified as very soluble. Molecules 2, 3, and 4 were classified as soluble, while Molecules 1, 6, and 7 were moderately soluble (Table 5).

GI absorption also helped narrow down the best compounds. Six of the seven molecules were predicted to have high GI absorption. Molecule 1 was the only compound predicted to have low GI absorption (Table 5), which suggests that even though it meets Lipinski's rules, it may not be absorbed efficiently when taken orally.

Overall, based on the data summarized in Table 5, all seven compounds met the required drug likeness scores and were allowed to continue on in the study.

Table 5. *Summary of Lipinski's Rule of Five parameters (molecular weight, hydrogen bond donors, hydrogen bond acceptors, and consensus LogP), ESOL solubility classification, and predicted gastrointestinal (GI) absorption for the seven compounds using the SwissADME server*

Molecular ID	Molecular Weight (Da)	H-Bond Donors	H-Bond Acceptors	Consensus LogP	Lipinski's Violations	ESOL Solubility	GI Absorption
Z764690862	486.82	2	8	4.88	None	Moderately Soluble	Low
Z73447142	384.45	2	5	2.88	None	Soluble	High

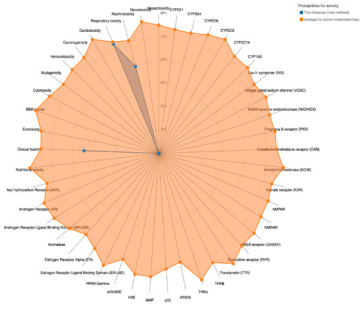
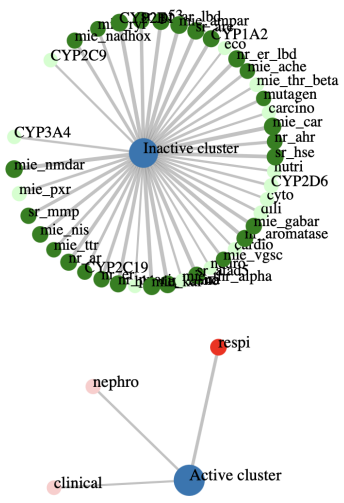
Molecular ID	Molecular Weight (Da)	H-Bond Donors	H-Bond Acceptors	Consensus LogP	Lipinski's Violations	ESOL Solubility	GI Absorption
Z52103291	363.41	3	3	2.11	None	Soluble	High
Z225520308	346.40	2	4	2.37	None	Soluble	High
Z225654462	316.36	2	4	1.18	None	Very Soluble	High
Z27664946	415.44	4	4	2.67	None	Moderately Soluble	High
Z280289292	432.53	2	5	3.80	None	Moderately Soluble	High

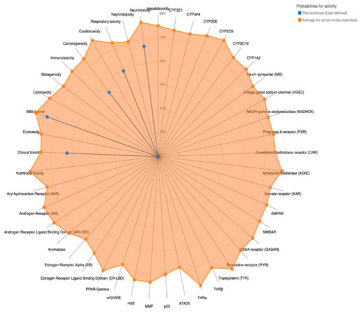
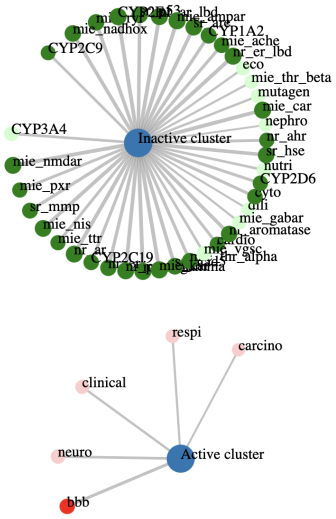
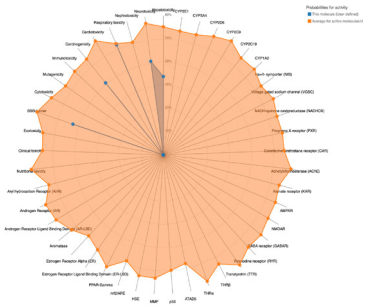
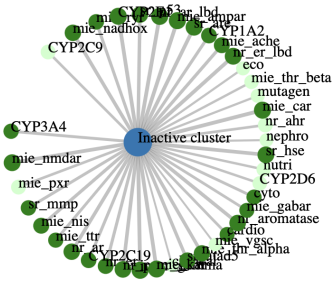
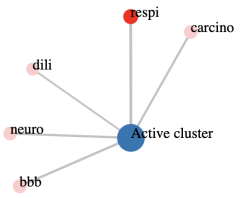
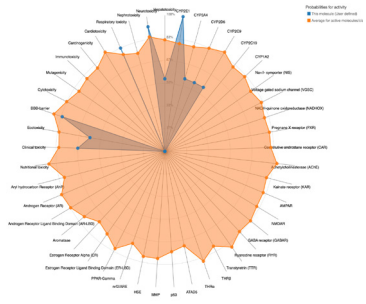
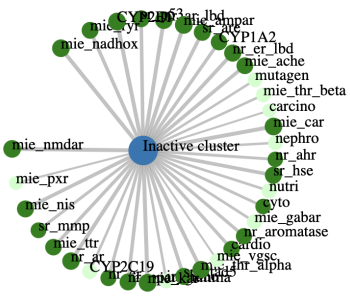
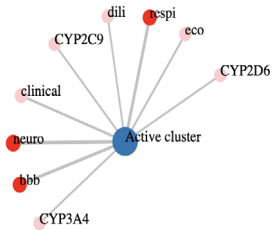
Identifying Drug Toxicity with Protox 3

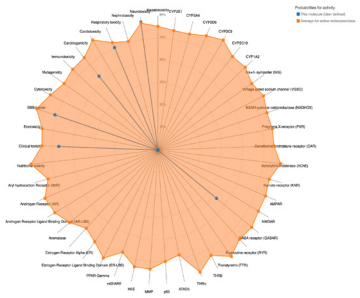
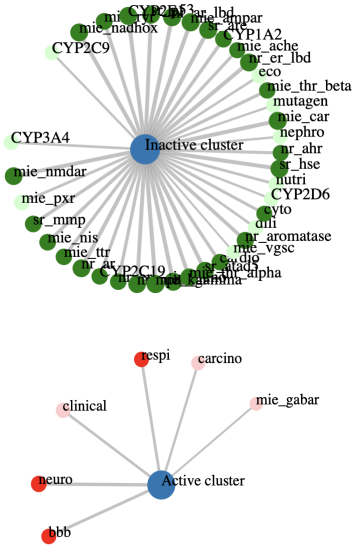
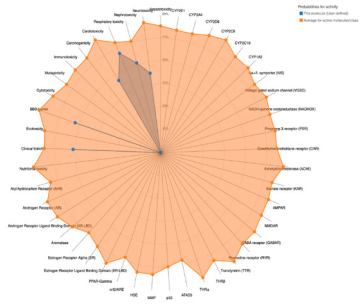
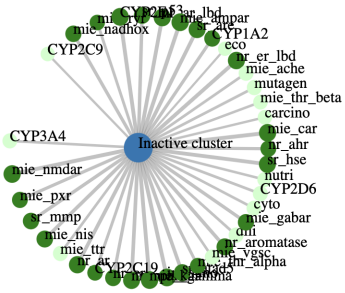
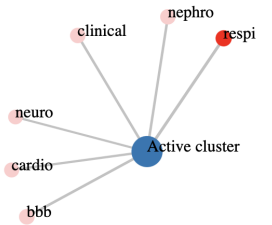
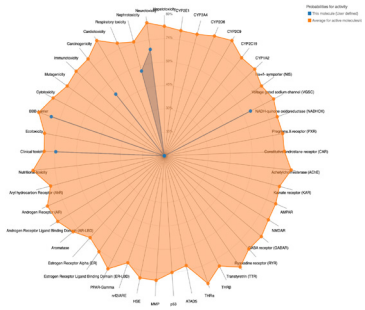
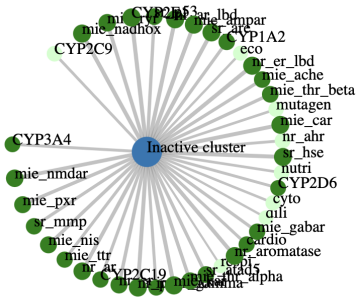
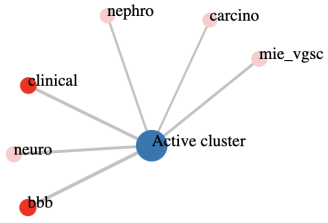
The purpose of this experiment was to evaluate the predicted toxicity of the top compounds using Protox 3 and determine whether their toxicity levels are within the FDA's limits (Table 6). The toxicity was evaluated using predicted LD50 values, toxicity class, and toxicity radar charts. In general, a higher LD50 means the compound is less toxic, and a lower LD50 means it is more toxic.

The predicted LD50 values ranged from 300 mg/kg to 2500 mg/kg (Table 6). Z280289292 had the highest LD50, 2500 mg/kg, and had a toxicity class of 5, which means it has the lowest predicted toxicity out of the group. Z225654462 (1500 mg/kg) and four other compounds- Z73447142, Z764690862, Z52103291, and Z225520308 (1000–1100 mg/kg)- were placed in toxicity class 4, which indicates moderate toxicity. Z27664946 had the lowest LD50 value of 300 mg/kg and was classified as toxicity class 3, meaning it is more toxic than the others.

Table 6. *Outcomes from predicted toxicity analysis using Protox 3. LD50 (mg/kg) represents the predicted dose required to cause death in 50% of test subjects, and toxicity class categorizes compounds based on toxicity level. The toxicity radar charts display predicted toxicity endpoints compared to FDA reference thresholds*

Molecule	LD50 (mg/kg)	Predicted Toxicity Class	Toxicity Radar Chart	Active and Inactive Network Chart
Z280289292	2500	5		

Molecule	LD50 (mg/kg)	Predicted Toxicity Class	Toxicity Radar Chart	Active and Inactive Network Chart
Z225654462	1500	4		
Z73447142	1100	4		 
Z764690862	1000	4		 

Molecule	LD50 (mg/kg)	Predicted Toxicity Class	Toxicity Radar Chart	Active and Inactive Network Chart
Z52103291	1000	4		
Z225520308	1000	4		 
Z27664946	300	3		 

The toxicity radar charts compare each compound's predicted toxicity endpoints to FDA limits. Most of the compounds stayed within the FDA limits across the chart. Z52103291 had one point slightly above the FDA limit, but it was only about 1% higher, so it is still safe. In contrast, Z764690862 had multiple points above the FDA limit, which suggests higher risk across several toxicity categories. Because of this, Z764690862 is the least favorable option from a toxicity standpoint and will not be moving on in the study.

The active and inactive network charts show predicted biological targets related to toxic effects. The active charts represent proteins the compounds may interact with that are connected to toxicity pathways, while the inactive charts represent predicted non-interacting targets.

Overall, most of the compounds showed predicted toxicity levels within the FDA limits.

Conclusion

This study used several computational drug discovery tools to search for small molecules that could block PCSK9, a protein that contributes to high LDL cholesterol. By combining virtual screening, molecular docking, and drug-likeness analysis, two compounds – Z73447142 and Z52103291 – were identified as the strongest potential inhibitors.

Z7344714 had a docking score of –7.1420 kcal/mol and an RMSD of 0.034. This means that it has really stable binding. It has a molecular weight of 384.45 Da, 2 hydrogen bond donors, and 5 hydrogen bond acceptors, and no Lipinski's Rule of Five violations. It also has a consensus LogP of 2.88, was predicted to be soluble, and a high GI absorption. It also had an LD50 of 1100 mg/kg with a predicted toxicity class of 4.

Z52103291 had a docking score of –7.1030 kcal/mol and an RMSD of 0.032. It has a molecular weight of 363.41 Da, 3 hydrogen bond donors, and 3 hydrogen bond acceptors, and no Lipinski's Rule of Five violations. Its consensus LogP was 2.11, it was soluble, and had a high GI absorption. It had an LD50 of 1000 mg/kg with a toxicity class of 4. Although one value on the radar chart was about 1% above the FDA limit, it was only slightly higher so it is still considered safe.

There are a few limitations to this study. First, all experiments were done virtually, so we do not know if the compounds will behave the same way in real cells or in humans. The docking and toxicity predictions might not translate to real biological results. Also, only two chemical libraries were screened, so other potentially better compounds may exist that were not included in this study. Because of this, lab testing has to be done to confirm that the selected compounds actually have the predicted effectiveness from our study.

Overall, Z73447142 is the top compound because it showed slightly stronger binding and a slightly higher LD50 value, which means that it is more stable and safe. This compound should continue for future lab testing and Z52103291 is a good second candidate if Z73447142 isn't effective in a lab setting.

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GSK3-TARGETED SMALL MOLECULES AS THERAPIES FOR ALZHEIMER'S DISEASE

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Abstract

Alzheimer's disease (AD) is a progressive neurological disorder that affects memory, thinking, and behavior. It is one of the leading causes of dementia worldwide, and current treatments mainly focus on managing symptoms rather than slowing or stopping disease progression. Research has identified glycogen synthase kinase-3 (GSK3) as a key enzyme involved in abnormal tau phosphorylation, which contributes to the development of Alzheimer's disease. Targeting GSK3 may provide a potential therapeutic approach. In this study, computational methods, including virtual screening and molecular docking, were used to evaluate small molecules as possible GSK3 inhibitors. Docking simulations were performed using SwissDock, and binding affinity was measured using FullFitness scores and estimated Gibbs free energy (ΔG). Several compounds demonstrated strong predicted binding within the enzyme's active site, suggesting stable interactions. These results indicate that certain small molecules may have potential as GSK3-targeted therapies. However, further experimental testing would be required to confirm their effectiveness and safety.

Keywords: *Drug Discovery, virtual screening, Alzheimer's disease, GSK3*

1. Introduction

1.1. Background

The most prevalent cause of dementia is Alzheimer's disease, a neurological condition that gradually deteriorates an individual's memory and cognitive abilities. It can often take five, ten, or even twenty years to show symptoms ("Alzheimer's Disease: Get the Facts." 2024). Beginning with minor memory loss, it could eventually result in the inability to do everyday tasks, have a proper conversation, or interact with the surrounding environment (CDC. "About Alzheimer's." 2024). This disease is fatal; every 65 seconds, someone in the US gets Alzheimer's, but by 2050, it is expected to increase to every 33 seconds. An estimated 500,000 Americans lose their lives to Alzheimer's disease each year, making it the 10th leading cause of death with no cure in the US, as well as one of the most

expensive diseases in the nation. Treatment for AD, which includes healthcare, long-term care, and hospice care, was expected to cost $321 billion in 2022, and by 2050, it is projected to cost more than $1 trillion. Medicare and Medicaid cover about 65% of out-of-pocket medical costs. However, due to an anticipated increase in yearly payments, Alzheimer's is predicted to raise Medicare and Medicaid spending by more than 330% by 2050 (Skaria A. P., 2022).

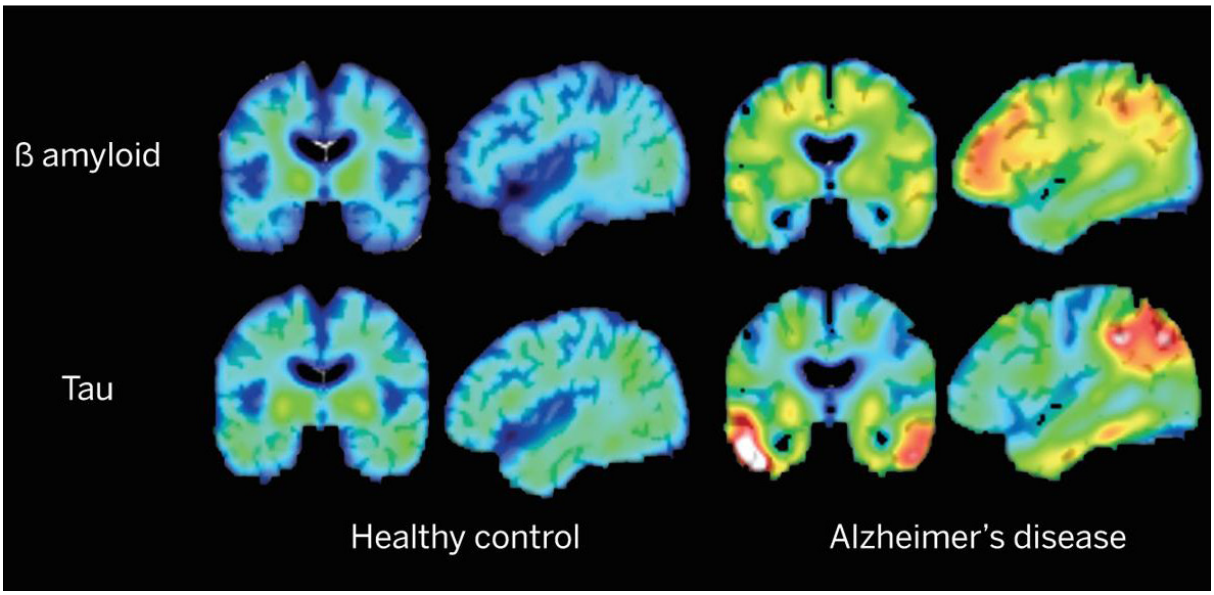
1.2. Acetylcholinesterase theory

AChE is a neurotransmitter that travels through nerve cells to send messages from the brain to the body. It plays a significant role in memory, learning, attention, emotion, and spontaneous muscle activity (Li S., Li A. J., Zhao J., Santillo M. F., Xia M., 2022). Acetylcholinesterase, or AChE, is an enzyme typically found at postsynaptic neuromuscular junctions that breaks down acetylcholine. Acetylcholine is produced when choline and the acetyl group react, facilitated by an enzyme called choline acetyltransferase (Froede H. C., Wilson I. B., Kaufman H., 1986). However, in Alzheimer's disease, damage or death of the cells that produce it leads to the loss of acetylcholine in the brain, resulting in memory loss and confusion. In the brain, AChE usually breaks down acetylcholine. Slowing the breakdown of acetylcholine can be accomplished by blocking AChE, which leaves more acetylcholine available for memory and cognitive functions. This strategy has led to the development of medications known as AChE inhibitors, designed to improve the mental functioning of Alzheimer's patients. By preserving acetylcholine levels, these treatments may enhance nerve-cell communication and reduce specific symptoms associated with the condition (Selkoe D. J., Hardy J., 2016).

1.3. Amyloid theory

Amyloid-beta is a protein naturally produced by the brain. In Alzheimer's disease, this protein forms sticky plaques that build up in the spaces between brain cells. These plaques block communication among brain cells, resulting in memory loss and cognitive impairment. Scientists propose that eliminating amyloid plaques could reduce or potentially prevent Alzheimer's. Aducanumab and lecanemab are two recent medications designed to remove amyloid plaques and improve brain function (Musiek E. S., Holtzman D. M., 2015). This theory suggests that Aβ peptides aggregate, forming plaques, and that these plaques, along with soluble oligomers, disrupt neuronal function and trigger a cascade of events leading to disease progression (DiSabato D. J., Quan N., Godbout J. P., 2016).

Figure 1. *Brain scans comparing β-amyloid and tau levels in a healthy individual and a patient with Alzheimer's disease. The brighter yellow and red areas show greater protein buildup, which is much more visible in the Alzheimer's brain ("Alzheimer's Disease: Get the Facts." 2024)*



1.4. Neuroinflammation

In the brain and spinal cord, neuroinflammation is a complicated inflammatory response that is brought on by a variety of triggers, such as infections, trauma, or neurodegenerative illnesses. It involves the production of inflammatory mediators and the activation of immune and glial cells (Beese, Megan. 2025). Chronic neuroinflammation can harm neurons and impair brain function, although temporary inflammation may be helpful in repair. Numerous neurological disorders, including multiple sclerosis, Parkinson's disease, and the most common, Alzheimer's disease, are associated with this chronic inflammation. Neuroinflammation may exacerbate the accumulation of damaging plaques and tangles in Alzheimer's disease, resulting in cognitive decline and memory loss (Kumar, Anil, et al., 2023).

1.5. FDA-approved drugs for Alzhiemer's disease – Donepezil

Donepezil, one of the five FDA-approved medications for Alzheimer's disease at the moment, is frequently recommended to assist in treating symptoms, including disorientation and memory loss. Although donepezil increases acetylcholine levels, a neurotransmitter crucial for memory and learning, it does not halt the progression of the illness. Although these drugs can offer short-term respite, their effects are usually short-lived. Millions of individuals worldwide are still affected by Alzheimer's (Hooper C., Killick R., Lovestone S., 2008). Therefore, new therapies that address the disease's fundamental causes – such as tau tangles, amyloid plaque accumulation, and neuroinflammation – are desperately needed.

1.6. GSK3 – the connection between GSK3 and Alzheimer's disease

An enzyme called glycogen synthase kinase 3 (GSK3) is involved in metabolism, cell division, and brain development, among other biological processes. GSK3α and GSK3β are its two primary forms, with GSK3β being especially significant in the brain. GSK3 becomes hyperactive in Alzheimer's disease and is closely associated with the formation of tau tangles, one of the main characteristics of the condition. Tau changes form and clumps inside neurons when GSK3 adds too many phosphate groups to the tau protein, a process known as hyperphosphorylation. These tau tangles eventually cause brain cells to die because they prevent them from communicating with one another. Apart from its involvement in tau pathology, GSK3 may also have an impact on amyloid-beta plaque formation and neuroinflammation, both of which are linked to the advancement of Alzheimer's disease (Lauretti E., Dincer O., Praticò D., 2020). GSK3 is being investigated as a potential target for the creation of intriguing and more effective Alzheimer's treatments due to its profound influence on several disease pathways.

1.7. Literature Review

Numerous studies investigating the involvement of Glycogen Synthase Kinase-3 (GSK3) in Alzheimer's disease (AD) have generated a thorough understanding of the illness's fundamental causes and possible treatment approaches. GSK3 is introduced as a central kinase in AD pathophysiology in «The GSK3 Hypothesis of Alzheimer's Disease» (Lauretti E., Dincer O., Praticò D., 2020), which also highlights its role in tau hyperphosphorylation, a crucial step in developing neurofibrillary tangles. Furthermore, by affecting the processing of amyloid precursor protein (APP), GSK3 regulates the generation of amyloid-β, two characteristics characteristic of AD. According to the article, memory, cognitive function, and neurogenesis – all of which are significantly compromised in AD patients – are directly impacted by GSK3 disruption. This theory is expanded upon in another piece, "Glycogen Synthase Kinase-3 Signaling in Alzheimer's Disease" (Lauretti E., Dincer O., Praticò D., 2020), which discusses the interaction between GSK3 and other signaling pathways linked to AD neuropathology. It draws attention to how the kinase affects neurogenesis and synaptic function, indicating that GSK3 activity plays a role in neuronal injury and cognitive decline. The paper describes preclinical efforts to produce GSK3 inhibitors, highlighting GSK3's potential as a beneficial target. However, significant barriers remain to converting these inhibitors into clinical medications, particularly minimizing off-target effects and obtaining effective blood-brain barrier penetration. Based on both papers, GSK3 remains a potential target despite all

of these obstacles, and research is still being done to improve methods for regulating it to slow the progression of AD. According to the pooled research, GAK3 inhibition may have therapeutic potential, but more research is needed to determine its clinical practicality.

2. Methods

2.1 Experiment 1 – Identification of Binding Sites in GSK3

The goal of this experiment was to identify possible binding sites on the GSK3 protein where small molecules could bind. The three-dimensional structure of the GSK3 protein was analyzed using DoGSiteScorer, a computational tool that detects pockets on the surface of proteins.

The protein structure was uploaded into the DoGSiteScorer server. The program scanned the protein surface and identified several potential binding pockets. For each pocket, measurements such as volume, surface area, and drug score were calculated. The drug score estimates how suitable a pocket may be for binding drug-like molecules.

To further analyze the protein, a second tool called PrankWeb was used. PrankWeb predicts ligand binding sites using a machine-learning method that considers factors such as interaction energy and residue conservation. The program ranked the predicted binding pockets based on score, probability, and number of residues involved. The highest ranked pockets were selected as the most promising binding sites.

2.2 Experiment 2 – Virtual Screening

After identifying potential binding pockets, virtual screening was performed to find small molecules that could interact with the GSK3 protein. This step was carried out using the Pharmit platform, which allows large compound libraries to be searched using a pharmacophore model.

A pharmacophore represents the key molecular features required for interaction with a protein. These features can include hydrogen bond donors, hydrogen bond acceptors, and hydrophobic regions. In the Pharmit interface, these features were represented as spheres showing where interactions should occur.

The compound database was screened using the pharmacophore model, and molecules that matched the required spatial and chemical features were selected. After filtering the results, 15 compounds were identified as potential candidates. These compounds were selected for further evaluation in the molecular docking experiment.

2.3 Experiment 3 – Molecular Docking

The selected compounds were further analyzed using molecular docking to evaluate their potential interactions with the GSK3 protein. Docking simulations were performed using the SwissDock server.

The three-dimensional structure of the GSK3 protein and the structures of the selected compounds were uploaded into SwissDock. The program simulated how each molecule could fit into the predicted binding pocket of the protein.

SwissDock generated several possible binding conformations for each compound. For each docking result, two important values were calculated: FullFitness score and estimated Gibbs free energy (ΔG). These values estimate the strength and stability of the interaction between the protein and the ligand. Lower energy values indicate stronger predicted binding interactions.

The docking results were grouped into clusters, and the most favorable binding poses were selected based on the lowest energy values.

3. Results and Discussion

3.1. Experiment 1 – Identification of binding sites in GSK3

The purpose of this experiment was to identify potential binding pockets on the GSK3 protein that could serve as targets for small molecules. These pockets are important because drug molecules must bind to specific regions of a protein in order to affect its activity.

Using DoGSiteScorer, multiple pockets were detected on the surface of the GSK3 protein. Each pocket was evaluated based on its volume, surface area, and drug score. As shown in Table 1, pocket P0 had the highest drug score (0.81) and the largest volume, suggesting that it may be the most suitable binding site for small molecules. To support these findings, the protein was also analyzed using PrankWeb, which predicts binding sites

using machine learning. Two main binding pockets were identified. The highest-ranked pocket had a probability score of 0.947 and involved 36 residues, indicating a strong likelihood that this region is an important binding site.

The results from both tools identified similar regions of the protein as possible binding pockets. This agreement between the two methods increases confidence in the predicted binding sites and supports their use in later experiments.

3.2 Experiment 2 – Virtual Screening

The goal of this experiment was to identify small molecules that could potentially bind to the GSK3 binding pocket. Virtual screening allows a large number of compounds to be evaluated computationally before laboratory testing. Using the Pharmit platform, a pharmacophore model was created to represent the key interaction features required for binding to the protein. The program then searched a large compound database for molecules that matched these features.

After screening the compounds, 15 molecules were selected because they best matched the pharmacophore model. These compounds are considered promising candidates because their structures are compatible with the predicted binding site. The selected molecules were then used in the molecular docking experiment to further evaluate their interactions with GSK3.

3.3 Experiment 3 – Molecular Docking

The purpose of this experiment was to evaluate how strongly the selected compounds bind to the GSK3 protein. Molecular docking simulations were performed using SwissDock, which predicts how small molecules interact with a target protein.

Each compound was docked into the predicted binding site of the GSK3 protein. The docking program generated several possible binding orientations and calculated energy values for each interaction. Multiple compounds showed strong predicted binding interactions. For example, compound Z785802866 had one of the lowest estimated ΔG values at –9.73 kcal/mol, suggesting a strong and stable interaction with the protein. Other compounds, including Z29354210 and Z5129929917, also showed favorable binding energies.

Lower ΔG values indicate stronger predicted binding between the molecule and the protein. These results suggest that several of the screened compounds may have potential as GSK3 inhibitors. However, because these results are based on computational predictions, further laboratory experiments would be required to confirm their effectiveness.

Experiment No. 1 – How to identify binding sites in proteins?:

Geometric methods

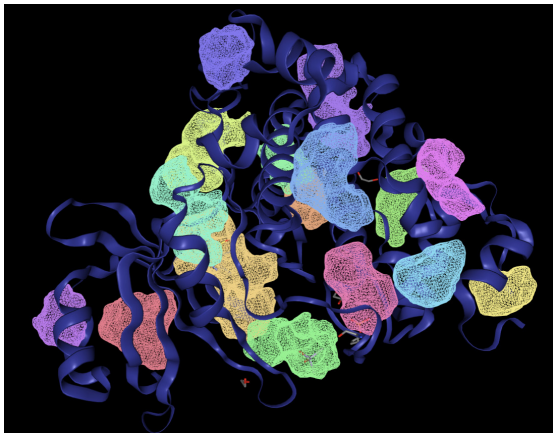
Using DoG Site Scorer

Table 1. *Binding sites identified in GSK3 using the geometric method, DoGsitescorer. Drug Scores listed below represent the most promising binding sites based on the volume and the surface area*

Name	Key (colors)	Volume A	Surface A	Drug Score
P_0		656.9	758.87	0.81
P_1		338.37	559.27	0.61
P_2		302.85	512.29	0.46
P_3		267.01	324.01	0.45
P_4		261.82	346.28	0.51
P_5		241.15	359.06	0.65
P_6		216.32	390.32	0.65
P_7		189.89	263.5	0.52
P_8		175.1	242.16	0.39
P_9		152.26	312.59	0.34

Name	Key (colors)	Volume A	Surface A	Drug Score
P_10		147.78	348.77	0.27
P_11		136.51	363.97	0.3
P_12		132.8	294.27	0.18
P_13		117.89	436.94	0.17
P_14		107.26	313.09	0.21
P_15		102.72	106.27	0.42

Figure 2. *Three-dimensional structure of the GSK3 protein with predicted binding pockets highlighted in different colors. Each colored region represents a potential binding site identified using DoGSiteScorer*



Explanation:

In this experiment, the size of the binding pockets is used to determine possible binding sites in proteins, specifically GSK3, using the geometric method. If a protein has openings or additional areas on its surface that are the proper size to hold tiny molecules, this technique can help identify them. This approach enables us to determine regions where a small molecule could fit by examining the sizes of these pockets. In the early phases of drug discovery, this method is essential since it helps identify possible binding sites for further research. Comprehending the dimensions and form of these pockets can help with the creation of targeted inhibitors or treatments for GSK3.

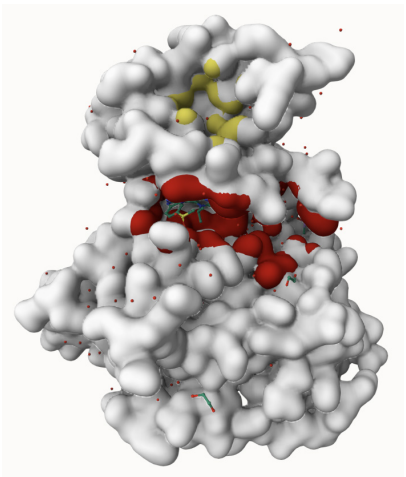
Energetic-based method

Using PrankWeb:

Table 2. *Predicted GSK3 binding sites identified using the energetic-based method PrankWeb. Binding pockets are ranked by score and probability, with Pocket 1 showing the highest likelihood of being a ligand binding site*

Rank	Key	Score	Probability	No. of residues	Avg conservation
1		36.76	0.947	36	2.075
2		2.17	0.051	10	0.444

Figure 3. *Binding sites colored in red and yellow in GSK3, as identified by the machine learning method, Prankweb*



Explanation:

In this experiment, the energy-based approach evaluates the binding energy to investigate the interactions between small compounds and protein binding sites. This method examines hydrogen bonding, hydrophobic forces, and electrostatic interactions to determine how firmly a chemical binds after finding possible sites.

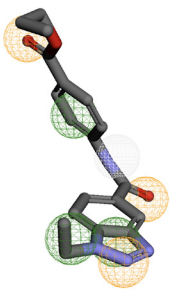
It also considers how protein mutations may change the energy and attraction at the binding site. This approach helps with drug design and understanding protein regulation, particularly for targets like GSK3, by predicting how well small molecules interact with the protein by combining size, energy, and possible mutations.

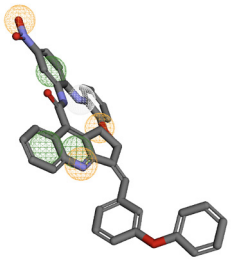
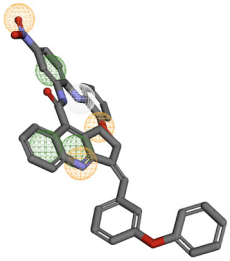
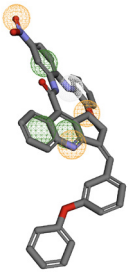
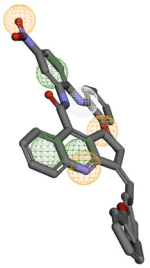
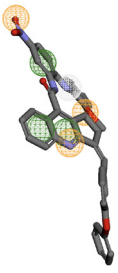
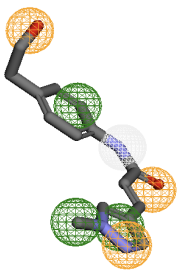
Figure 4. *Pharmacophore model used for virtual screening of potential GSK3 inhibitors on the Pharmit platform. The colored spheres represent key interaction features, such as hydrogen-bond donors, hydrogen-bond acceptors, and hydrophobic regions. The table on the right shows the compounds that matched the pharmacophore model along with their RMSD, mass, and number of rotatable bonds*

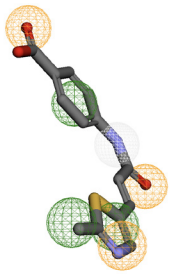
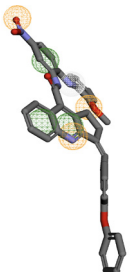
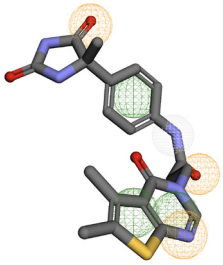
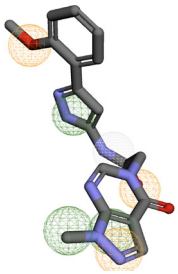
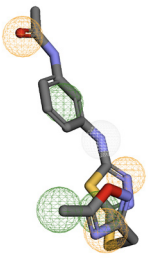
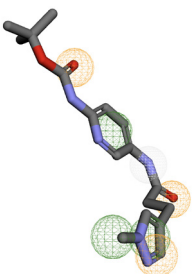
In this experiment, virtual screening was performed using a pharmacophore model on the Pharmit platform to identify small molecules that best fit the GSK3 protein. A pharmacophore is defined by three key elements: the number of interactions, the distance between those interactions, and the types of interactions, each represented as spheres. These features help predict how well a compound might bind to the protein. This phase aimed to filter down the chemical compounds to 15 proteins. This process is crucial in early drug discovery as it helps identify promising molecules for further testing.

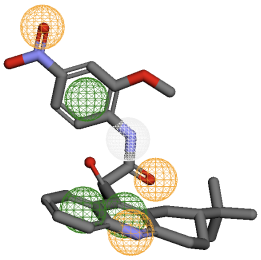
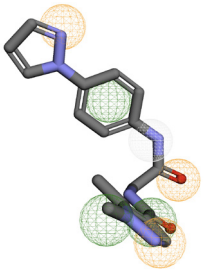
Below are the 15 compounds used in this experiment:

Table 3. *Structures of the 15 compounds selected from virtual screening. The table shows the chemical structures of each compound along with their corresponding compound IDs used for molecular docking analysis with the GSK3 protein*

Compound Name	Image:
Z293542101	

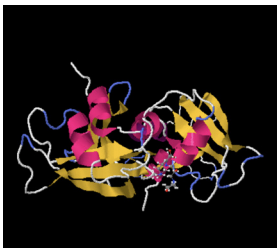
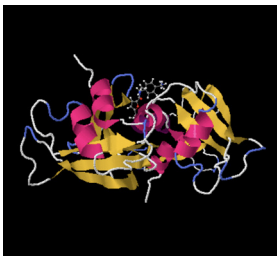
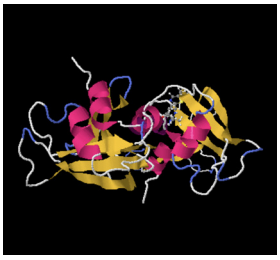
Compound Name	Image:
Z5129929917	
Z5129929917	
Z5129929917	
Z5129929917	
Z5129929917	
Z785802866	

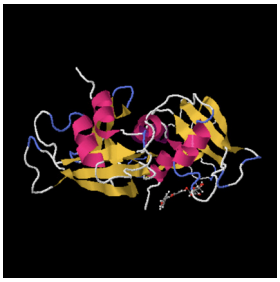
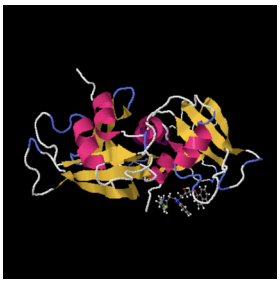
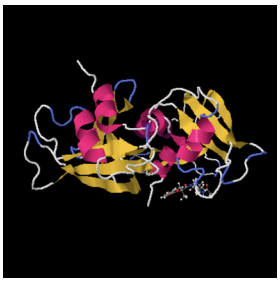
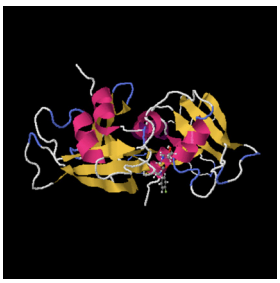
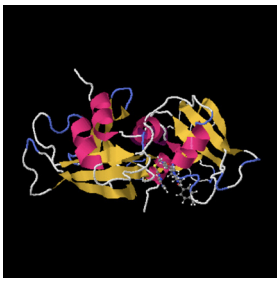
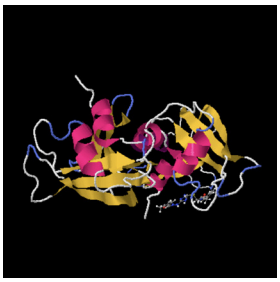
Compound Name	Image:
Z1443864055	
Z5129929917	
Z367619374	
Z927972308	
Z334849748	
Z1067608598	

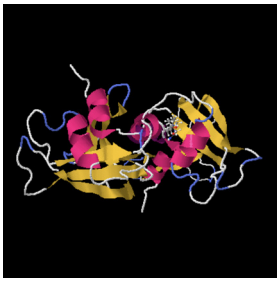
Compound Name	Image:
Z19182681	
Z1001918578	

Next Experiment: Using SwissDock
Molecular Docking:

Table 4. *Molecular docking results for selected compounds interacting with the GSK3 protein using SwissDock. The table shows the docking cluster, element number, FullFitness score, and estimated Gibbs free energy (ΔG) for each compound, along with images of the predicted binding poses within the protein. Lower ΔG values indicate stronger predicted binding interactions*

Name	Cluster	Element	FullFitness (kcal/mol)	Estimated ΔG (kcal/mol)	Picture
Z367619374mol2	10	13	−1243.79	−8.72	
Z19182681mol2	5	0	−1425.42	−7.59	
Z334849748mol2	0	8	−1537.07	−8.83	

Name	Cluster	Element	FullFitness (kcal/mol)	Estimated ΔG (kcal/mol)	Picture
Z785802866mol2	0	0	–1315.58	–9.73	
Z29354210mol2	18	3	–1367.05	–9.41	
Z927972308mol2	19	0	–1383.14	–7.25	
Z1001918578mol2	2	0	–1316.44	–8.75	
Z1443864055mol2	0	4	–1332.86	–8.39	
Z5129929917mol2	3	0	–1385.06	–9.23	

Name	Cluster	Element	FullFitness (kcal/mol)	Estimated ΔG (kcal/mol)	Picture
Z1067608598mol2	2	0	–1413.98	–7.55	

Conclusion:

This study investigated the potential of small molecules as inhibitors of the GSK3 protein, which is strongly associated with the progression of Alzheimer's disease. Computational methods were used to identify possible drug candidates. First, potential binding pockets on the GSK3 protein were identified using geometric and energetic prediction tools. Next, virtual screening using a pharmacophore model was performed to narrow a large compound library down to fifteen candidate molecules that matched the required interaction features. These compounds were then evaluated using molecular docking simulations with SwissDock to predict how strongly they bind to the protein. Several compounds showed favorable binding energies, suggesting stable interactions with the GSK3 binding site. These findings suggest that some of the screened compounds may have potential as GSK3 inhibitors and could serve as starting points for future Alzheimer's disease drug development, although additional experimental testing would be needed to confirm their effectiveness.

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VIRTUAL REALITY AS A REGULATED PSYCHOLOGICAL ENVIRONMENT: FROM SYMPTOM TREATMENT TO IDENTITY RECONSTRUCTION

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Abstract

The article considers virtual reality as a controlled psychological environment that can not only eliminate symptoms but also cause deeper changes aimed at restoring the integrity of the personality. It is shown that the development of virtual reality in psychology has led to its transformation from a simple technical tool for modeling situations to a structured therapeutic environment. It was proved that the limitations of the symptomatic approach are especially noticeable when psychological suffering affects bodily self-perception, personality continuity, and identity. The role of digital physicality, symbolic narrative, emotionally coordinated virtual environments, as well as ethical and neuropsychological aspects of immersion is revealed. An integrative model is proposed in which virtual reality is considered a tool for moving from treating symptoms to restoring identity.

Keywords: *virtual reality, regulated psychological environment, digital physicality, symbolic narrative, identity reconstruction, psychological help, emotional regulation, immersion, neuropsychological safety, VR therapy*

Relevance of the study

Currently, in psychology, virtual reality is increasingly perceived not only as a technical means to alleviate symptoms but also as a special, controlled environment for psychological impact. Its use goes beyond simply reducing anxiety, stress, or emotional tension, affecting deeper processes related to the perception of one's own body, emotional regulation, rethinking traumatic experiences, and the formation of a new self-image.

This topic is especially relevant because many crisis conditions, such as chronic stress, emotional burnout, the consequences of severe physical treatment, and disorders in the perception of one's body, are not limited to just individual symptoms. In such cases, it is necessary not only to correct distress

but also to restore a sense of inner integrity, subjectivity, and personal continuity. Virtual reality is of scientific and practical interest as a space where a combination of sensory experience, digital presence, symbolic modeling, and controlled psychological impact is possible.

The relevance of the study is also related to the fact that there are still no holistic theoretical models that could explain how virtual reality helps to move from symptomatic care to identity restoration. Despite the increase in the number of studies on VR therapy, only isolated approaches to this topic exist in the scientific literature. However, modern psychological practice requires a holistic understanding of the immersive environment as a tool for deep transformation of the psyche.

Thus, the study of virtual reality as a regulated psychological environment is an urgent area. It meets the demands of modern science and practice, which seek to find new approaches to psychological care aimed not only at relieving symptoms but also at restoring the integrity of the individual.

The purpose of the study

The purpose of this study is to theoretically substantiate the use of virtual reality as a controlled psychological environment and to create an integrated model that facilitates the transition from symptom-oriented psychological care to identity reconstruction.

Materials and research methods

The study examined scientific papers that investigated the use of virtual reality in psychology, psychotherapy, and rehabilitation, as well as in research on body perception and immersive environments. Special attention was paid to works devoted to the clinical effectiveness of VR therapy (Freeman et al., 2018; Maples-Keller et al., 2017), the mechanisms of psychotherapeutic changes (Kazdin, 2007; Wampold & Imel, 2015), and the features of emotional regulation in virtual space (Browning et al., 2020; Chirico & Gaggioli, 2019).

A separate group of sources consisted of works on physicality and the feeling of reality in a digital environment (Farman, 2012), as well as author's publications on virtual reality, VR narratives, immersive environments, and neuropsychological safety (Neumann-Zander, 2025).

The methodological basis of the research was the analysis and generalization of scientific literature, as well as a comparative theoretical approach and conceptual modeling.

The results of the study

Virtual reality (VR) has great potential in the treatment and rehabilitation of people with various neuropsychiatric diseases. Its use opens up new horizons for restoring cognitive and motor functions, reducing anxiety, and improving the emotional state of patients (Neumann-Zander N., 2025).

The development of virtual reality in psychology has gone from technical systems that create a presence effect to an effective means of clinical and psychological impact. Initially, VR was developed as a technology for modeling an artificial environment. However, it is precisely the ability to reproduce situations that are significant to a person in a controlled manner that has made it particularly in demand in psychology. Unlike ordinary observation or imaginary reproduction, the virtual environment allows you to combine emotional involvement with precise control of the parameters of the created situation. This is especially important for therapeutic practice.

One of the first applications of virtual reality in clinical practice was the treatment of phobias and anxiety disorders using exposure therapy. The virtual environment made it possible to safely and gradually introduce frightening stimuli while maintaining control over the intensity of exposure.

In the future, the scope of virtual reality has expanded significantly. It has been used not only in the treatment of anxiety disorders but also to combat post-traumatic conditions, pain, and stress, as well as in psychological rehabilitation programs. This has changed the very understanding of virtual reality. From a simple tool for creating stimuli, it gradually turned into a controlled therapeutic environment. In this environment, not only individual images are important, but also the level of immersion, the repeatability of the scenario, the manageability of the situation, and the ability to adapt the intervention to the patient's condition.

Currently, VR is considered an integral part of structured psychological intervention. This is confirmed by large clinical studies in which automated VR therapy in patients with psychosis has demonstrated a significant reduction in agoraphobic avoidance and distress levels compared to traditional therapy. Thus, virtual reality in psychology has evolved from a simple technical means for imitating perception to an organized therapeutic environment that can be effectively used within the framework of modern psychological assistance programs. Table 1 shows the results of some studies confirming this trend.

Table 1. *The main stages of the evolution of virtual reality in psychology*

Stage	Characteristic	Significance for psychology
Early technological stage	Creating presence-based systems	The idea of creating an artificial environment for experiencing
The stage of clinical experiments	The use of VR in exposure therapy of phobias	Confirmation of the therapeutic potential of VR
The modern stage	Using VR in Anxiety, PTSD, Pain, and Rehabilitation	Transition to the therapeutic environment model

A source: compiled by the author based on (Freeman D., Haselton P., Freeman J., Spanlang B., Kishore S., Albery E., Denne M., Brown P., Slater M., Nickless A., 2018; Maples-Keller J. L., Bunnell B. E., Kim S. J., Rothbaum B. O., 2017)

For a visual representation of the main directions of virtual reality application in psychological practice and confirmed therapeutic effects, it is advisable to refer to the data presented in Table 2.

Table 2. *Psychological goals and VR solutions*

The purpose of therapy	The VR Approach	Confirmed effect
Dealing with phobias	VR exposure	Reducing anxiety
Emotional regulation	Meditation scenes, CBT modules	Increasing resilience
Social adaptation	Interaction simulations, role-playing games	Confidence boost
Self-regulation training	Visualization of breathing, biofeedback VR	Reducing stress levels
Motivation activation	VR Game Scenarios	Increased engagement

A source: (Neumann-Zander N., 2025, p. 310)

Classical psychotherapy has proven effective in treating a variety of mental and behavioral disorders. However, the scientific literature constantly mentions some of its limitations, especially noticeable in cases of long-term, complex, and multicomponent diseases. Meta-analytical studies show that most clinical protocols aim at reducing symptoms, while long-term outcomes and patients' quality of life are evaluated much less frequently (Kazdin A. E., 2007).

One of these limitations is that many studies and practical recommendations focus on reducing symptom severity. At the same time, long-term functional results, subjective quality of life, social recovery, and sustainability of change are often overlooked.

In modern discussions about psychiatric and psychotherapeutic research, it is explicitly stated that excessive dependence on symptomatic scales can distort the assessment of therapeutic effects and make it difficult to analyze results important to patients in their daily lives (Wampold B. E., Imel Z. E., 2015).

The limitations of the symptom-centered approach are particularly evident in cases

where psychological suffering is associated not only with anxiety, depression, or stress, but also with a violation of self-image, loss of a sense of bodily integrity, a change in life scenario, and the need to rethink one's own experience. In such situations, a decrease in the severity of individual symptoms does not always lead to the restoration of a sense of subjective continuity and internal integrity of the individual. It is important to note that for some patients, it is important not only to reduce symptoms but also to be able to re-understand and include a traumatic or crisis event in their personal history, as well as restore a sense of authorship of their biography.

Another limitation is related to the availability and implementation of evidence-based psychological treatment methods. Despite the high prevalence of mental disorders, many people do not receive the necessary help. Access to such forms of treatment can be difficult due to barriers that arise at different levels: patient, specialist, organization, and the healthcare system as a whole. This means that even effective therapy in the traditional format cannot always provide enough services and does not always meet the needs of patients with prolonged and complex forms of maladaptation.

Modern psychological and interdisciplinary literature also notes that states of chronic stress, burnout, post-traumatic maladjustment, and the consequences of severe physical treatment often affect not only the emotional sphere but also our perception of our own body, our sense of the boundaries of the Self, and how we feel about ourselves in the world. One publication on digital physicality indicates that interaction with virtual environments is associated with the mechanisms of perception, representation, and transformation of bodily experience. This means that working only at the level of symptoms may not be sufficient if deeper levels of self-perception are affected (Neumann-Zander N., 2025).

Digital physicality is a modern interdisciplinary concept that describes the perception and sensation of bodily presence in a virtual environment. It arises at the intersection of sensory experience, technology, and consciousness when a user interacts with digital reality through avatars, interfaces, sensors, and immersive platforms (VR, AR, and MR). This concept is interpreted from the point of view of phenomenology, cognitive science, neuropsychology, media theory, and neuroesthetics (Farman J., 2012).

Digital physicality is the most important condition for the psychological impact of the virtual environment. It describes the state when a person begins to perceive their virtual body as something related to their own bodily experience. This condition includes three main components: a sense of bodily belonging, a sense of control over the actions of the virtual body, and awareness of one's location in the virtual space. It is thanks to the combination of these components that the virtual environment acquires not only visual visibility but also subjective psychological significance.

Experiments demonstrate that a sense of bodily belonging can occur when visual, tactile, and motor signals work together. Synchronous stimulation and matching movements of the real and virtual body can create the illusion that you are part of a virtual space. This means that the digital body can temporarily integrate into the structure of a person's bodily perception, and the virtual environment begins to feel like a real space for personal presence and actions.

For psychology, digital physicality is of great importance because it transforms virtual reality not just into an image but also into a real experience that can be felt. Virtual reality technologies can help in restoring contact with oneself during chronic stress and burnout. This is achieved through working with bodily self-perception, awareness of one's presence, and attention to inner states. Thus, digital physicality becomes a key mechanism for creating a regulated psychological environment. It allows us to move from external influences to the inner experience of virtual experience as an integral part of our state (Neumann-Zander N., 2025).

In modern psychology, narrative is considered the most important tool for understanding and organizing personal experience. It helps a person comprehend past events, understand their present, and see prospects for the future. With the help of an inner story, a person combines disparate experiences into a single self-image. Narrative is especially important in crisis situations, when serious illnesses, traumatic experiences, or

prolonged psychological stress disrupt the coherence of self-description and make the image of one's self fragmented.

In this context, symbolic narrative plays a twofold role: it serves not only as a way to tell about experience but also as a mechanism for internal reconstruction. Its value lies in the fact that it allows not only to reproduce past experience but also to rebuild its semantic structure. Due to this, the experienced event ceases to be perceived as an isolated traumatic episode and is included in a broader system of personal history. This kind of processing makes it possible to move from a state of internal rupture to the formation of a new, more holistic sense of self.

In the context of virtual reality, this means that we are moving from simply showing images to creating an environment in which a person becomes an active participant in their own story experience. Virtual reality allows you not only to observe certain scenes but also to live them in a symbolically organized space, where each element of the experience acquires personal meaning. This shifts the focus of attention from the experience itself to its internal interpretation, and the emotional reaction is complemented by the process of rethinking the meaning (Nargiza Noimann-Zander. 2025).

This mechanism is especially important during periods when a crisis affects not only the emotional state, but also the identity of a person. After serious physical treatment, prolonged stress, or other significant events, people often need not only to reduce anxiety and cope with their experiences, but also to restore a sense of inner unity. In such situations, the symbolic narrative becomes a powerful tool that helps a person rethink their past, present, and future, integrate new experiences into their self-image, and gain a more stable inner position (Neumann-Zander N., 2025, p. 47).

Emotionally coordinated virtual environments are digital spaces in which visual, audio, and interactive elements adapt to the user's current condition and psychological assistance tasks. In such environments, virtual reality becomes not just a background, but also a specially organized context that helps reduce stress, restore emotions, and create a sense of internal control. The transition from static environments to adaptive systems significantly increases the effectiveness of VR therapy, allowing us to take into account the psychophysiological state of a person (Neumann-Zander N., 2025, p. 129).

Open scientific research confirms that virtual reality can be an effective tool for emotional regulation. In particular, systematic reviews and meta-analyses demonstrate that the use of VR interventions in combination with relaxation, mindfulness, and pain control techniques improves emotional well-being and reduces stress levels (Chirico A., Gaggioli A., 2019).

Combined with relaxation, mindfulness, and pain control practices, VR interventions can help improve emotional and psychological well-being. The works on VR relaxation, which were included in meta-analytical and review studies, mainly used natural virtual environments such as forest and water landscapes. The results of these studies have shown that such interventions can be easily implemented and are effective in the short term to increase relaxation and reduce stress (Browning M. H.E.M., Mimnaugh K. J., van Riper C. J., Laurent H. K., LaValle S. M., 2020).

The ethics and neuropsychological safety of immersive immersion are important aspects that should be considered when using virtual reality in psychological and clinical practice. An immersive environment affects not only attention and emotions but also body perception, spatial orientation, a sense of control, and the subjective boundary between the real and virtual worlds.

Within the author's concept, the transition from treating symptoms to restoring identity is carried out through the sequential passage of several levels of exposure. The first level involves creating a safe immersive environment where meaningful events can be experienced under control. The second level is digital physicality, where the virtual body and space become part of a subjectively meaningful experience. The third level forms a symbolic narrative that allows not only to experience an event but also to rethink it in the context of personal history. The fourth level is characterized by an emotionally coordinated organization of the environment, in which the parameters of the virtual space adjust to the user's condition, supporting mental regulation. The combination of these

levels creates conditions for the transition from symptomatic improvement to internal reconstruction of self-image.

Within this concept, identity reconstruction is considered not as a simple change in self-esteem but as a process of restoring a holistic sense of self. During this process, a person reunites bodily experience, emotional reactions, biographical meaning, and ideas about their future. In open works devoted to narrative reconstruction in virtual reality, it is noted that immersion in the virtual world can restore a person's sense of control over their story and contribute to a more harmonious perception of themselves. Therefore, within this model, VR acts not just as a tool for correcting symptoms but also as a regulated psychological environment that promotes deeper changes in subjectivity.

Conclusions

In modern psychology, virtual reality should be considered not only as a technological tool for eliminating symptoms, but also as a special regulated environment for psychological impact. Its therapeutic potential is due to the ability to combine safe immersion, bodily involvement, symbolic processing of the experience and the emotionally harmonious organization of the digital space.

Research has shown that a symptom-based approach, although it has practical value, may be ineffective if the crisis affects a person's self-perception, integrity, and identity. In such cases, the mechanisms of digital physicality and symbolic narrative play a special role, which help to move from external influence to internal reconstruction of one's image.

The proposed integrative model demonstrates that the long-term effect of VR therapy is associated with not only reducing anxiety, distress or stress, but also with restoring the integrity of self-perception, a sense of self-determination and internal control. This opens up new horizons for the development of psychological assistance aimed at deeper transformation and restoration of personality.

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REVISION OF AESTHETIC STANDARDS OF MANICURE AND PEDICURE WITH AN EMPHASIS ON TAKING CARE OF THE HEALTH OF THE NAIL PLATE

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Abstract

The article is devoted to rethinking the aesthetic standards of manicure and pedicure in terms of maintaining the health of the nail plate. The article shows that the use of resistant coatings and related technologies for preparing and removing the material can lead to mechanical damage to the nail, such as thinning, brittleness, delamination and cracks. The article discusses the anatomical and physiological features of the nail apparatus, in particular, the importance of the matrix as a growth zone and the layered structure of the nail plate. The key physiological aspects of nail health are considered: their thickness, growth rate and the effect of hydration. Special attention is paid to the risk factors that arise when removing coatings and when using UV and LED lamps for polymerization. The sanitary requirements that must be observed during the pedicure process, including the treatment of equipment, are also considered. Based on the analysis of open clinical and professional sources, a practice-oriented concept is proposed. As part of this approach, the criteria for a "beautiful result" are complemented by an assessment of the condition of the nails and periarticular tissues after removing the coating and during repeated procedures.

Keywords: *nail plate, nail machine, matrix, and manicure, pedicure, resistant coatings, coating removal, mechanical damage, nail hydration, UV/LED polymerization, sanitary treatment, and gentle protocols*

Relevance of the study

The study is particularly relevant because in the modern manicure and pedicure industry, resistant coatings and technologies that require careful preparation of the nail plate have become widespread. These procedures include filing and polishing the nails, as well as regular removal of the material. Professional dermatological sources indicate that it is the mechanical impact that occurs during cutting and removing the coating that can significantly injure the nails. Regular repetition

of such procedures often leads to brittleness, delamination and cracks of the nail plate.

The problem becomes particularly relevant due to the need for polymerization of gel materials under ultraviolet or LED lamps. Experimental studies on cellular models show that the radiation used in UV nail dryers can cause DNA damage and mutational changes. This requires careful risk assessment and compliance with precautionary measures in practice. In these conditions, it becomes relevant to rethink aesthetic standards (criteria for a "beautiful" result) from the point of view of preserving the nail plate. This makes it possible to develop more gentle protocols, improve the quality and safety of services, and reduce the likelihood of negative consequences with prolonged and repeated use of resistant coatings.

The purpose of the study

The purpose of this study is to prove the need to review aesthetic standards in the field of manicure and pedicure. At the same time, the emphasis is on maintaining the health of the nail plate. In the course of the work, practical recommendations will be developed to help reduce the risk of nail damage during preparation, wearing and removal of resistant coatings.

Materials and research methods

The study was based on open clinical and professional sources devoted to the anatomy and physiology of the nail apparatus, as well as the characteristics of the nail plate, such as thickness, growth rate and hydration level. In addition, recommendations on the safe removal of stubborn coatings, precautions when using UV and LED polymerization, and sanitary standards in the field of pedicure were considered.

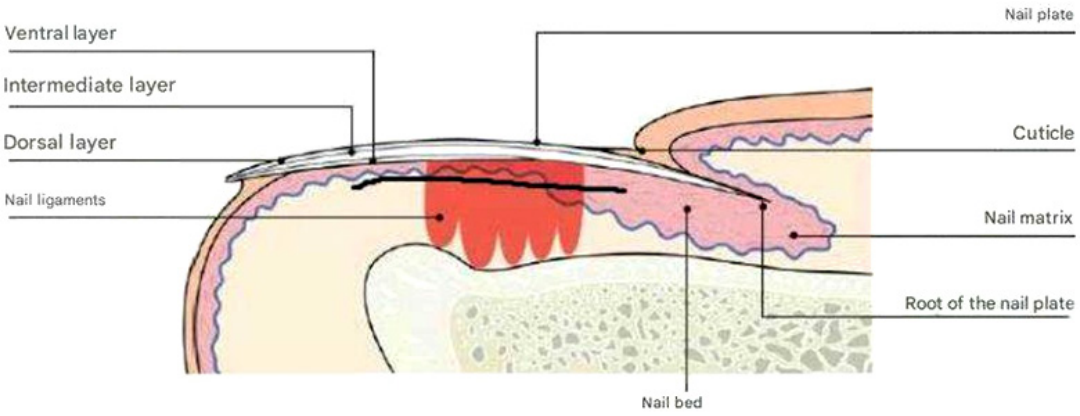
The methods of analytical review and comparative analysis are used in the work. We compared information about the structure and physiological features of nails with typical technological stages of manicure and pedicure. We also systematized risk factors and developed practical recommendations based on minimizing mechanical and chemical effects and compliance with sanitary standards.

The results of the study

The nail plate is a part of the nail apparatus, which includes not only the plate itself, but also the surrounding soft tissues: proximal and lateral nail rollers, the cuticle, matrix (growth zone), nail bed, hyponychia. The matrix is located under the proximal nail roller and is the main site of formation of the nail plate. The cells (onychocytes) formed from the keratinocytes of the matrix shift in the distal direction, creating a dense keratinized plate. In this case, a significant part of the material for the plate comes from the proximal part of the matrix (Anatomy, Shoulder and Upper Limb, Nails).

When assessing the condition of the nail plate, it is important to understand that damage to the matrix can lead to different consequences than changes that affect only the plate itself. The matrix is responsible for the quality of new growth, while the plate is the final product of keratinization and is not capable of regeneration like living tissue, but only grows during the renewal process.

Figure 1. *Anatomical structure of the nail apparatus (transverse section of the nail plate and adjacent structures) (Terminal Layer)*



From the point of view of morphology, the nail plate is described as a lamellar structure consisting of three tightly connected layers: dorsal, intermediate and ventral (see the figure 1).

It is known that the dorsal and intermediate layers are mainly formed from the matrix, while the ventral layer is formed by the so-called "sterile matrix" or nail bed. The formulations may differ from source to source, but the principle of the three-layered nail plate remains unchanged. This fact is of great practical importance for careful nail care. The "strength" of the nail plate is ensured not only by its thickness, but also by the integrity of the layers, as well as the connections between them. In addition, the contact state of the plate with the nail bed is important, which describes relief structures that increase the area of adhesion.

The physiological features of nails, which often serve as the basis for assessing their safety, include plate thickness and growth rate. Table 1 shows the average thickness of the nail plates, which differ for the nails of the hands and feet, as well as depending on gender.

Table 1. *The average thickness of the nail plate in men and women*

Indicator (average values)	Fingernails (mm)	Toenails (mm)
Nail thickness in women	0.5	1.38
Men's nail thickness	0.6	1.65

A source: (Common nail changes and disorders in older people:)

The growth rate of the nail plate is a quantity that can be measured. It directly affects how quickly nails "compensate" for damage by growing back. This leads to an important conclusion for manicure and pedicure masters: any aesthetic procedures that affect the appearance of the plate will "come off" the hands and feet at different speeds. Therefore, when assessing the condition of nails, for example, changes in shape, surface or color as they grow, it is necessary to take into account this difference in the rate of renewal.

Hydration is a key factor affecting the mechanical properties of the nail plate. Scientific reviews emphasize that the water in the nail is contained in two forms: bound and free. Its interaction with protein structures, including disulfide bonds, plays a significant role in hydration processes, differing from the skin. According to clinical data, the normal water content in the nail is about 18%. A decrease in this level can lead to increased brittleness, while its excess contributes to excessive flexibility. Therefore, when assessing the condition of nails, it is necessary to pay attention not only to their appearance, but also to the signs that reflect the balance of hydration and the integrity of the layered structure (Understanding the Formidable Nail Barrier:).

Aesthetic standards in the field of manicure and pedicure have evolved in parallel with the development of services and materials. From the desire for "neat and well-groomed nails", we came to the desire to get a lasting and flawless decorative effect. At the end of the 19th century, manicure was firmly established as a salon service. In the 1930s, the spread of colored lacquers became an important milestone in the development of very decorative nail design. And in the second half of the 20th century, standards increasingly began to focus on "constructed" aesthetics: elongation, reinforcement, preset shapes and a perfectly flat surface.

The widespread use of gel systems and other resistant coatings has contributed to the fact that wear duration and gloss durability have become perceived as important quality criteria. At the same time, the nail care market continues to grow, which leads to frequent trend changes. Social networks, in turn, contribute to the rapid spread of visual images and the consolidation of new norms through popular references and repetitive designs. As a result, modern standards represent several competing models, from an emphasis on naturalness to complex decorative solutions. These standards largely depend on technology, marketing, and visual culture.

The aesthetics of manicure and pedicure, based on the principle of preservation, suggests that the result of the procedure is assessed not only by its appearance immediately after its completion, but also by how the integrity of the nail plate and surrounding tissues is preserved after removing the coating and during repeated sessions. In the professional recommendations of dermatologists, it is noted that in everyday practice, the main risks to the nail are associated not so much with coating as with its aggressive removal (scraping, "peeling") and excessive mechanical processing. Therefore, safe protocols are aimed at minimizing traumatic effects and careful removal of material.

From an aesthetic point of view, a "beautiful" manicure and pedicure is, first, a properly organized process. It involves minimizing skin contact with acetone, avoiding forced removal of the coating and mandatory restoration of the barrier properties of the skin around the nail after the procedure. The American Academy of Dermatology (AAD), in its open recommendations for gel manicure, separately highlights the practice of removing the coating using cotton swabs soaked in acetone and fixing with foil. This minimizes the contact of acetone with the skin of the hands, leaving it mainly on the nails (Table 2). This approach is closely related to the principle of preservation: the less chemical and mechanical impact, the more likely it is to preserve the surface of the nail plate and the periarticular skin in a condition suitable for subsequent procedures without accumulation of damage.

Table 2. *Examples of approaches that put "aesthetics" into preservation mode*

Procedure component	Safety-oriented practice	Based on what
Removing the gel coating	Local acetone contact: cotton swab + foil fixation on fingertips	AAD recommendations for more gentle removal
Mechanical impact	Rejection of rough coating removal; removal after softening	AAD Recommendations for preventing nail injury during removal
After the procedure	Skin restoration (moisturizing and care) to reduce dryness and irritation	AAD recommendations for post-gel care

A source: (Gel manicures: Tips for healthy nails)

A separate area in the field of "gentle aesthetics" is related to the use of ultraviolet (UV) and LED lamps for polymerization of materials. There are different views in the professional community about the risks associated with these lamps. On the one hand, it is believed that exposure to UV lamps for nails usually does not pose a great risk to the client, although accurate measurements and consideration of real conditions are necessary to accurately understand this issue. On the other hand, more recent studies and discussions of risks emphasize that radiation doses, characteristics vary between lamps, and that taking reasonable photoprotection measures can further reduce potential negative effects. Rethinking aesthetic standards is important for two reasons. First, the "quality of service" includes informing the client about simple protective measures, such as the use of fingerless barrier gloves or photoprotection of the skin of the hands. Secondly, the reduction of unjustified exposure becomes the norm, that is, the rejection of "drying just in case", if this is not required by technology and the manufacturer's instructions.

The principle of safety in pedicure also implies the need to take into account possible infectious risks. This is because foot aesthetics often includes water treatments and the use of special equipment. Proper cleaning and disinfection significantly reduce the chance of infection. Here are the basic processing frequency requirements: disinfection in front of each customer, regular processing at the end of the working day, it is important to observe the "contact time" of the disinfectant indicated on

the label. It usually takes about 10 minutes, but it can vary depending on the specific remedy (Preventing Pedicure Foot Spa Infections).

The minimum organizational requirements that directly support "gentle aesthetics" in pedicure are presented in Table 3.

Table 3. *The main organizational aspects that directly affect the quality and aesthetics of a pedicure*

The security element	What should be done
The frequency of disinfection of baths	Between each meeting with clients and at the end of the working day
Contact time of the vehicle	Keep the time indicated on the label (usually about 10 minutes, but it depends on the product)
Risk justification	Cases of infections related to hot tubs for feet used in pedicure have been described. This highlights the importance of following the processing rules

A source: author's development

To preserve the health of the nail plate, it is necessary to avoid its mechanical and chemical damage, as well as to observe hygienic standards. Open dermatological sources emphasize that when using resistant coatings, the greatest damage to nails is caused not so much by their application as by aggressive removal. It is not necessary to peel off or peel off the gel coating, as this leads to the removal of the surface layers of the nail plate and its thinning. A more reasonable solution would be to pre-soften the material with acetone and apply it locally to the nail plate. For example, you can use cotton swabs and fix them, which will reduce the risk of damage to the skin around the nail and the plate itself.

After removing the coating, it is recommended to carry out restorative nail care to prevent their dryness and brittleness. According to research, regular moisturizing of the skin of the hands and cuticles helps to maintain protective properties and reduce the risk of nail plate delamination. It is also worth considering that prolonged contact with water can weaken the nails, so it is recommended to use protective gloves when doing household chores.

Table 3 provides practical recommendations for nail care, as well as their preventive value.

Table 3. *Practical measures to preserve the nail plate and their preventive value*

Stage	Risk	Correct practice	How to understand that everything is done correctly	Effect
Nail preparation	Thinning due to overuse	Minimize sanding, do not «remove the layer» unnecessarily	No burning /hypersensitivity, no furrows	Less brittleness and layering
Treatment of the skin around the nail	Microtrauma, inflammation	Without aggressive cutting, without tearing the skin	No bleeding, no severe redness	Preservation of the skin barrier
Applying the material	Skin irritation, detachment	Apply strictly to the plate, do not get on the skin	The material does not get into the rollers and cuticle	Less irritation and injury when removing
The sock of the cover	Coating failure and injury to the nail	Do not pry or tear when the nail is detached	Removal is only planned, without rough tearing of the nail	Preservation of the upper layers of the nail

Stage	Risk	Correct practice	How to understand that everything is done correctly	Effect
Removing the coating	Thinning during peeling / scraping	Remove after softening or correctly layer by layer	There are no «pits», torn areas, white traumatic spots	Less damage to the plate
Solvent contact	Dryness and irritation of the skin	Apply locally to the nail, limit skin contact	The skin is not overdried, without cracks	Comfortable recovery
Household loads	Nail stratification from water/chemicals, chips	Gloves when cleaning, do not use nails as a tool	Less chipping and layering	Reduction of mechanical/chemical stress
Pedicure and sanitation	Infection risks	Cleaning and disinfection of equipment according to the regulations	There is an observance of exposure time, clean surfaces	Prevention of complications
When to change the protocol	Accumulation of damage	Reduce the load, increase the intervals, review the technique	The symptoms decrease in several cycles	Prevention of chronic injury

A source: author's development

In the field of pedicure, one of the key principles is strict adherence to sanitary standards. In open sources provided the sanitary control authorities emphasize it emphasized that pedicure baths must be thoroughly cleaned and disinfected after each client. In addition, it is necessary to use disinfectants in accordance with the manufacturer's instructions, observing the recommended exposure time. These precautions are aimed at preventing infectious complications that may occur as a result of microtrauma of the skin of the feet and periarticular tissues.

Conclusions

The safety of the nail plate should be no less important criterion for the quality of manicure and pedicure than the aesthetic result. The nail plate, like any other part of our body, is not capable of regeneration. It is updated only during the growth process. Damage that occurs with improper care can accumulate and manifest as brittleness, delamination, and cracks. To avoid this, it is necessary to take into account the anatomy of the nail apparatus, especially the role of the matrix, as well as physiological parameters such as thickness, growth rate and hydration. It is also important to consider technological risk factors. Compliance with these principles makes it possible to create a "gentle aesthetic" in manicure and pedicure, in which the priority is gentle preparation and removal of coating, limiting excessive exposure to solvents and the rational organization of the polymerization process. In pedicure, the principle of safety is complemented by strict compliance with sanitary requirements for the treatment of equipment, which significantly reduces the risk of infectious complications.

Thus, rethinking aesthetic standards in terms of maintaining the integrity and safety of procedures significantly reduces the risk of negative consequences with frequent use of resistant coatings.

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Section 6. Aesthetic medicine

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COMPARATIVE ANALYSIS OF COLD ATMOSPHERIC PLASMA GENERATION PARAMETERS AND CHARACTERISTICS OF PLASMA DEVICES USED IN AESTHETIC MEDICINE

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Abstract

The article discusses the theoretical and practical aspects of the use of cold atmospheric plasma in aesthetic medicine. It presents the physical principles of creating cold atmospheric plasma, as well as reveals the features of its formation and key parameters that determine the properties of a plasma discharge. Plasma devices are classified according to several criteria: the type of discharge, the method of exposure, the design features and the environment in which they operate. Particular attention is paid to the parameters of plasma generation as an object for comparative evaluation. These parameters include spatial, gas dynamic, and energy characteristics. A comparative analysis of plasma devices has been performed in terms of their technical and operational properties, which are important for cosmetology practice. The practical significance of equipment parameters affecting the controllability of procedures, the accuracy of exposure and reproducibility of results is considered. The article discusses in detail the security issues related to the use of plasma technologies. Key problems have been identified and prospects for further development of this area have been outlined. It is concluded that in order to ensure the safety and increase the efficiency of plasma devices, it is necessary to standardize their parameters and improve control systems.

Keywords: *cold atmospheric plasma, aesthetic medicine, cosmetology, plasma devices, plasma generation parameters, plasma jet, dielectric barrier discharge, hardware cosmetology, comparative analysis, safety of plasma technologies*

Relevance of the study

In the field of aesthetic medicine, there is a growing interest in hardware techniques that provide a controlled and gentle effect on the skin. One of the promising directions is the use of cold atmospheric plasma. This

technology allows procedures to be carried out with minimal thermal damage and high processing accuracy.

Cold atmospheric plasma is a partially ionized gas that forms at atmospheric pressure and has a low temperature. This makes it an ideal tool for non-invasive and minimally invasive cosmetic procedures. The effectiveness and safety of such procedures largely depend on the parameters of plasma generation and the design of the devices used.

Many plasma devices on the market differ in principle of operation and technical characteristics. However, there is no single approach to comparing them, which makes it difficult for cosmetologists to choose the equipment and optimal operating modes.

Therefore, a comparative assessment of the parameters of cold atmospheric plasma generation and the characteristics of plasma devices is becoming an urgent task aimed at improving the effectiveness and safety of cosmetic procedures.

The purpose of the study

The purpose of this study is to compare the parameters of cold atmospheric plasma generation and the characteristics of plasma devices used in aesthetic medicine in terms of their usefulness in cosmetology.

Materials and research methods

The research examined scientific papers on plasma physics at atmospheric pressure, as well as the principles of operation of plasma devices and their use in aesthetic medicine. In addition, the technical characteristics of modern plasma devices were reviewed.

The following methods were used in the work: analysis and generalization of scientific literature on the research topic, comparative analysis of technical parameters of various plasma devices.

The results of the study

Cold atmospheric plasma is a partially ionized gas that is formed at atmospheric pressure because of an electric discharge. Unlike high-temperature plasma, it is characterized by a nonequilibrium state in which the energy of electrons significantly exceeds the energy of heavy particles. At the same time, the gas temperature remains low, usually below 40–50 °C, which makes it safe for use in aesthetic practice (Gerasimenko M. Yu., Zaitseva T. N., Evstigneeva I. S., 2019, p. 79).

The key feature of cold atmospheric plasma is the combination of active physical and chemical components. These include charged particles (electrons and ions), ultraviolet radiation, electric fields, and reactive oxygen and nitrogen species (RONS), which are formed because of the interaction of high-energy electrons with gas molecules. This combination of factors determines the functional properties of plasma and makes it especially attractive for hardware cosmetology (Batdyeva A. I., 2022).

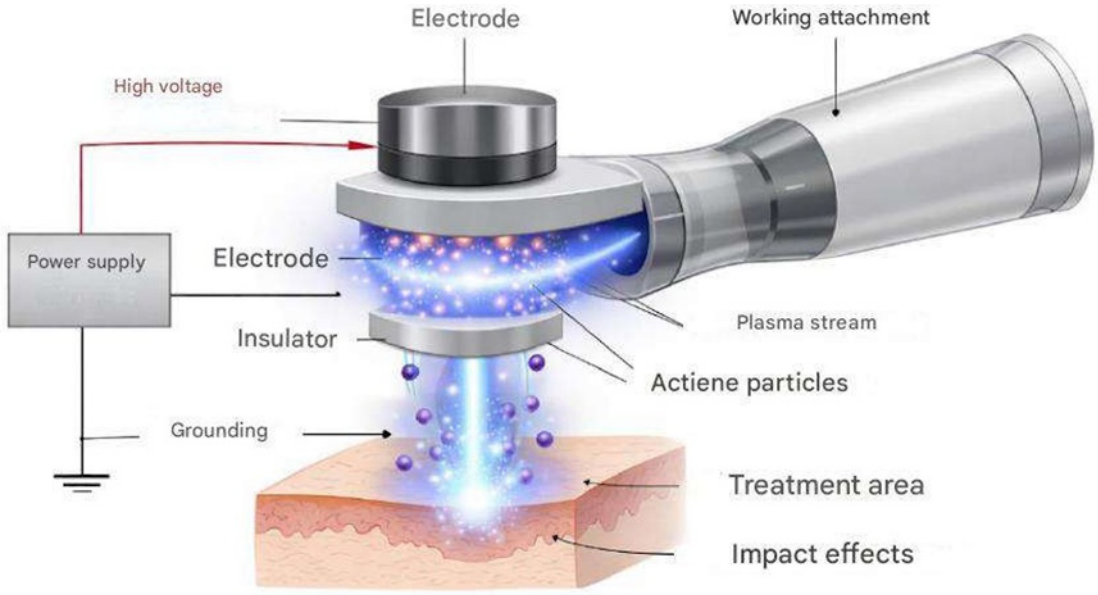
Plasma is formed in various ways in cosmetic devices. Plasma jets and dielectric barrier discharges (DBD) are the most popular. In the first case, plasma is created in a gas stream and supplied as a directed jet. In the second case, plasma is formed at the point of contact of the electrode with the treated surface. These two types of discharges are used in most modern plasma devices used in aesthetic medicine.

From a physical point of view, the plasma parameters depend on the characteristics of the electric discharge and the gaseous medium in which it occurs. The main parameters include voltage, frequency, power, electron density, and plasma temperature. For example, cold atmospheric plasma is characterized by an electron temperature at the level of fractions of an electron volt and a particle concentration reaching $10^{14} – 10^{17}$ m^{-3}. This indicates a high reactivity at a relatively low thermal load.

In scientific and applied practice, electrical and optical diagnostic methods are used to correctly describe and compare plasma processes. The electrical characteristic includes an analysis of voltage, current, and pulse shape, while the chemical characteristic includes an assessment of the composition of active particles using spectroscopy. These approaches are necessary to ensure reproducibility of the results and the ability to compare different devices.

To visually explain the principle of formation of cold atmospheric plasma in cosmetology devices, we propose to consider the scheme of plasma discharge occurrence and its penetration into the working area shown in the figure.

Figure 1. *Schematic diagram of cold atmospheric plasma generation in a cosmetology device (developed by the author)*



The classification of plasma devices used in aesthetic medicine is based on three main criteria: the physical principle underlying the generation of a discharge, the method of action on the treated surface, and the design features of the devices. There are several main types of cold atmospheric plasma sources in the scientific literature, which have become the basis for the creation of modern cosmetology devices (Table 1).

Table 1. *The main types of plasma devices and their characteristics*

Classification criteria	Device type	Brief description
Type of discharge	Plasma jet	Directed plasma flow, requires gas
	DBD-rank	Plasma generation between electrodes without gas
Method of exposure	Direct	Plasma is formed in the treatment area
	Indirect	Plasma is supplied through a stream or medium
Construction	Single-electrode	Simple layout, compact design
	Coaxial	Stable discharge, high controllability
	With a dielectric barrier	Current limitation, safety
Working environment	Inert gases	Stability and focus
	Atmospheric air	Easy operation

A source: author's development

When comparing plasma devices used in aesthetic medicine, special attention is paid to the characteristics that determine the spatial distribution of plasma and its interaction with the treated surface. These characteristics include length and shape of the plasma jet, diameter of the impact zone. Scientific studies show that the jet length can vary from a few millimeters to several centimeters, depending on the type of device, voltage and gas used. This, in turn, affects the accuracy and locality of processing.

Another important parameter is the distance from the plasma source to the treated surface. Experiments show that increasing this distance reduces the concentration of active particles and reduces the intensity of ex-

posure, while the minimum distance ensures maximum plasma flow density.

In practical application, this requires taking into account the geometry of the nozzle and the stability of the working tool position. One of the key parameters is the uniformity of the plasma discharge. Depending on the generation mode, the discharge can be diffuse or filamentous (filamentous). A diffuse discharge is characterized by a uniform distribution of plasma, while separate microchannels form a filament discharge. These characteristics directly affect the processing quality and reproducibility of the results, which becomes especially important when comparing different devices.

Another important parameter to consider when working with a plasma jet is the gas flow rate. It has been noted in scientific papers that changes in gas flow rate affect the jet length, discharge stability, and distribution of active particles. An increase in the flow velocity, as a rule, leads to an elongation of the jet and an improvement in its directivity; however, this may affect the plasma density (Shemshuk M. I., Korotkiy V. N., Serov D. N., 2018, p. 62).

For a more objective assessment of the efficiency of plasma jet devices, an energy density indicator is used, which demonstrates the amount of energy transferred per unit area. This parameter depends on the device's power, exposure time, and processing area, and allows you to compare different operating modes.

The comparison of plasma devices used in aesthetic medicine is based on an assessment of their technical, design and operational characteristics, which affect the controllability of the process and the stability of plasma generation. Scientific papers emphasize that the key factors determining the differences between devices are the type of plasma source, the gas medium used, the configuration of the electrodes and the power supply (Table 2).

Table 2. *Comparative characteristics of plasma devices*

Comparison criteria	Plasma jet	DBD devices
Controllability of impact	High (adjustable by nozzle and gas)	Average (depending on electrode position)
Length of the plasma region	Up to 30–40 mm	Limited by the discharge zone
Discharge stability	High when using gas	Depends on design
Energy consumption	From mW to tens of watts	Usually lower for localized discharge
Construction	More complex (gas, nozzle)	Simpler
The possibility of adjustment	Wide	Limited

A source: according to scientific research

The differences between them are due to a number of physical and technical characteristics. Controllability, stability of plasma generation, and the ability to fine-tune modes are especially important for cosmetology practice. This ensures the predictability of the result and the convenience of the specialist's work.

The practical value of plasma device parameters in aesthetic medicine is determined by their effect on the controllability of the procedure, reproducibility of the result, and comfort of the specialist. Specialized sources emphasize that the stability of the electrical characteristics and operating modes of the device ensures predictable effects, which is especially important when performing repetitive cosmetic procedures and standardizing protocols (Vorobyov K. P., Zinnurova A. B., Bakina O. V., Spirina L. V., Zhavoronok T. V., 2024, p. 359).

One of the most important aspects is the possibility of fine-tuning the operating modes of the plasma device. Modern models are equipped with power, frequency and pulse duration control systems, which allows them to be adapted to various tasks and conditions. Digital interfaces and pre-installed programs greatly simplify the choice of modes and reduce the likelihood of errors when using the equipment.

Ergonomics and the design of the working nozzles also play a key role. As noted in scientific and technical descriptions, the shape and size of the nozzle determine the accuracy of positioning and the convenience of performing procedures. Compact and weight-balanced devices significantly reduce the workload of a specialist and increase processing accuracy, especially when working with small areas.

The stability of the parameters during the procedure is crucial. In a number of studies, it has been found that fluctuations in voltage or power can negatively affect plasma characteristics, which in turn will affect the uniformity of exposure. Therefore, devices equipped with a parameter monitoring and stabilization system are considered preferable for practical use.

It is also worth noting the convenience of maintenance and operation. Devices that do not require complex preparation, replacement of gas cylinders or frequent calibration are becoming increasingly popular in cosmetology rooms. This makes it possible to significantly reduce the preparation time for procedures and increase overall work efficiency (Borkhunova E. N., Taganov A. V., 2017, p. 87).

The safety of using cold atmospheric plasma in aesthetic medicine depends on several factors: the physical characteristics of the discharge, the design of the equipment, and compliance with operating rules. Scientific publications emphasize that one of the most important aspects is the control of thermal effects. When set correctly, the plasma temperature should be close to the ambient temperature, which minimizes the risk of overheating of the treated surface.

Control of electrical characteristics plays a key role in ensuring process safety. Current limitation, the use of dielectric barriers and switching power modes help to prevent uncontrolled discharge transition. The technical descriptions note that modern devices are equipped with parameter stabilization systems and automatic shutdown when deviating from the set modes.

Maintaining distance and exposure time is also an important aspect. Experimental studies show that reducing the distance between the electrode and the surface leads to an increase in energy density, which requires precise control of the tool position. Increasing the exposure time, in turn, contributes to the accumulation of energy, so the parameters of the procedure must be strictly regulated.

It is also important to consider the electrical safety and grounding requirements of the equipment. The use of certified devices that comply with safety standards significantly reduces the risk of electric shock and ensures stable operation of the device. In addition, it is necessary to strictly follow the manufacturer's instructions and regularly check the technical condition of the equipment.

Despite the rapid development of plasma technologies in aesthetic medicine, a number of problems remain related to their practical application. The main problems and directions of plasma technology development are presented in Table 3.

Table 3. *The main problems and directions of development of plasma technologies*

Aspect	Existing problems	Development prospects
Parameter estimation	Differences in measurement techniques	Standardization of indicators
Reproducibility	Dependence on external conditions	Stabilization and control systems
Mode management	Limited setup	Intelligent control systems
Device design	Limited versatility	Miniaturization and ergonomics
Practical application	Lack of unified protocols	Development of application standards

A source: author's development

Further development of plasma technologies in the field of cosmetology is associated with the improvement of parameter control methods, standardization of characteristics

and modernization of device designs. These tasks will make the use of plasma equipment in aesthetic practice more efficient and reliable.

Conclusions

The study revealed that the parameters of cold atmospheric plasma generation and the design features of plasma devices significantly affect the controllability, stability and reproducibility of hardware procedures in aesthetic medicine. It is established that the type of discharge determines the differences between the devices, the medium used, the configuration of the electrodes and the power supply modes. This requires a comprehensive approach to their assessment.

The practical significance of the parameters lies in the possibility of fine-tuning the operating modes, which ensures ease of operation and increases the predictability of results in cosmetology practice. The safety of using plasma technologies is achieved by monitoring electrical and energy characteristics, observing the distance and time of exposure, as well as using certified equipment.

It has been revealed that the main obstacles to the development of plasma technologies in aesthetic medicine are the lack of uniform methods for assessing parameters and insufficient standardization of application protocols. The prospects for further progress are related to the introduction of monitoring and control systems, as well as standardization of characteristics and improvement of device designs. This, in turn, will improve the efficiency and reliability of using plasma technologies for aesthetic purposes.

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