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Green-Synthesized Colloidal Metal–B-Escin Bioconjugates for Nasal Delivery: A Hypothetical Prophylactic and Therapeutic Product Against SARS-CoV-2 Variants

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Abstract

The emergence of SARS-CoV-2 variants continues to challenge global healthcare systems, necessitating the exploration of innovative preventive modalities. This study proposes a novel nasal prophylactic approach that combines the antiviral properties of B-escin, a natural compound, with green synthesized gold and silver nanoparticles. B-escin, extracted from horse chestnut seeds, exhibits notable efficacy against coronaviruses, while nanoparticles provide enhanced features for targeted delivery and stability. Through integrated computational analyses, including molecular docking, molecular dynamics simulations, and quantum mechanical calculations, we evaluate the potential of this combined strategy against prevalent COVID-19 variants, such as Alpha, Beta, Gamma, Delta, and Omicron. Specifically designed for nasal administration, our investigation highlights the synergistic interactions between B-escin and nanoparticles, elucidating their collective impact on viral targets specific to each variant within the nasal mucosa. Computational results demonstrate increased antiviral activity and target specificity when combining B-escin with gold and silver nanoparticles, surpassing individual efficacy. Moreover, we explore the influence of nanoparticle characteristics, such as size, morphology, and surface functionalization, on the observed synergistic effects. These findings underscore the potential of a nasal prophylactic utilizing natural compounds and nanotechnology, offering a promising frontline defense against the diverse spectrum of SARS-CoV-2 variants. While these findings underscore the potential of a nasal prophylactic utilizing natural compounds and nanotechnology, this study is entirely computational, and experimental validation is necessary to confirm its real-world applicability.

Keywords: SARS-CoV-2, COVID-19, B-escin, Nanoparticles, Nasal delivery, Antiviral therapy, Computational modeling, Variant-specific targeting

Introduction

The ongoing global pandemic caused by SARS-CoV-2 has presented unprecedented challenges to healthcare systems worldwide. The rapid emergence of multiple variants, including Alpha, Beta, Gamma, Delta, and Omicron, has complicated efforts to control the virus's spread and severity. Although vaccines remain a cornerstone of prevention, the high mutation rate of the virus, combined with vaccine hesitancy and waning immunity, has underscored the need for complementary preventive strategies [1,2].

Among these strategies, nasal prophylactics have garnered significant interest due to their ability to directly target the primary site of viral entry and replication within the upper respiratory tract. Nasal delivery systems provide localized protection, minimizing systemic side effects and enhancing therapeutic efficiency [3].

B-escin, a natural compound derived from horse chestnut seeds, has shown promising antiviral properties against a variety of viruses, including coronaviruses. Its

ability to inhibit viral entry and replication, coupled with its biocompatibility, positions it as a compelling candidate for COVID-19 prophylaxis [4,5]. Additionally, nanotechnology has emerged as a transformative tool in the development of antiviral treatments. Gold and silver nanoparticles (NPs), with their tunable physical and chemical properties, have demonstrated potential for drug delivery, antiviral activity, and stability enhancement [6-15]. However, despite these promising attributes, the potential synergistic effects of combining B-escin with green synthesized nanoparticles (**Figure 1**) for SARS-CoV-2 prophylaxis remain largely unexplored. There is limited understanding of how nanoparticle functionalization influences B-escin's antiviral efficacy, its molecular interactions with viral targets, and its stability in a nasal formulation. This study aims to bridge this gap by employing computational approaches to evaluate the feasibility and effectiveness of a nanoparticle-B-escin combination as a nasal prophylactic against SARS-CoV-2 variants. The interaction between B-escin and nanoparticles, along with their collective impact on viral targets in the nasal mucosa, is a central focus of this investigation. By targeting the nasal mucosa, the proposed prophylactic could potentially serve as an early-line defense against SARS-CoV-2, complementing existing vaccination efforts and mitigating the spread of new variants. Its localized delivery may offer rapid antiviral action at the primary site of infection, reducing viral load and transmission risk. Furthermore, as a non-invasive, self-administered intervention, a nanoparticle-based nasal prophylactic could provide an accessible and convenient preventive measure, particularly in populations with low vaccine coverage or emerging variant threats. Its ease of use and potential for broad distribution make it a viable adjunct to current preventive strategies. Ultimately, this work provides a proof-of-concept for a nanoparticle-based nasal prophylactic (**Figure 2**), offering a promising frontline defense against the evolving spectrum of SARS-CoV-2 variants.

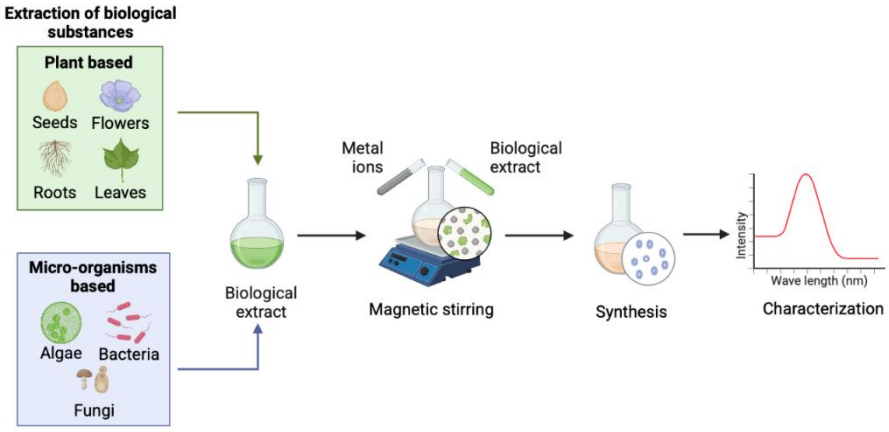

Figure 1 Methodology for the green synthesis of nanoparticles using biological extracts.

Figure 2 Conceptual framework of a nasal formulation incorporating nano-bioconjugates.

Materials and methods

Computational analyses

To evaluate the antiviral potential of the proposed combination treatment, computational approaches were employed to simulate interactions between B-escin, nanoparticles, and SARS-CoV-2 variants spike protein [16-30].

Molecular docking

Molecular docking was conducted to predict the binding affinity and orientation of B-escin within the active sites of SARS-CoV-2 spike protein. The docking was performed using AutoDock Vina, with protein structures obtained from the Protein Data Bank (PDB). The docking results were analyzed for binding energy, hydrogen bonding, and hydrophobic interactions.

Molecular dynamics simulations

MD simulations were performed using GROMACS to evaluate the stability and flexibility of the docked complexes. Systems were solvated in a TIP3P water model, neutralized with ions, and subjected to energy minimization and equilibration under physiological conditions (300 K, 1 atm). Trajectory analysis included root-mean-square deviation (RMSD), root-mean-square fluctuation (RMSF), and interaction energy.

Quantum mechanical calculations

The interaction energy and electronic properties of B-escin with nanoparticles were further analyzed using density functional theory (DFT) in the Gaussian software package. Parameters such as binding energy, charge distribution, and molecular orbitals were assessed to understand the synergistic effects at the molecular level.

Nanoparticle synthesis and modeling

Gold and silver nanoparticles were selected for their antiviral properties, biocompatibility, and ease of functionalization. The following parameters were considered for nanoparticle characterization:

Nanoparticle size and morphology

Particle size (10 - 50 nm) was optimized for nasal delivery to ensure deep penetration into the nasal mucosa without systemic absorption. Spherical morphology was chosen due to its stability and higher surface area-to-volume ratio.

Surface functionalization

B-escin was conjugated to the nanoparticle surface through thiol or amine linkages to enhance stability and ensure targeted delivery. Surface charge and hydrophilicity were optimized to prevent aggregation and promote mucosal adhesion.

Synergistic interaction evaluation

The combined antiviral activity of B-escin and nanoparticles was assessed in silico using interaction energy and docking scores. Simulations included comparative analysis of B-escin-nanoparticle complexes versus standalone treatments, and variant-specific docking simulations against Alpha, Beta, Gamma, Delta, and Omicron with spike proteins.

Hypothetical experimental validation

Though this study focuses on computational approaches, the proposed methodology can be validated through:

In vitro studies

Testing B-escin-nanoparticle formulations against SARS-CoV-2 pseudovirus in nasal epithelial cell cultures.

Ex vivo models

Assessing mucosal adhesion and antiviral activity in human nasal tissue models.

In vivo studies

Evaluating safety and efficacy in animal models infected with SARS-CoV-2 variants.

Results and discussion

Molecular docking revealed strong binding affinities of B-escin to key SARS-CoV-2 spike protein targets and computational simulations demonstrated that the B-escin-nanoparticle treatment-maintained efficacy across multiple SARS-CoV-2 variants (**Figures 3 - 7**), as detailed in our previously published work [31]. Molecular dynamics (MD) simulations and quantum

mechanical calculations provided valuable insights into the B-escin-nanoparticle complexes, where they confirmed the stability of both the B-escin-protein and B-escin-nanoparticle complexes. Key findings included: Minimal structural fluctuations, as indicated by average root-mean-square deviation (RMSD) values; reduced flexibility in binding site residues, particularly in the spike protein receptor-binding domain (RBD), suggesting a stabilizing effect from the nanoparticle conjugates; and enhanced interaction energies, demonstrating stronger and more stable binding. Quantum mechanical analysis using density functional theory (DFT) further revealed the synergistic effects of the B-escin-nanoparticle complexes. Both nanoparticles showed stronger binding energies with B-escin, surpassing the standalone binding energy of B-escin to viral proteins. Additionally, the conjugation of B-escin to nanoparticles led to enhanced charge redistribution, optimizing electrostatic interactions with viral targets. Frontier molecular orbital analysis highlighted increased electron density near the conjugation sites, correlating with improved reactivity and antiviral activity.

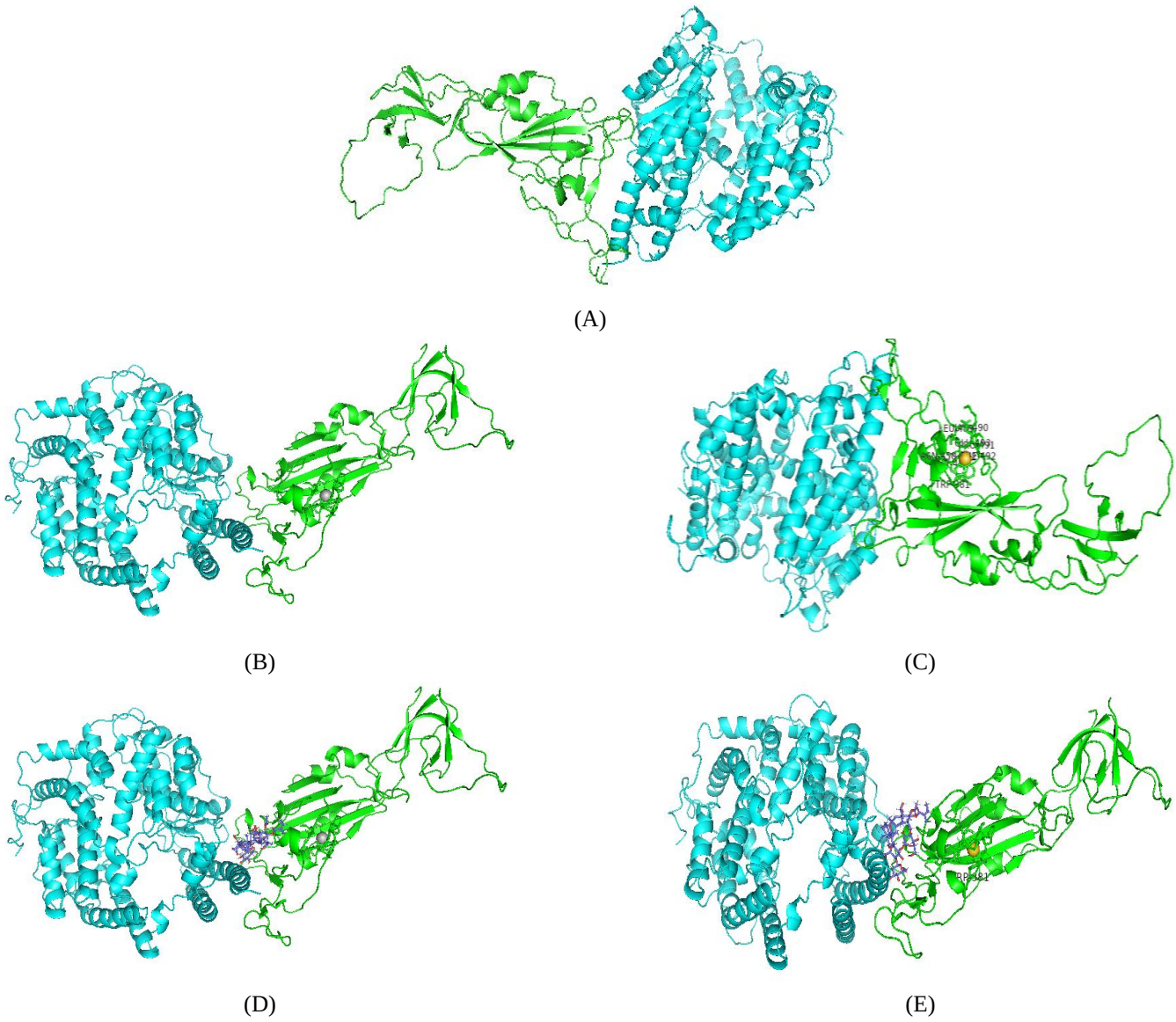

Figure 3 The 3D structure of ACE2-Spike Alpha variant complex docked using HDOCK where ACE2 is shown in cyan and Spike Alpha variant is shown in green (A), 3D structures of silver NP docked in ACE2-Spike Alpha variant (B), 3D structure of gold NP docked in ACE2-Spike Alpha variant (C), 3D structure of ACE2-Spike Alpha variant complex showing the synergetic binding of silver NP and B-escin (D) and gold NPs and B-escin (E).

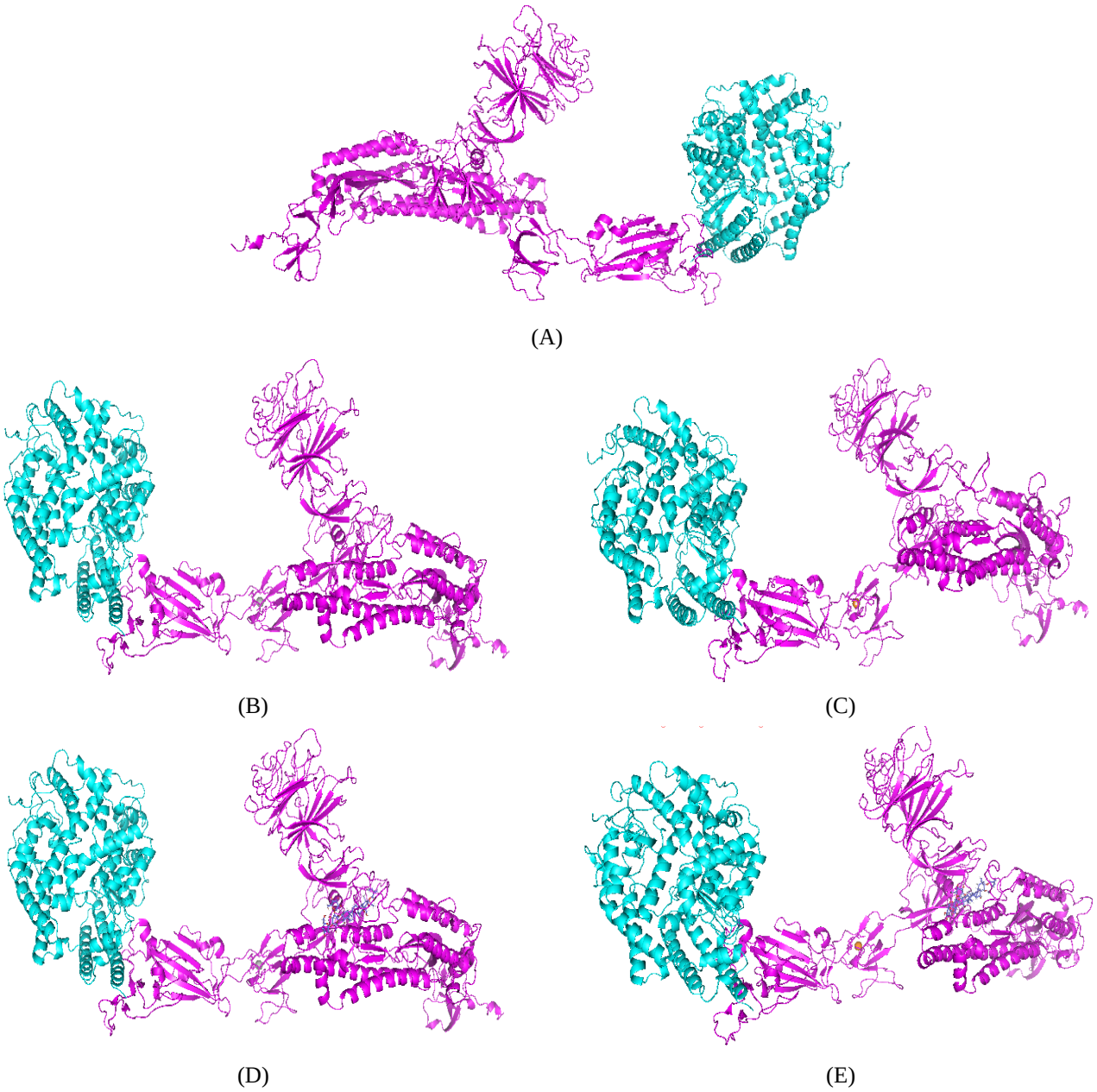

Figure 4 The 3D structure of ACE2-Spike Beta variant complex docked using HDOCK where ACE2 is shown in cyan and Spike Beta variant is shown in magenta (A), 3D structures of silver NP docked in ACE2-Spike Beta variant (B), 3D structure of gold NP docked in ACE2-Spike Beta variant (C), 3D structure of ACE2-Spike Beta variant complex showing the synergetic binding of silver NP and B-escin (D) and gold NPs and B-escin (E).

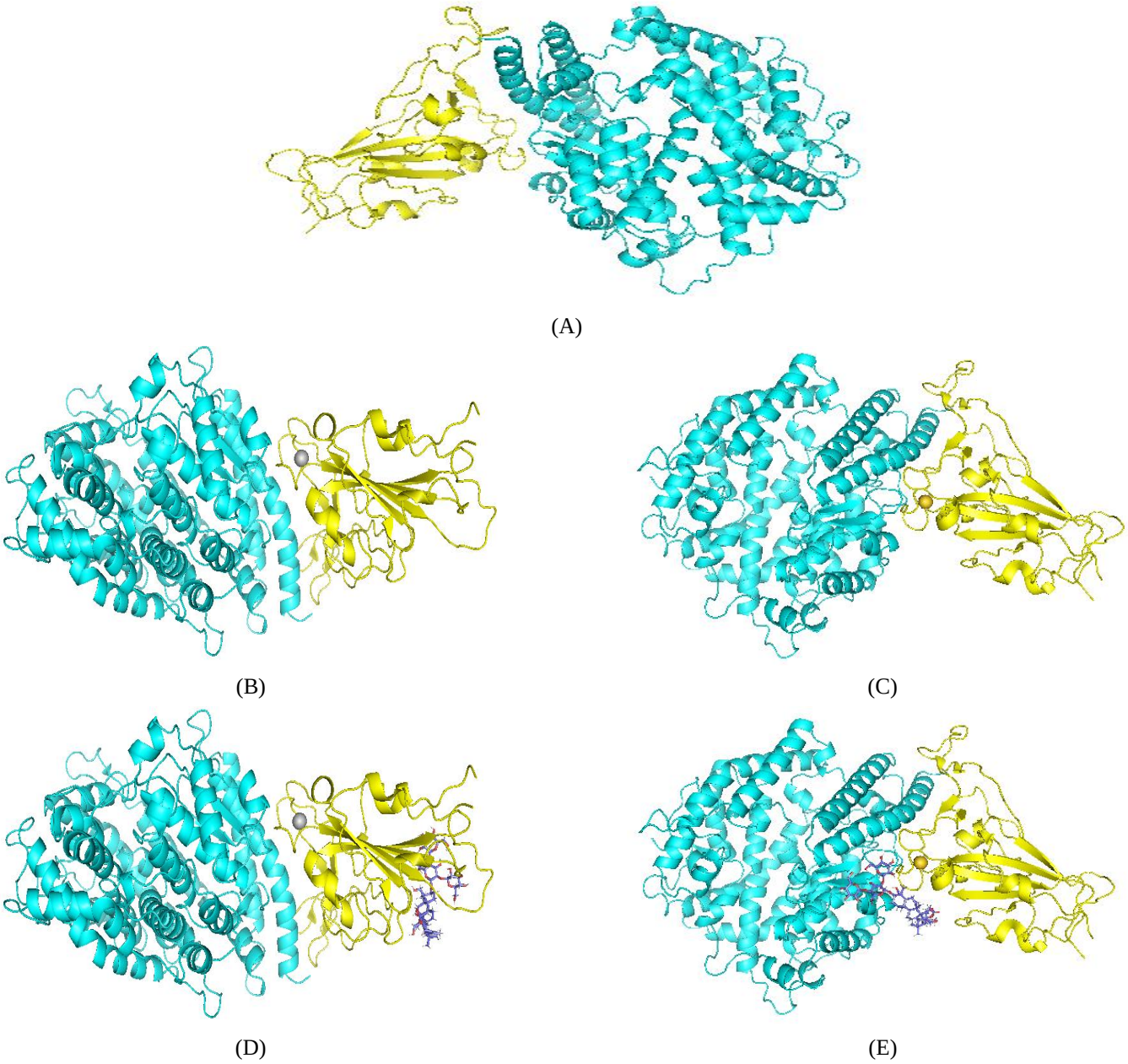

Figure 5 The 3D structure of ACE2-Spike Delta variant complex docked using HDOCK where ACE2 is shown in cyan and Spike Delta variant is shown in yellow (A), 3D structures of silver NP docked in ACE2-Spike Delta variant (B), 3D structure of gold NP docked in ACE2-Spike Delta variant (C), 3D structure of ACE2-Spike Delta variant complex showing the synergetic binding of silver NP and B-escin (D) and gold NPs and B-escin (E).

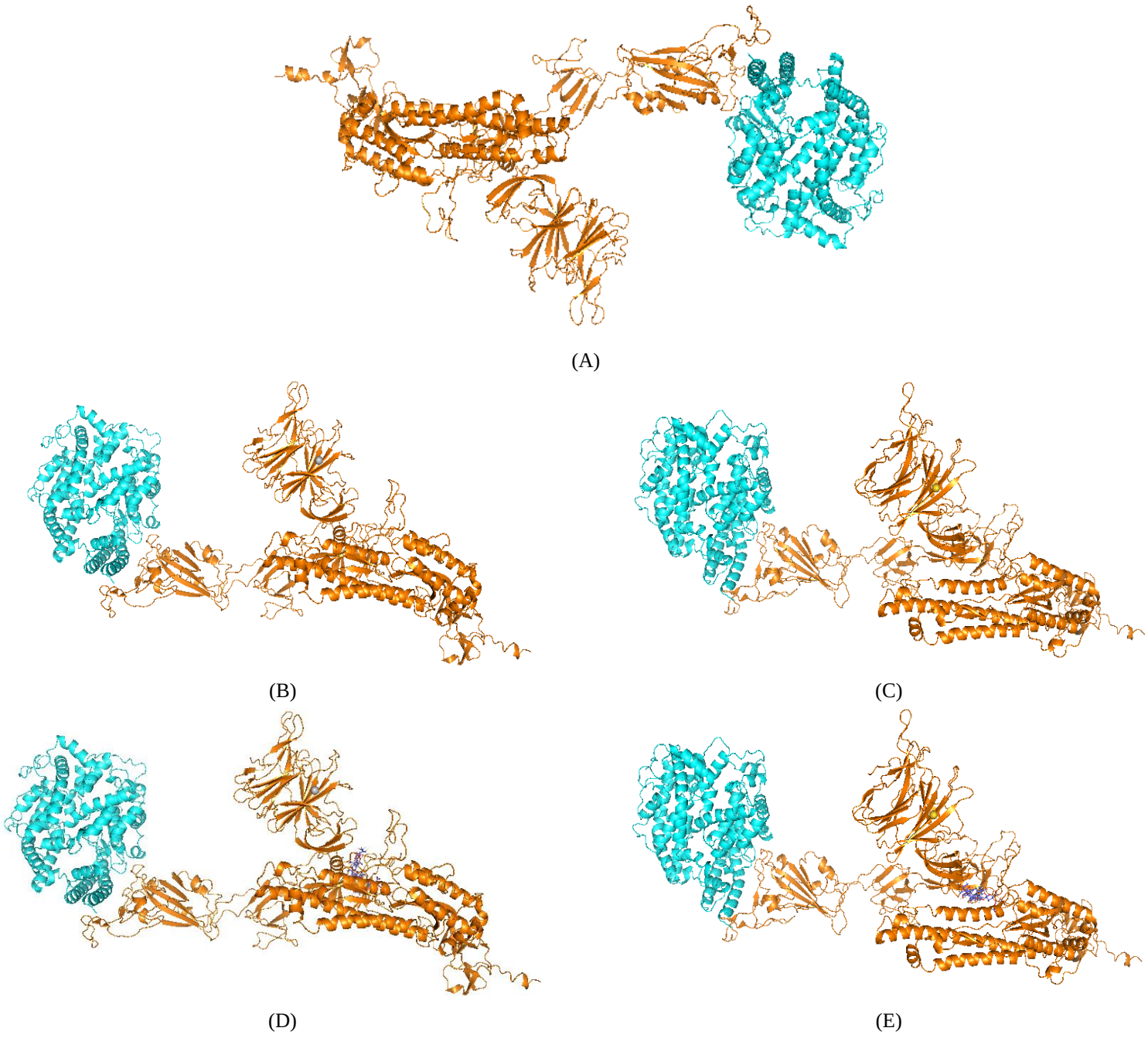

Figure 6 The 3D structure of ACE2-Spike Omicron variant complex docked using HDOCK where ACE2 is shown in cyan and Spike Omicron variant is shown in orange (A), 3D structures of silver NP docked in ACE2-Spike Omicron variant (B), 3D structure of gold NP docked in ACE2-Spike Omicron variant (C), 3D structure of ACE2-Spike Omicron variant complex showing the synergetic binding of silver NP and B-escin (D) and gold NPs and B-escin (E).

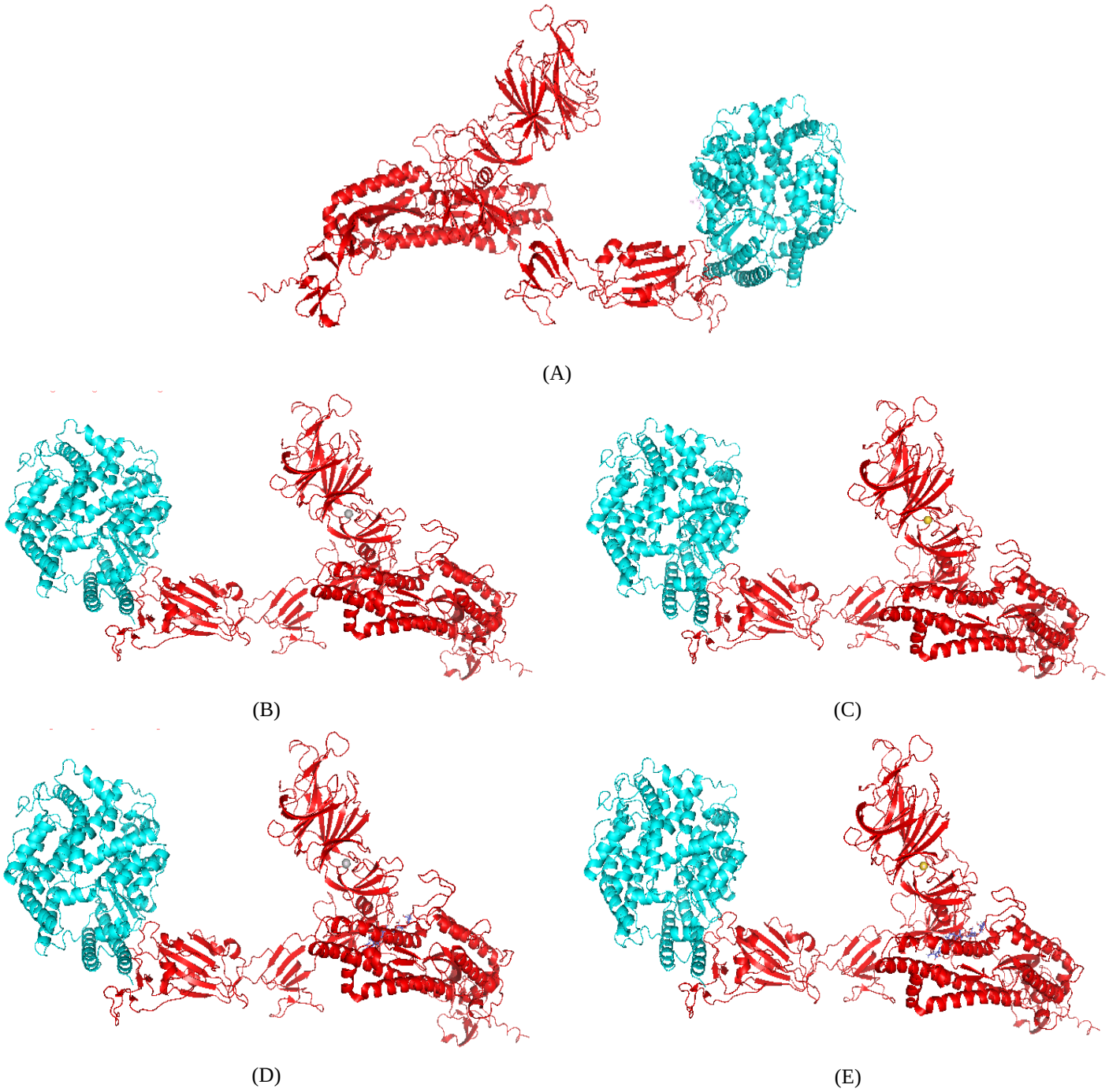

Figure 7 The 3D structure of ACE2-Spike Gamma variant complex docked using HDOCK where ACE2 is shown in cyan and Spike Gamma variant is shown in red (A), 3D structures of silver NP docked in ACE2-Spike Gamma variant (B), 3D structure of gold NP docked in ACE2-Spike Gamma variant (C), 3D structure of ACE2-Spike Gamma variant complex showing the synergetic binding of silver NP and B-escin (D) and gold NPs and B-escin (E).

The findings from this study underscore the potential of a nasal treatment combining B-escin and nanoparticles in combating SARS-CoV-2 variants. The computational analyses demonstrated that this combination exhibits superior binding affinity and stability compared to B-escin alone [32-34]. These results highlight the advantages of incorporating nanoparticles for targeted delivery and enhanced antiviral activity [35,36].

The molecular docking and molecular dynamics simulations reveal that B-escin-nanoparticle complexes exhibit stronger interactions with SARS-CoV-2 spike

protein [34,37]. The significant improvement in binding energy and stability is attributed to the high surface area and tunable properties of nanoparticles, which enhance the molecular interactions at the viral interface.

The prophylactic effectiveness across multiple SARS-CoV-2 variants, particularly Alpha, Beta, Gamma, Delta, and Omicron, suggests that it could serve as a robust therapeutic option in the face of ongoing viral evolution [37,38]. While a slight increase in binding efficacy was observed with the highly mutated Omicron variant, the combination therapy still outperformed B-escin alone, indicating its adaptability, that could be due to significant mutations in the receptor-binding domain of the Omicron spike protein, which may alter the structure and charge distribution, thereby affecting the interaction with B-escin-NPs.

The size, morphology, and surface functionalization of nanoparticles play critical roles in optimizing the treatment. Smaller nanoparticles demonstrated better mucosal penetration and interaction energies, while spherical shapes provided enhanced stability. Functionalization with thiol or amine groups ensured stronger conjugation with B-escin, preventing aggregation and improving mucosal adhesion [2,5].

The results of this study pave the way for experimental validation and eventual clinical application. Nasal delivery systems are particularly advantageous for treating respiratory infections due to their localized action, ease of administration, and minimal systemic side effects [1]. By targeting the nasal mucosa, this treatment could potentially prevent viral entry and replication at an early stage of infection.

While computational approaches provide valuable insights, experimental validation is essential to confirm these findings. Future studies should focus on developing scalable synthesis protocols for B-escin-functionalized nanoparticles, conducting *in vitro* and *in vivo* studies to evaluate antiviral efficacy and safety, and investigating the long-term stability and storage conditions of the nasal formulation. While also nanoparticles offer promising advantages for antiviral applications, their potential toxicity, particularly when used in nasal formulations, must be carefully considered. Nanoparticles can interact with biological tissues in ways that may cause adverse effects, such as irritation or damage to the nasal mucosa. Factors such as particle size, surface charge, and surface functionalization play critical roles in determining biocompatibility. To mitigate these risks, the design of nanoparticles should prioritize biocompatibility, with considerations for size optimization to ensure efficient clearance via the mucociliary system and the use of surface coatings that enhance safety. Additionally, comprehensive toxicological assessments are essential to evaluate the long-term impact of nanoparticle exposure on the nasal mucosa and overall health.

In a broader context, this approach has the potential to address significant global health challenges, particularly in regions with limited access to vaccines or other preventive measures. A nanoparticle-biomolecule-based nasal prophylactic could provide an accessible, non-invasive, and cost-effective solution, complementing existing vaccination strategies and reducing transmission in underserved populations. By offering a rapid and localized antiviral action, such a prophylactic could help mitigate the spread of SARS-CoV-2 and its variants, particularly in areas where vaccine distribution is constrained or uptake is low, ultimately contributing to global efforts to control the pandemic.

Conclusions

This study demonstrates the potential of a novel nasal treatment combining B-escin, a natural compound, and nanoparticles to address the challenges posed by SARS-CoV-2 variants. Our computational analyses revealed enhanced antiviral activity and variant-specific efficacy, highlighting the synergistic interactions between B-escin and nanoparticles, which could potentially offer a more targeted approach against the evolving landscape of SARS-CoV-2. These findings provide a strong rationale for the further development and experimental validation of this approach, with the possibility of creating a new prophylactic strategy to complement existing vaccination efforts. Furthermore, while this study is focused on SARS-CoV-2, the approach holds potential for broader applications against other coronaviruses and possibly even a wide range of respiratory viruses. Given the similarities in viral entry mechanisms, the combination of B-escin and nanoparticles may offer a versatile platform for targeting multiple viral pathogens.

The results underscore the promising role of nanotechnology in improving the delivery and

effectiveness of antiviral compounds, particularly in high-risk populations or regions with limited access to vaccines. However, it is important to note that while computational models offer valuable insights, experimental validation is crucial to confirm the findings and evaluate the safety and efficacy of this treatment *in vivo*. Future studies should focus on optimizing nanoparticle design, evaluating long-term safety profiles, and conducting clinical trials to assess the therapeutic potential of this approach. Additionally, expanding the scope to include other viral variants and exploring combinations with other antiviral agents may further enhance the treatment's effectiveness. Ultimately, this work contributes to the growing body of research on nanotechnology-based solutions for COVID-19 and provides a foundation for the development of effective, accessible, and scalable treatments for global use.

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