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Computational interpretation of biochemical characteristics of hyaluronic acid (HA) as essential skin-care ingredient and exploring its molecular-level explanations and predictions: perspective

Abstract

Human skin, the largest organ of the body, exhibits a wide variety of types-oily, dry, combination, sensitive, and normal having each a distinct physiological and biochemical characteristics. Improving skin health requires individualized protection strategies that align with specific skin types, barrier functions, and environmental exposures. Among the growing concerns in dermatological sciences, climate change has emerged as a significant threat for keeping skin healthier. Rise in temperatures, UV radiation, pollution, and humidity fluctuations are key concerns which contributes in maximum trans epidermal skin water loss, oxidative stress, premature aging, and inflammation, disproportionately affecting especially sensitive and dry skin types. Recent dermatological studies revealed how nurturing the skin deeper with using skin-care ingredients by awaking ourselves to understand how active dermal ingredient like hyaluronic acid (HA) interact with skin at the molecular level. However, their topical bioavailability and molecular interactions with skin receptors and enzymes vary significantly, necessitating computational modeling to predict efficacy. To elucidate these interactions, molecular docking studies have been conducted targeting skin-associated proteins such as CD44 (the primary receptor for HA). Docking simulations revealed strong binding affinities between HA and CD44 domains, affirming HA's skin-adhesive and moisture-retaining properties. Hence, protecting the skin amidst environmental stressors requires a personalized, science-backed approach, incorporating both preventive (e.g., UV shields, barrier creams) and active like Hyaluronic acid (HA) and vitamin, Vitamin E based strategies. Climate-resilient skincare formulations are needed to get prepared by molecular docking and biochemical interpretations to offer promising personalized skin-care regime and skin-therapeutic tools.

Keywords: hyaluronic acid, vitamin C, cosmeceutical approach, autodoc, ligplot+ diagram

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Kirti Rani, Krittika Ghatak
Amity Institute of Biotechnology, Amity University, India

Correspondence: Dr. Kirti Rani, Associate Professor, Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida, Sec-125, Gautam Buddha Nagar, Noida-201313 (UP), India, Tel +91-9990329492

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Introduction

The human skin is an intricate and multifunctional organ that serves as our first line of defense against the external environment.[1,2] Far from being a uniform surface, skin is classified into different types- namely oily, dry, sensitive, combination, and normal-each possessing distinct physiological characteristics, lipid composition, hydration levels, and response to external stimuli. These variations influence how skin interacts with both environmental aggressors and topical treatments. In recent years, the growing threat of climate change has added a new dimension to dermatological concerns. Rising global temperatures, intensified ultraviolet (UV) radiation, increased levels of air pollution, and fluctuating humidity are not just environmental issues they directly disrupt skin homeostasis. These changes accelerate trans epidermal water loss, promote the generation of reactive oxygen species (ROS), impair the skin barrier, and trigger premature aging and inflammatory responses, particularly in individuals with dry or sensitive skin. In this shifting environmental landscape, safeguarding skin health demands an evidence-based, personalized approach that addresses the unique needs of each skin type. Emerging research highlights the importance of integrating bioactive compounds such as hyaluronic acid (HA) and vitamin C (ascorbic acid) into dermal care routines. HA, a naturally occurring glycosaminoglycan found abundantly in the skin's extracellular matrix, is revered for its ability to bind up to 1,000 times its weight in water. This makes it an indispensable agent for hydration, elasticity, and barrier repair. Vitamin C, on the other hand, is a potent antioxidant and a co-factor in collagen synthesis, helping neutralize ROS, lighten hyperpigmentation, and maintain skin firmness. However, their efficacy depends not just on their topical presence but also on how effectively they interact with skin-specific receptors and enzymes at the molecular level. To investigate these interactions in depth, researchers have turned to molecular docking, a computational method used to predict the binding affinity and stability of molecular interactions. Docking studies have demonstrated high-affinity binding between hyaluronic acid and the CD44 receptor, a major HA-binding protein involved in skin hydration, wound healing, and cell adhesion. Similarly, vitamin C exhibits stable interactions with prolyl hydroxylase and other enzymes critical for collagen stabilization and tissue regeneration. These in silico results correlate with in vivo and in vitro observations, confirming the mechanisms behind their skin-benefiting properties. Furthermore, combined docking simulations suggest a synergistic effect when HA and vitamin C are co-applied, enhancing not only dermal penetration but also bioavailability and antioxidant response. As climate extremes increasingly impact skin health, the integration of advanced computational tools with biochemical research opens the door to climate-adaptive skincare strategies. Such approaches go beyond conventional moisturization or sunscreen use-they involve targeted, molecule-specific interventions tailored to an individual's skin type and environmental exposure. By grounding product development in molecular docking insights and

receptor-ligand dynamics, researchers and formulators can design more effective, science-driven treatments that strengthen the skin's defense mechanisms, support regeneration, and promote long-term resilience. In conclusion, the convergence of skin type biology, environmental science, and molecular pharmacology offers a powerful pathway to revolutionize how we protect and optimize skin health in a rapidly changing world.

Previous explored data for studying skin benefits of hyaluronic acid (ha) and vitamin c (ascorbic acid)

Skin is well reported dynamic biological shield to defend the body against pathogens, harmful UV radiation, mechanical injuries, and chemical exposures also including its intricate network to maintain moisture levels and enabling sensory perception. Skin thickness: three-tiered architecture is reported not to have uniform throughout the body based on the density and composition of the epidermis (Outer Defense Line) and dermis (Functional Core) including stratum lucidum on palms and soles as extra protective layer. Well documented fact belongs to beneath the dermis where hypodermis or subcutaneous fascia lies, a layer rich in adipose tissue, blood vessels, and sensory receptors that serves as the body's natural insulator and shock absorber.[1-6] Barrier function and defence mechanics is reinforced by two main components named, 1) cell envelope that composed of cross-linked structural proteins like filaggrin, desmoplakin, and cystatin, it forms an insoluble layer along the inner surface of the plasma membrane and 2) Lipid envelope: A hydrophobic outer coating that prevents water evaporation and blocks external irritants.[7-12] Complexity of skin has been explored that one square inch of skin contains of about 19 million cells, 1,000 nerve endings, 60,000 melanocytes, and 20 blood vessels that highlight the skin's dense cellular environment to serve as a most vital sensory and protective organ of body.[13-17] Hence, hyaluronic Acid (HA) is hyaluronan found to be present in the Human Body: a multifunctional biomolecule, glycosaminoglycan (non-sulfated glycosaminoglycan composed of repeating disaccharide units of D-glucuronic acid and N-acetyl-D-glucosamine) considered an essential for maintaining tissue hydration and structural integrity throughout the body. Skin is found to contain highest concentration of about 50% HA as body's total HA stores to retain moisture, enhance plumpness, and preserve skin elasticity. Apart this, HA is found abundantly in joints (within synovial fluid for lubrication and shock absorption), the vitreous humor of the eye (where it maintains shape and offers cushioning), articular cartilage, oral tissues, and umbilical cord Wharton's jelly including.[18-22] HA is well known to report for maintaining hydration within deeper layers with Stratum granulosum (stratum granulosum located between the stratum spinosum and stratum corneum that composed of granular keratinocytes that contain keratohyalin and lamellar granules) that prevents water from escaping the skin's surface. Comparative Insights of HA: An Alternatives to Hyaluronic Acid: While HA is highly effective in hydration and repair, several alternative agents have been studied for similar benefits, especially in formulations aimed at sensitive or acne-prone skin. Other compounds have key similarity with hyaluronic acid are Lactic acid, Aloe vera, Beta-glucan, D-Panthenol (Pro-Vitamin B5), Lactobionic acid and Gluconolactone.[20-25]

Computational intervene to exploit these biochemical findings in exploring their virtual prospects

Hence, molecular docking is a key computational tool in bioinformatics, structural biology, and pharmaceutical research to explore virtually the effective binding affinity of targeted biomolecules via determining intermolecular interactions and visualizing specific binding sites. These are considered essential a virtual screening method for drug designing, biomolecular pathway analysis, and understanding molecular recognition to save time and resources before moving to experimental validation. In this computational study design, the docking study was proposed to focus on the interaction between hyaluronic acid (HA), a naturally occurring polysaccharide known for its role in skin hydration, tissue repair, and cell signaling, and CD44, a transmembrane glycoprotein widely recognized as the principal receptor for HA. CD44-HA interactions are found to have integral role in many physiological and pathological processes, including wound healing, inflammation, and particularly cancer metastasis. By simulating this interaction through docking, insights into binding specificity, affinity, and conformational compatibility were obtained, which are crucial for understanding how these molecules interact at a molecular level and for designing therapeutic inhibitors or enhancers. To conduct this docking simulation, the structure of target protein, CD44 was obtained from the RCSB Protein Data Bank (PDB ID: 1UUH) and prepared in UCSF ChimeraX (v1.11) by removing crystallographic water molecules and irrelevant heteroatoms, followed by addition of hydrogens, charge assignment, and energy minimization to relieve local geometrical strain prior to docking.

The ligand, hyaluronic acid, being a highly polymeric and flexible molecule, was simplified into a smaller tetrasaccharide unit to make it computationally tractable. Oligosaccharide ligands, including hyaluronic acid fragments (HA4), was constructed and geometry-optimized using the GLYCAM-Web platform. Subsequent docking simulations were performed using molegro Virtual Docker (v7.0) and, for each protein–HA oligomer-protein complex, five independent docking poses were generated. Binding affinities were systematically evaluated using MolDock score, Rerank score, and hydrogen-bond energy to assess the stability and quality of the interactions (Table 1).

Table 1 Docking scores of HA4 with CD44.Five docking poses were generated per protein using Molegro virtual docker. MolDock score, Rerank score, and hydrogen-bonding energy are reported; more negative values indicate stronger predicted binding

Oligomer	Pose No.	MolDock score	Rerank score	HBond
HA4	1	-68.4534	-17.7348	-14.1851
	2	-66.2072	143.417	-18.3751
	3	-61.9145	31.106	-11.5642
	4	-50.1933	315.623	-7.63161
	5	-45.5258	445.274	-10.3317

As summarized in Table 1, the docking analysis revealed favourable binding interactions between the hyaluronan tetramer (HA4) and the receptor CD44. Across the five generated docking poses, the top-ranked conformations exhibited negative MolDock scores, indicating energetically favourable binding within the hyaluronan-binding groove of CD44. The best-scoring pose demonstrated a MolDock score of −68.45, accompanied by a hydrogen-bond contribution of −14.19, suggesting stable ligand engagement and significant polar interactions within the binding pocket. Subsequent poses showed a gradual reduction in binding favourability, with MolDock scores ranging from −66.21 to −45.53. Although the MolDock scores remained negative, indicating retained binding interactions, the corresponding Rerank scores increased substantially in the lower-ranked poses, reflecting reduced stability and less optimal ligand orientations within the binding groove. Hydrogen-bond contributions were observed across

all poses (−18.38 to −7.63), further supporting the role of hydrogen bonding in stabilizing the HA4–CD44 complex. Collectively, these results indicate that HA4 is capable of forming stable interactions with CD44, with the highest-ranked poses demonstrating the most energetically favourable binding conformations within the receptor's hyaluronan-recognition site.

The docking process and optimization behaviour are further illustrated through the energy convergence plot presented which depicts the stabilization of binding energy across docking iterations. The docking energy convergence plot (Figure 4) demonstrated rapid optimization during the early stages of the search, as indicated by the steep decline in the best pose energy. As the iterations progressed, both the best pose energy and the mean population energy gradually stabilized, suggesting convergence of the docking algorithm and identification of a stable binding conformation between the ligand HA4 and the receptor CD44. The best energy is lower than the mean energy because it represents the most energetically favorable binding pose identified during the docking process, whereas the mean energy reflects the average energy of all candidate poses within the population, many of which are less optimal.

By this docking simulation, the open-source software AutoDock (Molegro Virtual Docker) was used which is one of the most reliable tools for predicting protein-ligand interactions. Additionally, UCSF Chimera, a powerful visualization and editing platform, was used for molecular preparation, file format conversions, and post-docking visualization. The docking process began with ligand and receptor preparation. The protein receptor CD44 was retrieved from the Protein Data Bank (PDB) and pre-processed in Chimera. This preprocessing involved removing water molecules, which could interfere with docking, adding hydrogen atoms, and assigning Gasteiger charges to ensure appropriate electrostatics for interaction. The final receptor structure was saved in .pdb format and then converted to. pdbqt format using Molegro Virtual Docker, which is required for docking.26 The ligand, hyaluronic acid, being a highly polymeric and flexible molecule, was simplified into a smaller tetrasaccharide unit to make it computationally tractable. The structure was initially obtained in .sdf format, often from PubChem, and then converted to .pdb format using Open Babel or Chimera. Hydrogen atoms were added, charges assigned, and finally, the structure was converted to. pdbqt format in AutoDockTools; Molegro Virtual Docker (Figure 1). These preparatory steps ensured that both the receptor and ligand are ready for accurate docking simulations, the grid box was defined using AutoDockTools. The grid is a three-dimensional space surrounding the active site of the receptor, allowing the ligand to explore potential binding poses (Figure 2-4). For CD44, the grid box was placed over the Link module, the canonical hyaluronan-binding domain. This ensures the ligand searches within a biologically relevant region. A Grid Parameter File (GPF) was generated to define grid dimensions and spacing, and a Docking Parameter File (DPF) was created to configure docking algorithm parameters like the number of genetic algorithms runs, energy evaluations, and torsional degrees of freedom.[27] The actual docking was also performed using the Command Prompt (CMD) interface in previous reported data which allowed precise control over docking execution. Commands were issued to run AutoGrid, which computes the energy grid maps, and AutoDock. Using UCSF Chimera's ViewDock tool, both the receptor and ligand .pdbqt files and the .dlg file were loaded. More negative binding energy are found to indicate stronger, more stable interactions in proposed computation studied on HA-CD44 interactions.[28] Further inspection revealed key molecular interactions, such as hydrogen bonds between the hydroxyl groups of HA and polar residues of CD44, and electrostatic interactions between HA's carboxyl groups and positively charged amino acids like arginine or lysine.[27,28] These interactions are critical for biological function and validate the docking approach. Ligand flexibility, as observed through torsion angles, also influences the docking result; too much flexibility may suggest a less stable complex unless well-supported by strong interactions. For enhanced reliability, advanced analyses such as Root Mean Square Deviation (RMSD) with Cluster analysis were suggested to top-ranked poses confirm the consistency and convergence of docking predictions to identify dominant binding modes.[27-29] Hence, this docking study using AutoDock (Molegro Virtual Dcoking) and Chimera provided a comprehensive understanding of the interaction between hyaluronic acid and CD44. The combination of ligand-receptor preparation, grid configuration, CMD-based docking execution, and post-docking analysis offered a robust computational framework to simulate and analyze molecular interactions. This study demonstrates how docking can elucidate the molecular basis of CD44-hyaluronan binding, which is vital in fields like cancer biology, tissue engineering, and regenerative medicine. Such insights can aid in the development of therapeutic agents, targeted drug delivery systems, or topical formulations that modulate CD44 activity in diseases where hyaluronan binding plays a central role. After successfully performing molecular docking such as docking hyaluronic acid (HA4) with the CD44 receptor using Molegro Virtual Docking, the next essential phase involves a detailed structural and functional analysis of the resulting protein-ligand complex. This post-docking evaluation provides insights into the nature, strength, and biological relevance of the interaction. One of the most effective platforms for this analysis is PDBsum, a comprehensive web-based tool that offers graphical summaries and detailed breakdowns of protein-ligand complexes. This unified structure is then uploaded to the PDBsum Generate portal, a free utility that analyzes custom PDB files and returns a set of highly informative interaction plots and structural summaries (Figure 1-4).[30] Once submitted, PDBsum delivers a wealth of interaction data. A core feature is the Protein-Ligand Interaction Summary, which includes the number and nature of hydrogen bonds, hydrophobic interactions, salt bridges, and water-mediated contacts. These non-covalent interactions play a critical role in stabilizing the ligand within the receptor's binding pocket. In addition to interaction mapping, PDBsum also projects the ligand-binding site onto the protein's secondary structure, identifying whether the ligand resides in an alpha-helix, beta-sheet, or loop region, and whether this overlaps with known functional domains. This topological insight is important for understanding the biological impact of ligand binding.[31] Collectively, this post-docking workflow from format preparation and PDBsum analysis to functional prediction and visualization—forms a vital bridge between in silico modeling and biological hypothesis generation, paving the way for potential drug discovery, therapeutic development, or deeper molecular understanding of protein-ligand interactions and to be used assess the draggability of the site.[32] Hence, these findings suggest that HA forms a stable and biologically meaningful complex with CD44, potentially influencing downstream cellular functions such as migration, inflammation, or tumor progression. The successful integration of docking simulations and interaction analysis not only validates the computational model but also provides a solid foundation for further experimental and therapeutic exploration targeting the HA–CD44 axis. CD44 is found to reported to promote bacterial growth of Streptococcus pneumoniae and its spread in pneumococcal pneumonia from lungs to blood and spleen in wild-type versus CD44-deficient mice including in clinical studies done in Escherichia coli peritonitis or urinary tract infections having high bacterial load especially in bacterial skin infections.[33-34] The HA-CD44 axis study is also proposed to explore their crucial

role in fungal skin infections to pinned the mechanism for pathogen internalization and its respective host immune modulation. Fungal hyaluronic acid (HA) interaction with host cell surface receptor CD44 was studied to confirm the role of HA-CD44 axis in skin fungal infection: an immune evasion mechanism where fungal pathogens, Cryptococcus neoformans (Cn), used hyaluronic acid (HA) on their surface to bind to the host cell surface receptor CD44. Hence, this reported interaction further triggered a signaling cascade by allowing fungus to be internalized by macrophages and survive intracellularly, rather than being it get destroyed.[35-36]

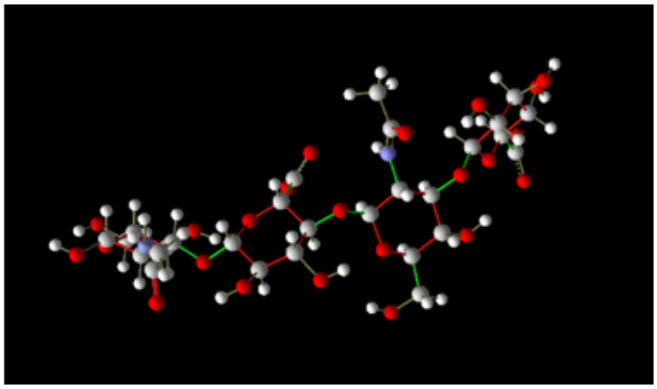

Figure 1 HA4 made in GLYCAM-Web loaded in molegro virtual docker.

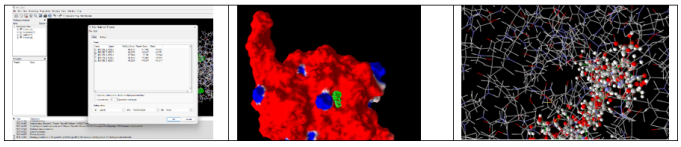

Figure 2 Showing pose organizer, surface cavities & pose proteins result of molecular docking interaction of CD44 and HA4.

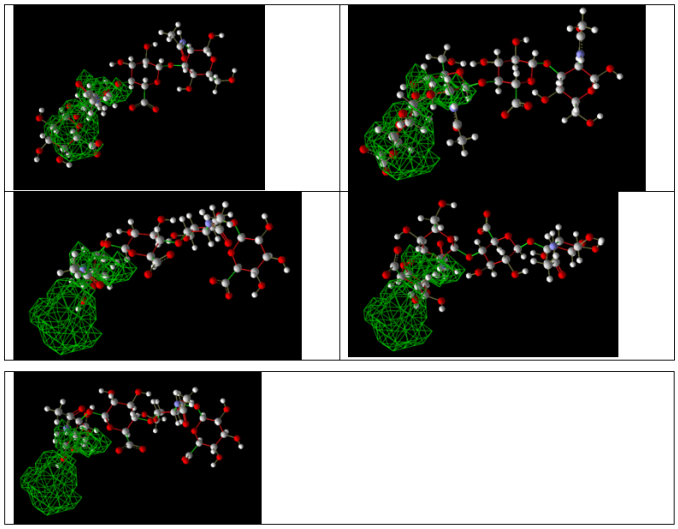

Figure 3 Showing all 5 individual poses interacting with the cavities as a result of molecular docking interaction of CD44 and HA4.

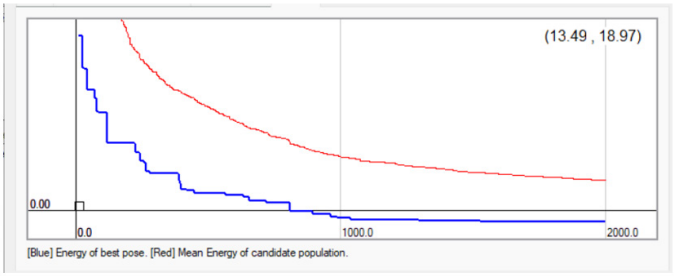

Figure 4 Energy convergence graph from Molegro virtual docker for the docking interaction between CD44 receptor and HA4 ligand (Hyaluronic Acid fragment).

Conclusion

The molecular docking study revealed a strong and specific interaction between hyaluronic acid (HA) and the CD44 receptor, with the lowest binding energy conformations showing favorable affinity within the canonical hyaluronan-binding domain (link module) of CD44. Post-docking analysis using PDBsum provided a detailed interaction map, highlighting multiple stabilizing forces such as hydrogen bonds, hydrophobic contacts, and electrostatic interactions between HA and key residues like arginine, lysine, and tyrosine. The present study employed molecular docking to investigate the interaction between the hyaluronic acid tetramer (HA4) and the receptor CD44, providing computational insights into their binding behaviour. Docking simulations generated multiple ligand conformations, with the top-ranked poses exhibiting negative MolDock scores, indicating energetically favourable binding interactions within the hyaluronan-recognition region of CD44. The best docking pose demonstrated the strongest predicted interaction, supported by notable hydrogen-bond contributions, suggesting stable ligand engagement within the receptor binding groove. Analysis of multiple poses revealed a gradual decrease in binding favourability across lower-ranked conformations, which likely reflects variations in ligand orientation and interaction stability within the binding cavity. The energy convergence analysis further confirmed the reliability of the docking simulation, showing rapid optimization during the early stages of the search followed by stabilization of both the best pose energy and the mean population energy, indicating successful convergence of the docking algorithm and identification of a stable binding conformation. These findings collectively suggest that HA4 is capable of forming a stable interaction with CD44 and provide structural insight into the molecular recognition between these biomolecules. Considering the established role of CD44–hyaluronan interactions in processes such as cell adhesion, inflammation, and tumor progression, the present findings contribute to understanding the molecular basis of HA–CD44 binding. However, as molecular docking provides predictive insights based on computational models, the results should be interpreted as preliminary. Further validation using complementary computational approaches such as molecular dynamics simulations, as well as experimental studies including binding assays or structural analyses, will be necessary to confirm the stability and biological relevance of the predicted HA4–CD44 interaction. Such integrative studies could support the development of therapeutic strategies targeting the HA–CD44 signalling axis.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

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