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DISCOVERY OF SMALL MOLECULE INHIBITORS AGAINST MATRIX METALLOPROTEINASE ENZYMES IN SKIN ANTI-AGING TREATMENT USING COMPUTATIONAL APPROACH

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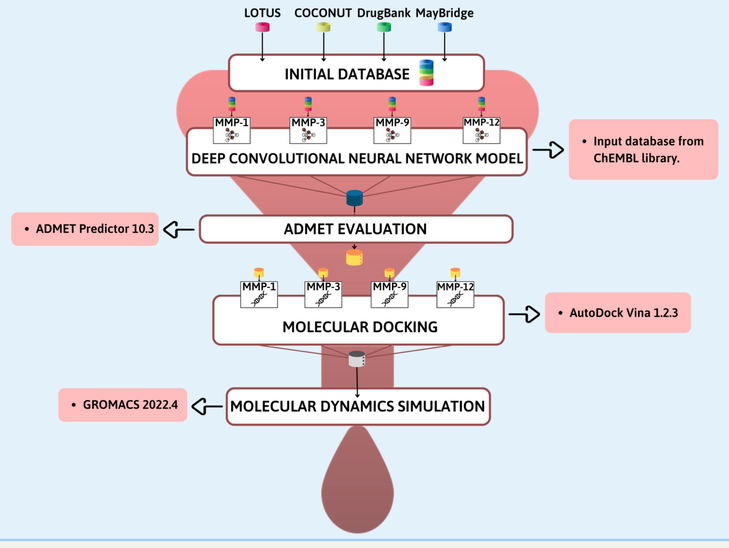
BACKGROUND

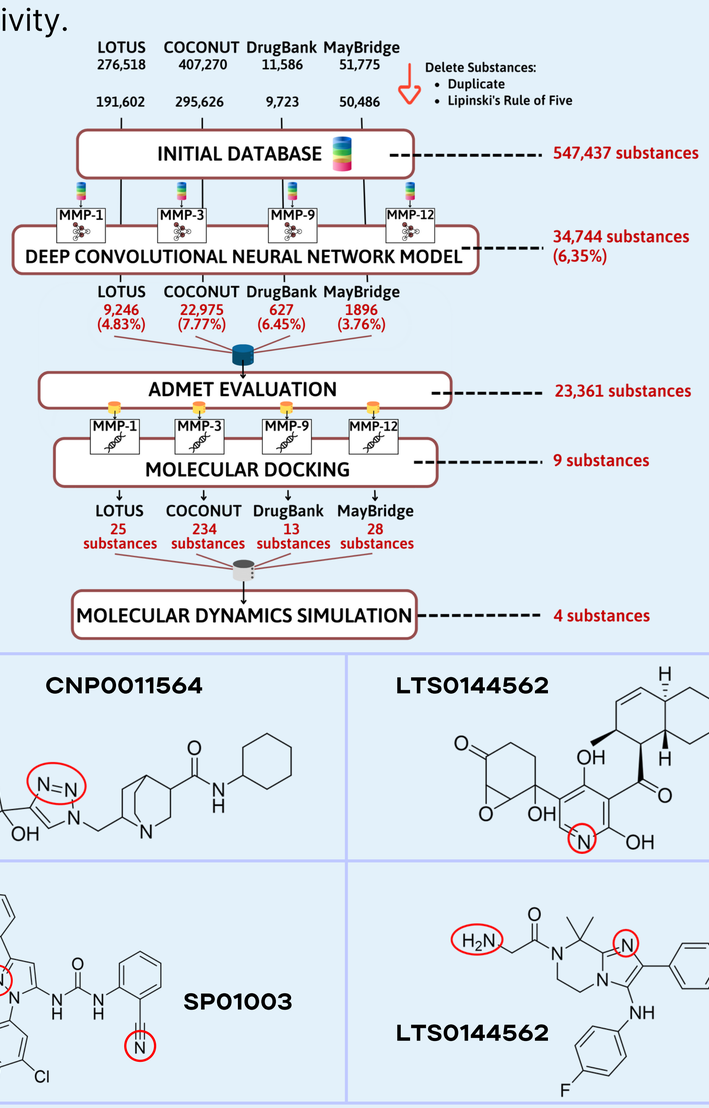
Skin aging due to the destruction of the extracellular matrix (ECM) system, which ensures the skin's structural integrity, is a significant concern for skin health. Four proteins in the matrix metalloproteinase family (MMPs) are overexpressed in skin aging and play an essential role in ECM hydrolysis, including MMP-1, MMP-3, MMP-9, and MMP-12. The study focuses on identifying broad-spectrum inhibitors for all four enzymes against skin aging.

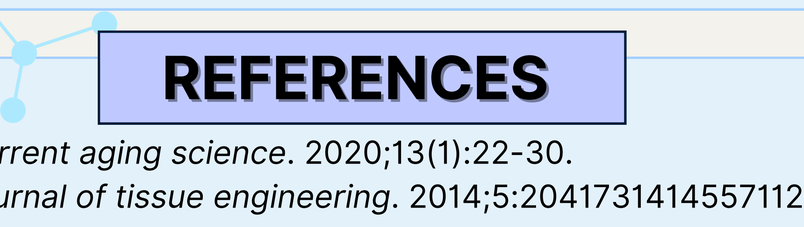
MATERIAL AND METHODS



CONCLUSION

The study successfully developed a deep learning model and virtual screening process for four human MMPs, which are significant targets in skin aging. Over 500,000 compounds were screened through the entire process, and four potential broad-spectrum inhibitors of MMPs were found to show promise for skin anti-aging therapy. Four compounds required free binding energy results and in vitro testing in further research to further assess binding ability and confirm their bio-activity.





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1. *Current aging science*. 2020;13(1):22-30.
2. *Journal of tissue engineering*. 2014;5:2041731414557112.

RESULT

CONVOLUTIONAL NEURAL NETWORK

547,437 substances

DEEP CONVOLUTIONAL NEURAL NETWORK MODEL

Enzym	IC50 of inhibitor	Number of inhibitors	Number of non-inhibitors
MMP-1	≤ 10μM	1560	389
MMP-3	≤ 10μM	1135	375
MMP-9	≤ 10μM	1671	554
MMP-12	≤ 10μM	323	164

ChEMBL data

Model	Optimization algorithm	Learning rate	Epoch	Neurons-first-fully	Dropout rate	Accuracy	Precision	Recall	MCC	AUC	F1-score
MMP-1	Adam	0.0005	30	128	0.8	0.78	0.80	0,84	0,54	0,77	0,82
MMP-3	Adam	0.001	40	256	0.4	0.82	0.80	0,91	0,63	0,82	0,84
MMP-9	Adam	0.0005	50	128	0.4	0.86	0.85	0,93	0,71	0,89	0,89
MMP-12	Adam	0.0005	50	16	0.6	0.89	0.87	0,93	0,78	0,88	0,90

Fig 1. Results of training deep learning models (DCNN) and screening databases through the model.

Enzym	LOTUS	COCONUT	DrugBank	MayBridge	Total
MMP-1	132,691	194,324	6333	28.919	362,267
MMP-3	65,539	101,874	3305	13.994	184,712
MMP-9	145,481	215,537	6815	32.028	399,961
MMP-12	72,089	109,294	2900	13.095	197,378

34,744 substances

Potential broad-spectrum inhibition

ADMET

Tab 1. Admet evaluation results

Database	Initial data	Satisfy all ADMET thresholds
LOTUS	9246	6157
COCONUT	22,975	15,525
DrugBank	627	446
MayBridge	1896	1233
Total	**34,744**	**23,361**

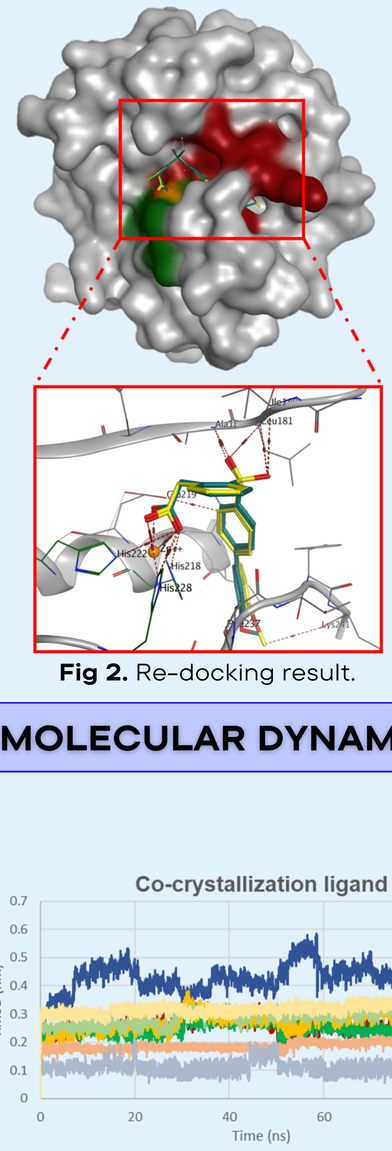

Fig 2. Re-docking result.

MOLECULAR DOCKING

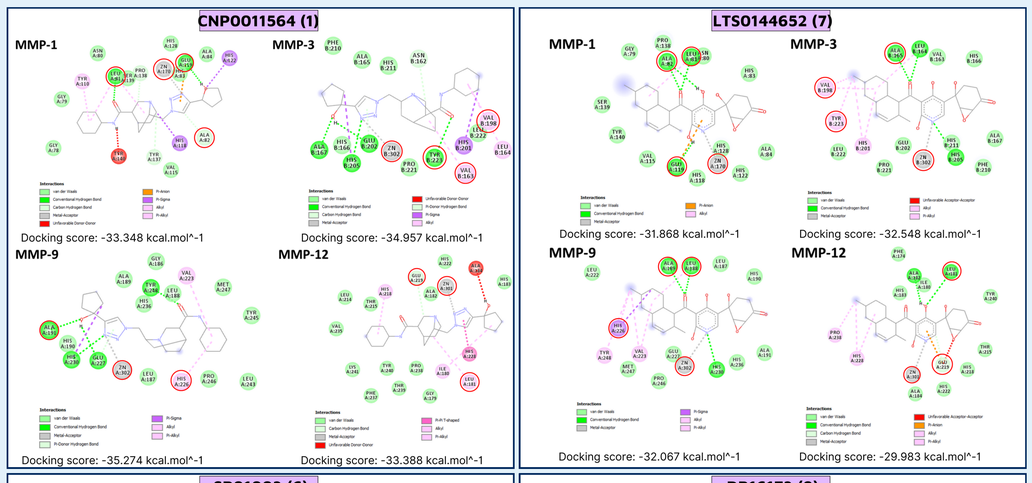

Fig 3. Docking scores and interactions with four MMPs of potential ligands.

MOLECULAR DYNAMICS SIMULATION

Fig 4. RMSD plot of co-crystallization ligand.

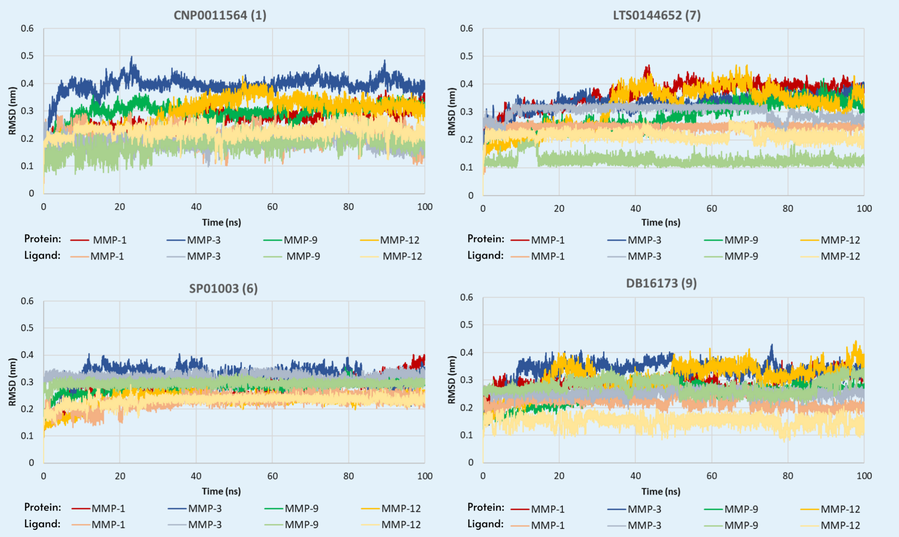

Fig 5. RMSD plot of four potential ligands.

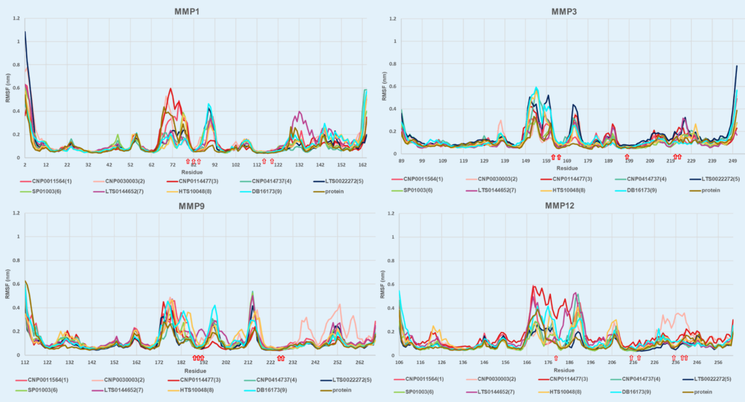

Fig 6. RMSF plot of nine potential ligands.

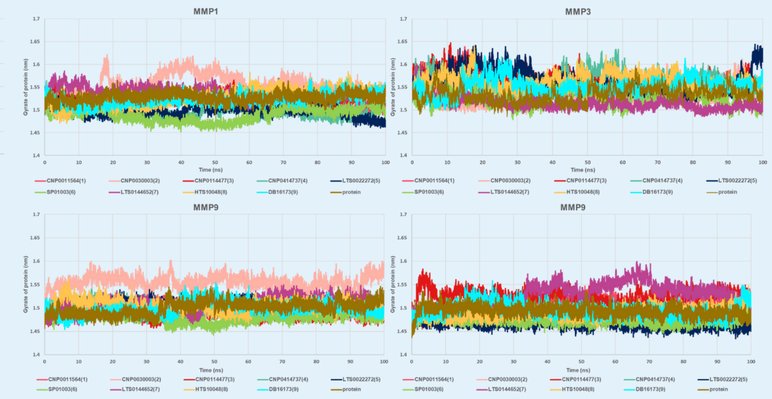

Fig 7. Rg plot of nine potential ligands.