Introduction

Ageratum conyzoides (Asteraceae) is widely used in traditional medicine for wound healing through topical applications of its leaves, suggesting bioactive compounds with potential wound-healing effects 1,2, while its wound-healing properties are recognized, the exact molecular mechanisms remain largely unclear, presenting a gap suitable for in silico exploration. Ageratum conyzoides is known to contain bioactive compounds such as flavonoids, alkaloids, and terpenoids, which are associated with anti-inflammatory, antimicrobial, and tissue-regeneration activities. Its frequent use in local medicine underscores its relevance and ethnobotanical importance, making it a logical focus for further study.

**Methodology**

**Data Mining**

A systematic approach was employed to mine phytochemical data for *Ageratum conyzoides* from four databases: [NPASS](https://bidd.group/NPASS/) 3, [PubChem](https://pubchem.ncbi.nlm.nih.gov/) 4, [ChEMBL](https://www.ebi.ac.uk/chembl/), and [KNApSAcK](https://www.knapsackfamily.com/KNApSAcK/). Each database was queried to identify phytochemicals associated with the plant, followed by consolidation and curation of the data to ensure a high-quality dataset free from duplicates. The first step involved querying the selected databases using the scientific name *Ageratum conyzoides*. The searches aimed to retrieve phytochemicals, their molecular structures, and any associated bioactivity data. In NPASS (Natural Product Activity and Species Source Database), a search was conducted on its web interface using the plant name, which returned a list of compounds along with their biological activities 3. PubChem was accessed via its REST API, where the plant name was used as a query to retrieve compounds and their molecular identifiers (e.g., SMILES and InChIKey) 4,5. ChEMBL was queried through its molecule search feature, retrieving compounds linked to the plant 6,7. KNApSAcK, a metabolomics database, provided compounds associated with the plant when searched using its scientific name. For compounds whose 3D structures could not be obtained using CAS numbers, the [NCI Cactus](https://cactus.nci.nih.gov/translate/) Online SMILES Translator was utilized to generate 3D molecular structures 8.

**Data Consolidation and Duplicate Removal**

The results from each database were downloaded in tabular format and consolidated into a single master dataset. The consolidated data included compound names, molecular structures, biological activities, and database-specific identifiers. Duplicates were removed using molecular identifiers as primary criteria and names as secondary criteria further duplicate scanning based on sdf structure was done by RDKit. All compounds that were tagged as irritants and/or Health Hazards were removed at this stage while those tagged as environmental hard only were retained but tagged as disadvantaged.

**ADMET STUDIES**

A detailed assay for conducting ADMET property predictions using the pkCSM (https://biosig.lab.uq.edu.au/pkcsm/) 9platform was performed as follows. First, the preparation of the input data involved the collection and conversion of chemical structures into their corresponding SMILES (Simplified Molecular Input Line Entry System) notation, a widely used textual representation of molecular structures. SMILES strings were extracted by RDKit 10. Each compound’s SMILES string was paired with its name for easier identification and organized into a plain text file, ensuring each line contained a single SMILES string followed by an optional compound name separated by a space. At the pkCSM platform, the ADMET module was selected for a comprehensive prediction of the Absorption, Distribution, Metabolism, Excretion, and Toxicity properties of the compounds. The prepared SMILES file was then uploaded into the input section of the platform. Careful attention was paid to formatting, verifying that each SMILES string was syntactically correct to avoid processing errors. The pkCSM platform employes its predictive models to calculate various ADMET parameters based on the structural features of the input molecules. Key absorption parameters included Caco-2 permeability, water solubility, and human intestinal absorption. Distribution was assessed through predictions such as blood-brain barrier permeability and volume of distribution. For metabolism, the compounds’ interactions with cytochrome P450 enzymes (CYPs), including substrate and inhibition potential for enzymes like CYP1A2, CYP2D6, and CYP3A4, were evaluated. Excretion data were analyzed for renal clearance and related properties. Additionally, toxicity endpoints such as AMES toxicity, maximum tolerated dose, and hepatotoxicity were predicted pkCSM 9. The results served as a preliminary evaluation of the compounds’ pharmacokinetic and safety profiles, forming the basis for further in vitro and in vivo validation studies. Python-based clustering analysis was further done on the obtained ADMET properties (Figure S1).

**Wound Healing ADMET properties prioritization**

To identify and visualize the top-performing compounds based on their ADMET properties, a dataset containing ADMET parameters was analyzed. The analysis aimed to rank compounds and select the best candidates for wound healing applications. The ADMET properties prioritised for wound healing included water solubility, Caco-2 permeability, fraction unbound (human), blood-brain barrier (BBB) permeability, intestinal absorption, maximum tolerated dose (human), AMES toxicity, hepatotoxicity, skin sensitization, and CYP3A4 inhibition. First, the raw data was normalized to ensure uniform scaling of all ADMET properties, allowing fair comparison across all features. Min-max normalization was applied, scaling all values between 0 and 1. A composite score was calculated for each compound by averaging the normalized values of the relevant ADMET properties. The compounds were then ranked based on their composite scores, with the highest-ranking compounds considered the most promising for wound healing. Any compounds with missing or inconsistent values in the required ADMET properties were excluded from the analysis. Heatmap and bar plots were constructed for the best i5 compounds. The heatmap illustrated the ADMET property values for the top-performing compounds, while the bar plot showed their composite scores. This dual approach provided a detailed comparative view of how each compound performed across all evaluated parameters.

**Compound Target prediction.**

This was accomplished using BindingDB's advanced data search 11 , its data sources include BindingDB (curated from articles and patents) 11, ChEMBL (extracted from the ChEMBL database) 7, PubChem (derived from PubChem confirmatory bioassays) 4, PDSP Ki (extracted from PDSP Ki) 12, CSAR (extracted from CSAR data) 13, US Patents (extracted from US patents by BindingDB), and D3R (extracted from D3R) 14. These sources provide a comprehensive range of information on chemical and biological interactions. The compound smiles were uploaded and a search was conducted with an exact match. The obtained targets were further verified and taken for protein-protein interaction studies.

**Protein-protein interaction pathway prediction**

**Results and Discussion**

**Data mining**

The data mining process identified a total of 148 unique phytochemicals across four databases: 25 from NPASS, 95 from PubChem, 13 from ChEMBL, and 15 from KNApSAcK.

**Data Consolidation and Duplicate Removal**

During initial data consolidation, overlapping compounds were detected across multiple databases. After thorough processing, 22 duplicates were identified using SMILES and InChIKeys, 8 additional duplicates were resolved based on standardized compound names, 37 more duplicates were eliminated using SDF structural comparison. Following these refinements, the final dataset contained 81 unique phytochemicals, each documented with molecular identifiers, biological activities, and source database information. Among them, 11 were classified as irritants, 1 as corrosive, 3 as health hazards, 1 as acutely toxic, and 2 as environmental hazards.

**ADMET STUDIES**

The results of ADMET screening are presented in Figure S1 and in Supplementary File2, sheet1. The results contain Physicochemical properties, Absorption-related metrics, Toxicity predictions, and Safety measures. The Principal Component Analysis (PCA) plot in Figure S1 presents the clustering of compounds based on their ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties. The compounds were grouped into three distinct clusters (0, 1, and 2), each represented by a different color. Principal Component 1 (PC1) and Principal Component 2 (PC2) explains the variation in the dataset, capturing the most significant differences in ADMET characteristics. Cluster 0 (Purple) shows compounds that are mainly distributed in the negative PC1 region, with a moderate spread in PC2. Their ADMET properties likely share similarities in terms of physicochemical features such as solubility, permeability, or toxicity. Cluster 1 (Blue-Green) is located in the far-right section of the PCA plot, suggesting distinct ADMET properties compared to the other clusters. The compounds here might exhibit higher permeability or metabolic stability. Cluster 2 (Yellow) compounds are concentrated around the lower-left region, indicating they possess different ADMET characteristics from Cluster 1 and moderate similarity with Cluster 0. PC1 appears to differentiate compounds based on properties such as solubility and permeability. For example, compounds in Cluster 1 (right side) may have higher permeability and metabolic stability, whereas those in Cluster 2 (left side) could be more water-soluble but less permeable. PC2 might reflect toxicity-related properties, with compounds at the upper end having potentially higher toxicity risks, such as hepatotoxicity or CYP enzyme inhibition. Compounds in Cluster 1, being well-separated from the other clusters, may have superior drug-likeness properties (higher permeability, lower toxicity). These could be strong candidates for further drug development. Cluster 2, with its grouping near the lower-left region, might contain compounds that are less bioavailable or have higher clearance rates. Cluster 0, positioned between the two, could represent compounds with moderate ADMET profiles, making them potential candidates depending on the target pharmacokinetics.

**Wound Healing ADMET properties prioritization**

The heatmap (Figure 2) revealed significant variation across the ADMET properties of the top 15 compounds, particularly in water solubility and permeability parameters. Compounds such as **O** and **[N]=O** showed excellent profiles across multiple properties, making them leading candidates for further investigation. Conversely, compounds with negative maximum tolerated dose values, such as **CC(=O)OCC[N+](C)(C)C.[F-]**, may require structural modifications to enhance their safety profiles.

The bar plot visualized the composite scores, confirming the ranking and highlighting the small differences in scores among the top compounds (Figure S2). This suggests that many of these compounds could be viable candidates for therapeutic use, depending on the specific requirements of the formulation 15.

**Target prediction**

The target prediction study revealed various biological targets, primarily across neuronal, hormonal, and enzymatic pathways. The affinity values (Ki, IC50, and EC50) provided insights into the potential effectiveness of these ligands in modulating their respective targets. While some compounds demonstrated strong binding affinity, indicating potential therapeutic relevance, others exhibited weak or negligible interaction, suggesting limited biological impact at physiological concentrations.

Among the compounds assessed, BDBM50013775 exhibited the highest binding affinity to the oxytocin receptor in rats, with a Ki of 0.89 nM, signifying strong potential for hormonal regulation. Similarly, BDBM18125 displayed moderate affinity toward the muscarinic acetylcholine receptor M2 in rats (Ki = 700 nM), suggesting possible applications in neuropharmacology. Other notable interactions included the binding of BDBM50542904 to the cannabinoid receptor 1 in medicinal leech with a Ki of 1,000 nM, highlighting its potential involvement in pain modulation and inflammation control.

Despite these promising findings, several compounds exhibited weak or negligible interactions with their predicted targets. For instance, BDBM74574 demonstrated EC50 values exceeding 500,000 nM for importin subunit alpha-1 in humans and greater than 1,000,000 nM for metabotropic glutamate receptors 2 and 6, implying weak receptor activation. Similarly, BDBM50153109 displayed IC50 values exceeding 500,000 nM for DNA polymerase alpha and beta, suggesting poor inhibitory potential against these targets. The observed high-affinity interactions suggest that specific ligands could be further explored for their pharmacological applications, particularly in neurological disorders, hormonal regulation, and anti-inflammatory therapies. However, compounds with weak binding may require structural modifications to enhance their therapeutic potential 16,17.

**Targets in Wound Healing**

Wound healing is a complex biological process involving inflammation, tissue regeneration, and extracellular matrix remodeling. Several identified targets in this study are implicated in pathways relevant to wound healing, including receptors involved in inflammation control, cell proliferation, and tissue repair 18. Notably, the muscarinic acetylcholine receptor M2, the cannabinoid receptor 1, and the oxytocin receptor emerged as potential targets for further exploration in wound healing due to their roles in modulating inflammatory responses, neuroimmune signaling, and cellular repair mechanisms 19,20.

The muscarinic acetylcholine receptor M2 has been implicated in anti-inflammatory signaling and tissue regeneration 19. Acetylcholine, through muscarinic receptors, can regulate keratinocyte proliferation and fibroblast activity, both of which are crucial for effective wound healing. Given that BDBM18125 and BDBM10759 demonstrated moderate affinity for this receptor, further investigation of their interaction with wound-healing pathways may be warranted.

The cannabinoid receptor 1 plays a significant role in modulating inflammation and pain perception, both of which are integral to wound healing 19. Cannabinoid signaling is known to influence fibroblast migration and collagen deposition, key factors in tissue repair. The ligand BDBM50542904 exhibited a Ki of 1,000 nM for this receptor, suggesting that cannabinoid-based interventions may be explored further for wound-healing applications. Investigation into protein-protein interactions involving cannabinoid receptor 1 with other key mediators of wound healing, such as transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF), may provide deeper insights into its mechanistic role in tissue regeneration.

The oxytocin receptor also presents an interesting target for wound healing, as oxytocin has been shown to promote angiogenesis and enhance collagen synthesis in fibroblasts. The strong binding affinity of BDBM50013775 to the oxytocin receptor (Ki = 0.89 nM) suggests potential therapeutic implications for promoting tissue repair and reducing fibrosis in chronic wounds. Further protein interaction analysis may focus on oxytocin-mediated crosstalk with extracellular matrix proteins and inflammatory cytokines to determine whether its activation can enhance the resolution of tissue damage 21. The muscarinic acetylcholine receptor M2, cannabinoid receptor 1, and oxytocin receptor represent promising targets for further exploration in wound healing.

**Expanded Investigation of Potential Targets in Wound Healing**

While the muscarinic acetylcholine receptor M2 (CHRM2), cannabinoid receptor 1 (CB1R), and oxytocin receptor (OXTR) have emerged as promising targets for wound healing, additional receptors and molecular pathways identified in the target prediction results may play significant roles in tissue repair and regeneration. These alternative targets, involved in angiogenesis, inflammation regulation, and cellular migration, present further opportunities for therapeutic intervention in wound healing.

Neuropeptide Y (NPY) receptors, particularly the Y1 (NPY1R) and Y2 (NPY2R) subtypes, have been extensively studied for their involvement in angiogenesis and immune modulation 22. NPY1R has been demonstrated to promote endothelial cell proliferation and vascularization, processes that are essential for effective wound repair. Similarly, NPY2R has been implicated in regulating immune cell responses, thereby mitigating excessive inflammation and preventing prolonged wound healing delays. Given that BDBM10759 exhibits interactions with both NPY1R and NPY2R, these receptors should be further explored for their contributions to tissue regeneration. Their roles in vascular remodeling and immune homeostasis suggest potential applications in accelerating wound closure and reducing chronic wound complications 22.

Transforming growth factor-beta (TGF-β) signaling 23 is widely recognized as a central regulator of fibroblast activation, extracellular matrix deposition, and scar formation. Although not directly identified among the predicted targets, any receptor interactions that influence TGF-β pathways could be of particular relevance in modulating fibrosis and chronic wound repair. The TGF-β signaling cascade is involved in balancing regenerative and fibrotic responses, making it a key mechanism to explore in wound healing therapies.

ATP-binding cassette (ABC) transporters, including ABCB1 (P-glycoprotein) and ABCG2, are well known for their roles in cellular detoxification and multidrug resistance, but their contributions to wound healing have garnered increasing attention. These transporters regulate stem cell survival and migration, both of which are crucial processes for effective tissue repair. BDBM50338976 exhibited interactions with both ABCB1 and ABCG2, suggesting that these transporters may play a role in cellular responses within the wound microenvironment. Their potential involvement in chronic wounds, where impaired cell migration and inefficient healing are prevalent, underscores the need for further investigation into their mechanistic roles 24,25.

DNA polymerases, specifically DNA polymerase alpha and beta, are critical in DNA replication and repair, facilitating cell proliferation and tissue regeneration. While the binding affinity of BDBM50153109 and BDBM50338976 to DNA polymerase alpha and beta was relatively weak, their involvement in keratinocyte proliferation, a key step in epithelialization, suggests that modulating these enzymes could be beneficial in wound closure. Further studies assessing their activity in epidermal cell regeneration could provide insights into their therapeutic potential in accelerating re-epithelialization 26,27.

Beyond the muscarinic acetylcholine receptor M2, the muscarinic acetylcholine receptor M3 (CHRM3) has also been implicated in wound healing due to its role in cellular migration and smooth muscle contraction. CHRM3 activation has been linked to enhanced fibroblast activity, which is essential for extracellular matrix deposition and tissue remodeling. The interplay between CHRM3 and fibroblast-mediated wound repair suggests that this receptor warrants further exploration, particularly in wound environments where fibroblast function is impaired.

Importin α1 (KPNA1) functions as an adapter protein for nuclear import, facilitating the translocation of proteins with nuclear localization signals into the nucleus. This process is essential for various cellular functions, including proliferation and differentiation. A study demonstrated that KPNA1 is critical for satellite cell proliferation and survival, which are vital for muscle regeneration. In KPNA1 knockout mice, impaired nuclear localization of key proteins led to reduced satellite cell proliferation and increased apoptosis, resulting in compromised muscle regeneration. These findings suggest that KPNA1-mediated nuclear import is crucial for tissue repair processes 28.

Vasopressin receptors, including V1a and V1b, are G protein-coupled receptors involved in various physiological processes. The V1a receptor is predominantly found in vascular smooth muscle, where it mediates vasoconstriction, and in other tissues such as the liver and kidney. The V1b receptor is primarily located in the anterior pituitary gland, where it regulates the release of adrenocorticotropic hormone (ACTH). While these receptors play significant roles in cardiovascular regulation and stress responses, direct evidence linking them to wound healing is limited. However, their involvement in vasoconstriction and hormonal regulation could indirectly influence tissue repair processes 29.

Xanthine dehydrogenase/oxidase is an enzyme involved in purine metabolism, catalyzing the oxidation of hypoxanthine to xanthine and xanthine to uric acid. During this process, reactive oxygen species (ROS) are generated, which can contribute to oxidative stress. Oxidative stress plays a dual role in wound healing; moderate levels of ROS are essential for cell signaling and defense against pathogens, while excessive ROS can lead to tissue damage and impaired healing. Therefore, the activity of xanthine oxidase must be tightly regulated to balance ROS production during the healing process .

Beta-arrestins are multifunctional proteins that regulate G protein-coupled receptor (GPCR) signaling and mediate receptor desensitization, internalization, and signaling pathways. Beta-arrestin-1, in particular, has been implicated in various cellular processes, including cell migration and apoptosis. Recent studies have shown that beta-arrestin-1 can influence signaling pathways involved in inflammation and tissue repair 30.

**Final Evaluation: Targets for Protein-Protein Interaction Analysis**

Among all identified targets, the most relevant for wound healing and further protein-protein interaction (PPI) studies include muscarinic acetylcholine receptor M2 (CHRM2), cannabinoid receptor 1 (CB1R), and oxytocin receptor (OXTR) due to their roles in modulating inflammation, pain regulation, and fibroblast-mediated repair. Additionally, neuropeptide Y receptors (Y1R and Y2R) are promising candidates due to their influence on angiogenesis and immune regulation, while ATP-binding cassette transporters (ABCB1 and ABCG2) may contribute to stem cell migration and wound re-epithelialization. The muscarinic acetylcholine receptor M3 (CHRM3) remains an attractive target for investigating fibroblast activation and extracellular matrix remodeling.

Further protein-protein interaction studies should focus on determining how these targets interact with key wound-healing mediators such as vascular endothelial growth factor (VEGF), transforming growth factor-beta (TGF-β), inflammatory cytokines, and extracellular matrix proteins. Understanding these interactions will provide deeper mechanistic insights into wound healing pathways and aid in identifying novel therapeutic interventions aimed at accelerating tissue repair and minimizing fibrosis in chronic wounds.

**Conclusion**

The identified targets highlight multiple pathways implicated in wound healing, including angiogenesis, inflammation control, fibroblast migration, and epithelialization. These findings provide a foundation for further experimental validation, particularly in the development of targeted wound healing therapies using small-molecule modulators. Further studies could focus on optimizing the identified lead compounds to improve their safety and efficacy profiles. Additionally, validation through experimental assays would be crucial to confirm the computational predictions.

1. Okunade, A. L. (2002). Ageratum conyzoides L. (Asteraceae). *Fitoterapia*, *73*(1), 1–16. https://doi.org/10.1016/S0367-326X(01)00364-1

2. Nogueira, J., Gonçalez, E., … S. G.-I. J. of, & 2010, undefined. (n.d.). Ageratum conyzoides essential oil as aflatoxin suppressor of Aspergillus flavus. *Elsevier*. Retrieved May 24, 2022, from https://www.sciencedirect.com/science/article/pii/S016816050900539X

3. Zhao, H., Yang, Y., Wang, S., Yang, X., Zhou, K., Xu, C., Zhang, X., Fan, J., Hou, D., Li, X., Lin, H., Tan, Y., Wang, S., Chu, X. Y., Zhuoma, D., Zhang, F., Ju, D., Zeng, X., & Chen, Y. Z. (2023). NPASS database update 2023: quantitative natural product activity and species source database for biomedical research. *Nucleic Acids Research*, *51*(D1), D621–D628. https://doi.org/10.1093/NAR/GKAC1069

4. Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B. A., Thiessen, P. A., Yu, B., Zaslavsky, L., Zhang, J., & Bolton, E. E. (2021). PubChem in 2021: new data content and improved web interfaces. *Nucleic Acids Research*, *49*(D1), D1388–D1395. https://doi.org/10.1093/NAR/GKAA971

5. Kim, S., Cheng, T., He, S., Thiessen, P. A., Li, Q., Gindulyte, A., & Bolton, E. E. (2022). PubChem Protein, Gene, Pathway, and Taxonomy Data Collections: Bridging Biology and Chemistry through Target-Centric Views of PubChem Data. *Journal of Molecular Biology*. https://doi.org/10.1016/J.JMB.2022.167514

6. Gaulton, A., Bellis, L. J., Bento, A. P., Chambers, J., Davies, M., Hersey, A., Light, Y., McGlinchey, S., Michalovich, D., Al-Lazikani, B., & Overington, J. P. (2012). ChEMBL: a large-scale bioactivity database for drug discovery. *Nucleic Acids Research*, *40*(Database issue). https://doi.org/10.1093/NAR/GKR777

7. Mendez, D., Gaulton, A., Bento, A. P., Chambers, J., De Veij, M., Félix, E., Magariños, M. P., Mosquera, J. F., Mutowo, P., Nowotka, M., Gordillo-Marañón, M., Hunter, F., Junco, L., Mugumbate, G., Rodriguez-Lopez, M., Atkinson, F., Bosc, N., Radoux, C. J., Segura-Cabrera, A., … Leach, A. R. (2019). ChEMBL: Towards direct deposition of bioassay data. *Nucleic Acids Research*, *47*(D1), D930–D940. https://doi.org/10.1093/NAR/GKY1075

8. Bone, R. G. A., Firth, M. A., & Sykes, R. A. (1999). SMILES Extensions for Pattern Matching and Molecular Transformations:  Applications in Chemoinformatics. *Journal of Chemical Information and Computer Sciences*, *39*(5), 846–860. https://doi.org/10.1021/CI990422W

9. Pires, D. E. V., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of Medicinal Chemistry*, *58*(9), 4066–4072. https://doi.org/10.1021/ACS.JMEDCHEM.5B00104

10. *RDKit*. (n.d.). Retrieved March 31, 2023, from http://www.rdkit.org/

11. Liu, T., Lin, Y., Wen, X., Jorissen, R. N., & Gilson, M. K. (2007). BindingDB: a web-accessible database of experimentally determined protein–ligand binding affinities. *Nucleic Acids Research*, *35*(suppl\_1), D198–D201. https://doi.org/10.1093/NAR/GKL999

12. Raymond, J. R., Mukhin, Y. V., Gelasco, A., Turner, J., Collinsworth, G., Gettys, T. W., Grewal, J. S., & Garnovskaya, M. N. (2001). Multiplicity of mechanisms of serotonin receptor signal transduction. *Pharmacology and Therapeutics*, *92*(2–3), 179–212. https://doi.org/10.1016/S0163-7258(01)00169-3

13. Smith, R. D., Damm-Ganamet, K. L., Dunbar, J. B., Ahmed, A., Chinnaswamy, K., Delproposto, J. E., Kubish, G. M., Tinberg, C. E., Khare, S. D., Dou, J., Doyle, L., Stuckey, J. A., Baker, D., & Carlson, H. A. (2016). CSAR Benchmark Exercise 2013: Evaluation of Results from a Combined Computational Protein Design, Docking, and Scoring/Ranking Challenge. *Journal of Chemical Information and Modeling*, *56*(6), 1022–1031. https://doi.org/10.1021/ACS.JCIM.5B00387

14. Gathiaka, S., Liu, S., Chiu, M., Yang, H., Stuckey, J. A., Kang, Y. N., Delproposto, J., Kubish, G., Dunbar, J. B., Carlson, H. A., Burley, S. K., Walters, W. P., Amaro, R. E., Feher, V. A., & Gilson, M. K. (2016). D3R grand challenge 2015: Evaluation of protein–ligand pose and affinity predictions. *Journal of Computer-Aided Molecular Design*, *30*(9), 651–668. https://doi.org/10.1007/S10822-016-9946-8

15. Lipinski, C. A. (2004). Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discovery Today. Technologies*, *1*(4), 337–341. https://doi.org/10.1016/J.DDTEC.2004.11.007

16. Charles, S., & Mahapatra, R. K. (2023). Artificial intelligence based de-novo design for novel Plasmodium falciparum plasmepsin (PM) X inhibitors. *Journal of Biomolecular Structure and Dynamics*, 1–16. https://doi.org/10.1080/07391102.2023.2279700

17. Charles, S., Edgar, M. P., & Kasoma, N. A. (2023). The Hunt for Antipox Compounds against Monkeypox Virus Thymidylate Kinase and Scaffolding Protein Leveraging Pharmacophore Modeling,  Molecular Docking, ADMET Studies and Molecular Dynamics Simulation  Studies. *Virology & Mycology*, *12*(4), 1–14. https://doi.org/10.35248/2161-0517.23.12.280

18. Schultz, G. S., Chin, G. A., Moldawer, L., & Diegelmann, R. F. (2011). Principles of Wound Healing. *Diabetic Foot Problems*, 395–402. https://doi.org/10.1142/9789812791535\_0028

19. Wess, J., Eglen, R. M., & Gautam, D. (2007). Muscarinic acetylcholine receptors: Mutant mice provide new insights for drug development. *Nature Reviews Drug Discovery*, *6*(9), 721–733. https://doi.org/10.1038/nrd2379

20. Du, Y., Ren, P., Wang, Q., Jiang, S. K., Zhang, M., Li, J. Y., Wang, L. L., & Guan, D. W. (2018). Cannabinoid 2 receptor attenuates inflammation during skin wound healing by inhibiting M1 macrophages rather than activating M2 macrophages. *Journal of Inflammation (London, England)*, *15*(1), 25. https://doi.org/10.1186/S12950-018-0201-Z

21. Nashar, P. E., Whitfield, A. A., Mikusek, J., & Reekie, T. A. (2022). The Current Status of Drug Discovery for the Oxytocin Receptor. *Methods in Molecular Biology (Clifton, N.J.)*, *2384*, 153–174. https://doi.org/10.1007/978-1-0716-1759-5\_10

22. Brothers, S. P., & Wahlestedt, C. (2010). Therapeutic potential of neuropeptide Y (NPY) receptor ligands. *EMBO Molecular Medicine*, *2*(11), 429. https://doi.org/10.1002/EMMM.201000100

23. Baba, A. B., Rah, B., Bhat, G. R., Mushtaq, I., Parveen, S., Hassan, R., Hameed Zargar, M., & Afroze, D. (2022). Transforming Growth Factor-Beta (TGF-β) Signaling in Cancer-A Betrayal Within. *Frontiers in Pharmacology*, *13*, 791272. https://doi.org/10.3389/FPHAR.2022.791272/PDF

24. Vander Beken, S., de Vries, J. C., Meier-Schiesser, B., Meyer, P., Jiang, D., Sindrilaru, A., Ferreira, F. F., Hainzl, A., Schatz, S., Muschhammer, J., Scheurmann, N. J., Kampilafkos, P., Seitz, A. M., Dürselen, L., Ignatius, A., Kluth, M. A., Ganss, C., Wlaschek, M., Singh, K., … Scharffetter-Kochanek, K. (2019). Newly Defined ATP-Binding Cassette Subfamily B Member 5 Positive Dermal Mesenchymal Stem Cells Promote Healing of Chronic Iron-Overload Wounds via Secretion of Interleukin-1 Receptor Antagonist. *Stem Cells (Dayton, Ohio)*, *37*(8), 1057–1074. https://doi.org/10.1002/STEM.3022

25. Huls, M., Russel, F. G. M., & Masereeuw, R. (2009). The role of ATP binding cassette transporters in tissue defense and organ regeneration. *The Journal of Pharmacology and Experimental Therapeutics*, *328*(1), 3–9. https://doi.org/10.1124/JPET.107.132225

26. Kumar, A., Reed, A. J., Zahurancik, W. J., Daskalova, S. M., Hecht, S. M., & Suo, Z. (2022). Interlocking activities of DNA polymerase β in the base excision repair pathway. *Proceedings of the National Academy of Sciences of the United States of America*, *119*(10), e2118940119. https://doi.org/10.1073/PNAS.2118940119/SUPPL\_FILE/PNAS.2118940119.SAPP.PDF

27. Itkonen, H. M., Kantelinen, J., Vaara, M., Parkkinen, S., Schlott, B., Grosse, F., Nyström, M., Syväoja, J. E., & Pospiech, H. (2016). Human DNA polymerase α interacts with mismatch repair proteins MSH2 and MSH6. *FEBS Letters*, *590*(23), 4233–4241. https://doi.org/10.1002/1873-3468.12475

28. Choo, H. J., Cutler, A., Rother, F., Bader, M., & Pavlath, G. K. (2016). Karyopherin alpha 1 regulates satellite cell proliferation and survival by modulating nuclear import. *Stem Cells (Dayton, Ohio)*, *34*(11), 2784. https://doi.org/10.1002/STEM.2467

29. Koshimizu, T. aki, Nakamura, K., Egashira, N., Hiroyama, M., Nonoguchi, H., & Tanoue, A. (2012). Vasopressin V1a and V1b receptors: from molecules to physiological systems. *Physiological Reviews*, *92*(4), 1813–1864. https://doi.org/10.1152/PHYSREV.00035.2011

30. Daly, C., Guseinov, A. A., Hahn, H., Wright, A., Tikhonova, I. G., Thomsen, A. R. B., & Plouffe, B. (2023). β-Arrestin-dependent and -independent endosomal G protein activation by the vasopressin type 2 receptor. *ELife*, *12*. https://doi.org/10.7554/ELIFE.87754