BCADD 2023

Evaluation of selected indigenous spices and herbs derived small molecules as potential inhibitors of SREBP1 and its implications for breast cancer using MD simulations and MMPBSA calculations

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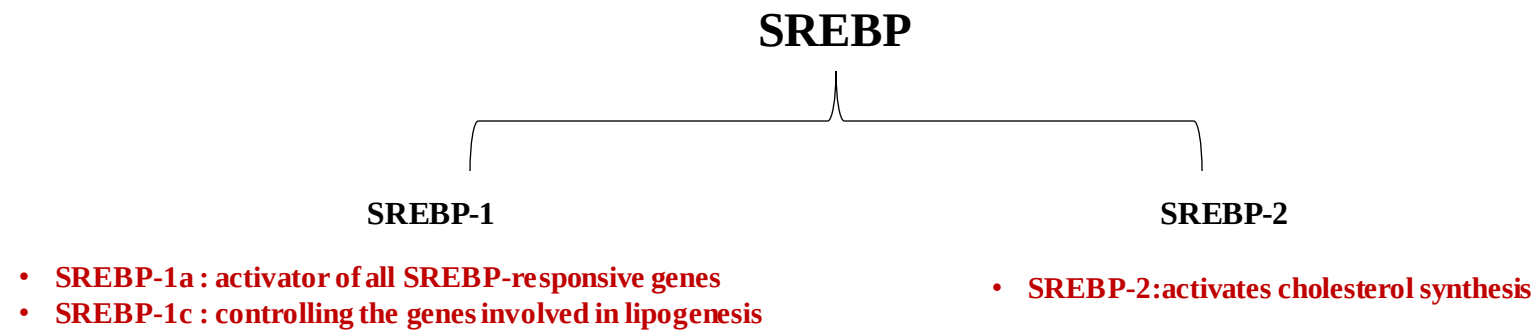
Introduction

- In breast cancer cells, there is often an increased demand for lipids to support rapid cell growth and proliferation.
- A Sterol regulatory element-binding protein 1 (SREBP1) is a transcription factor that plays a crucial role in regulating lipid and cholesterol metabolism in the body.
- SREBPs works as a mediator in transferring signals from oncogenic pathways to the activation of lipid synthesis and uptake.
- High levels of SREBP1 can lead to the upregulation of genes involved in lipid biosynthesis and may contribute to the increased lipid synthesis seen in breast cancer cells.

SELECTION OF SREBP1 ISOFORM AS A TARGET



- SREBP-1 is linked to lymph node metastasis, tumor-node metastasis, and tumour differentiation.
- Lipid metabolism has been identified as being essential for tumor formation and progression. Indeed, multiple studies demonstrated that the lipid metabolism alteration shown in cell migration, invasion, and angiogenesis.

Why are indigenous spices and herbs as an inhibitor?

- About 1/3 of cancer cases can be prevented by Spices and Herbs.
- Thwart cancer-promoting factors, promote cell repair, and initiate cancer cell death.
- Exhibit strong anti-cancer and anti-mutagenic effects.
- They can modify non-coding RNAs and Upregulate tumor suppressive miRNAs.
- Inhibit uncontrolled growth of cancer cells through miRNA regulation.
- Natural compound chemical structures can be adjusted and improve solubility, metabolic processing, and absorption

Selected most common Indian spices & herbs

S. No.	Spice and herbs	Scientific name	References
1	Turmeric	*Curcuma longa*	Dosoky NS et al.,2018
2	True Cardamom	*Elettaria cardamomum*	Noumi E, Snoussi M, Alreshidi MM, et al.
3	Black cardamom	*Amomum subulatum*	Shailja Choudhary et al.,2020
4	Clove	*Syzygium aromaticum*	Nassar, Mahmoud et al.,2007
5	Cinnamon	*Cinnamomum cassia*	Abdelwahab, Siddig et al.,2014
6	Black pepper	*Piper nigrum*	Nikolić M, Stojković D, Glamočlija J, et al.
7	Cumin	*Cuminum cyminum*	Patil, Dr. Sahadeo et al.,2016
8	Fennel flower	*Nigella sativa*	Srinivasan, Krishnapura.,2018
9	Nutmeg and Mace	*Myristica fragrans*	R, G. et al.,2018
10	Fenugreek	*Trigonella foenum-graecum*	Syed, Qamar Abbas et al.,2020
11	Black mustard	*Brassica nigra*	Anubhuti Sharma and PK Rai.,2018
12	Coriander	*Coriandrum sativum*	Chahal, Khushminder et al.,2017
13	Onion	*Allium cepa*	Fredotović, Ž. et al.,2020
14	Garlic	*Allium sativum*	El-Saber Batiha et al.,2020
15	Holy Basil	*Ocimum tenuiflorum*	Mao QQ et al.,2019
16	Ginger	*Zingiber officinale*	Wakchaure, Rajesh & Ganguly, Subha. (2018)
17	Saffron	*Crocus sativus*	Zhang, Z. et al.,2013
18	Sweet And chili pepper	*Capsicum annuum*	Bal S et al.,2022
19	Indian bay leaf	*Cinnamomum tamala*	Kumar, Suresh et al.,2012
20	Star Anise	*Illicium verum*	Sharafan M et al.,2022

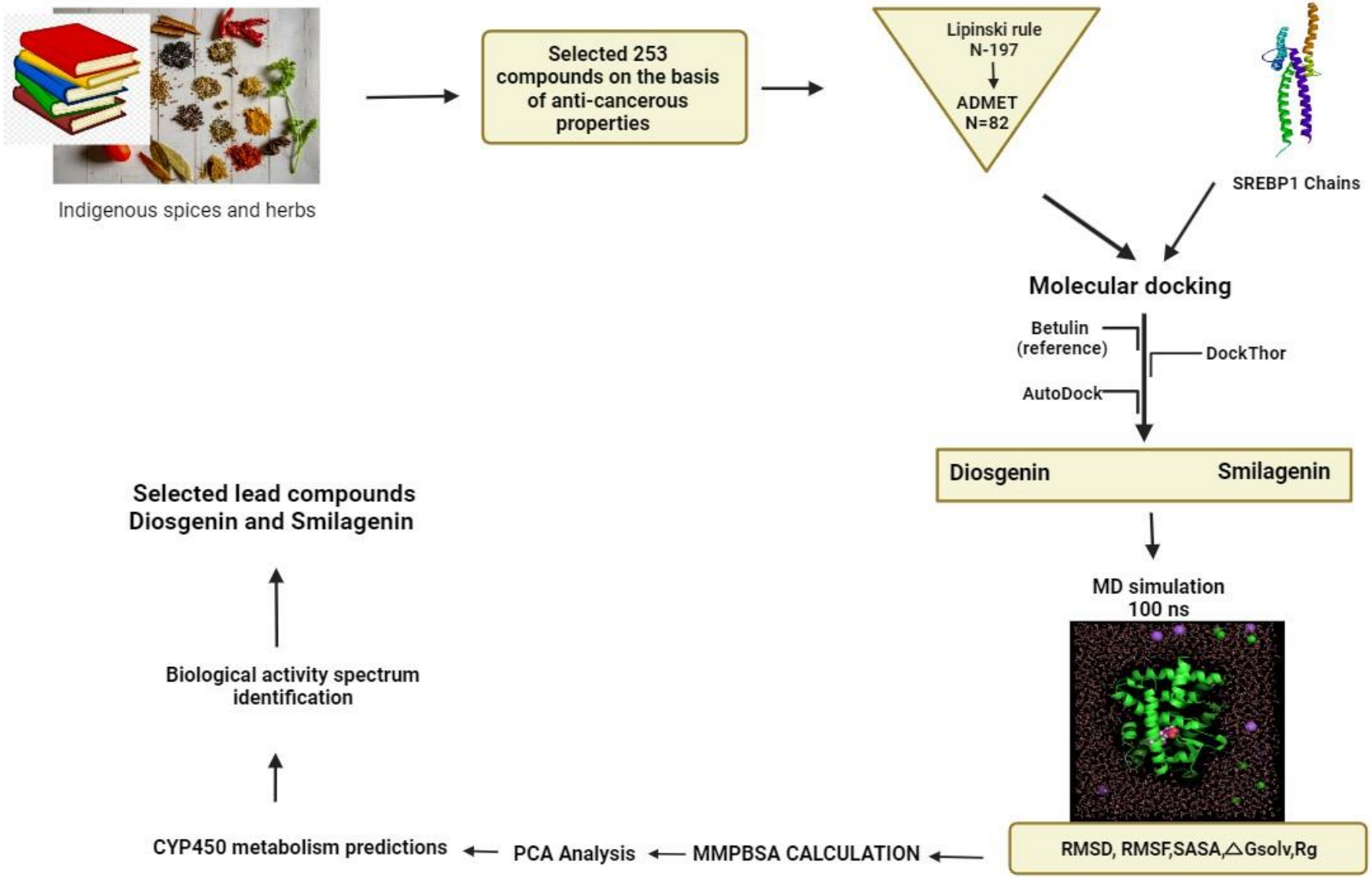


Figure 1:Flow chart of methodology

Drug likeness & ADMET Screening

- Out of 253 compounds, 197 passed the bioavailability filter, indicating they are likely to be suitable for use in drug development.
- 82 compounds were eliminated during ADMET screening due to potential issues related to absorption, distribution, metabolism, excretion, toxicity.

Top Filtered compounds

S. No.	Compounds	Spices and Herbs
1	Curcumenol	Turmeric
2	1,8-cineole	Cardamom
3	Eugenol	Clove
4	Cinnamaldehyde	Cinnamon
5	Piperine	Black pepper
6	Cuminaldehyde	Cumin
7	Thymoquinone	Fennel flower
8	Safrole	Nutmeg
9	Diosgenin,Smilagenin	Fenugreek
10	Allyl isothiocyanate	Mustard seed
11	linalool	Coriander
12	Diallyl disulfide	Onion
13	Allixin	Garlic
14	Gingerdiol	Ginger
15	Capsaicin	Chillies
16	Pivalic acid	Bayleaf
17	Anethole	Star Anise

Molecular docking (MD)

- DockThor and Autodock 4.2.6 were used.
- Diosgenin (ADT ΔG: -6.57 kcal/mol, DockThor ΔG: -8.27 kcal/mol) and Smilagenin (ADT ΔG: -6.46 kcal/mol, DockThor ΔG: -8.29 kcal/mol) emerged as top-performing compounds. While betulin (ADT ΔG: -4.27 kcal/mol, DockThor ΔG: -8.27 kcal/mol)
- Findings highlight Diosgenin and Smilagenin as premium molecules for efficient interaction with SREBP1a chain.

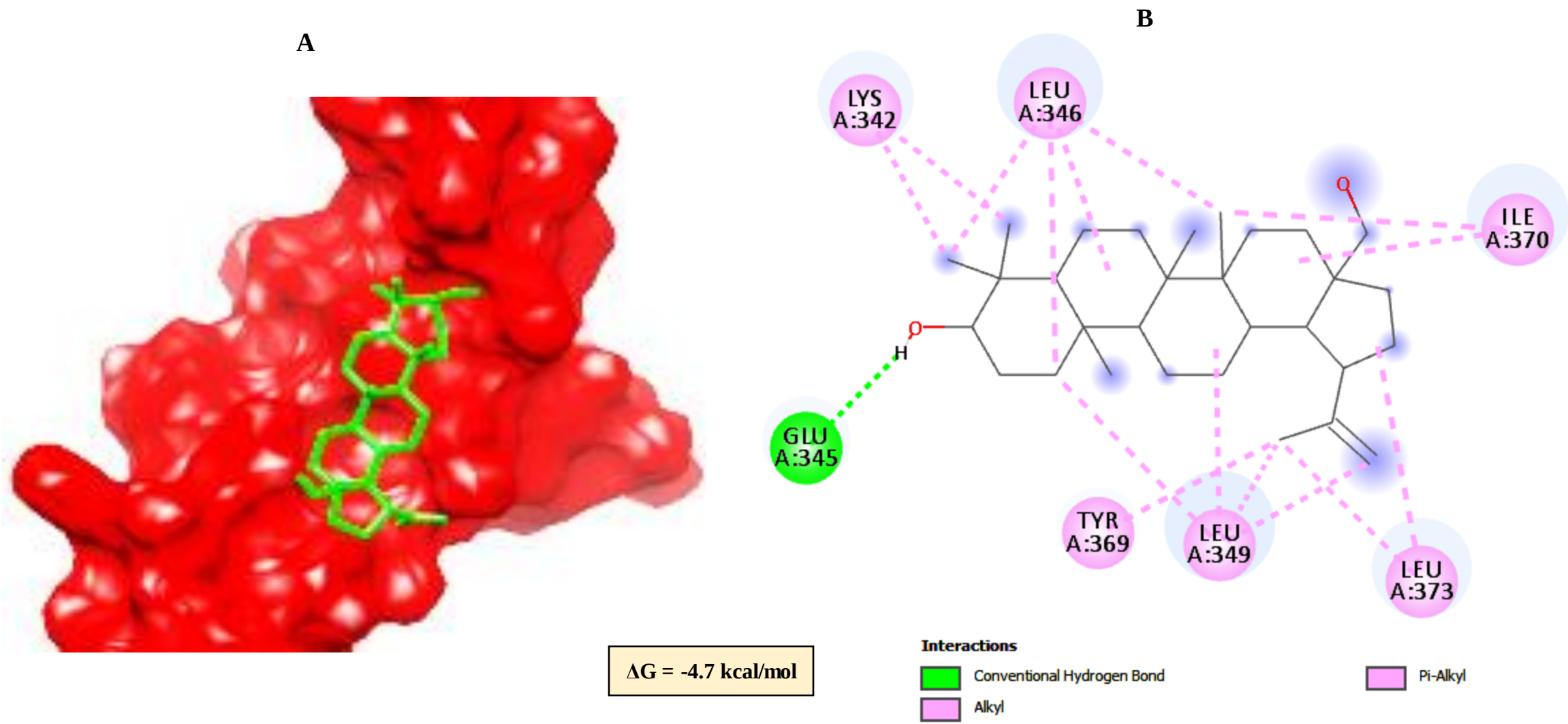


Figure-2. SREBP1a–Betulin complex. A) A 3D image of betulin (green stick) linked to SREBP1a. B) A 2D representation of the betulin residues that bind to SREBP1a. The bond type is color-coded on the inner annotation. The number shows the location within the chain, while the capital letters identify the chain to which the residue belongs.

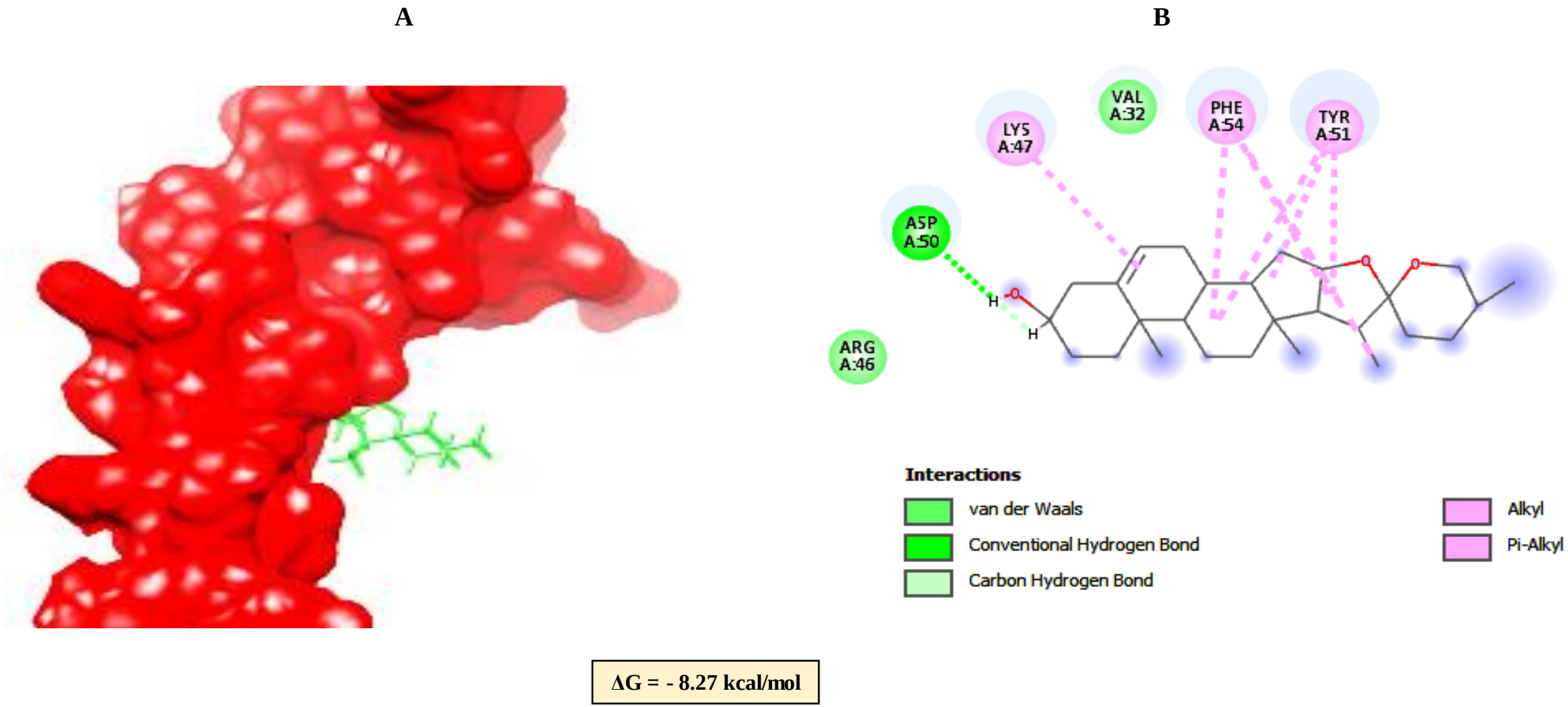


Figure 3. SREBP1a–Diosgenin complex. A) A 3D image of diosgenin (green stick) linked to SREBP1a. B) A 2D representation of the diosgenin residues that bind to SREBP1a. The bond type is color-coded on the inner annotation. The number shows the location within the chain, while the capital letters identify the chain to which the residue belongs.

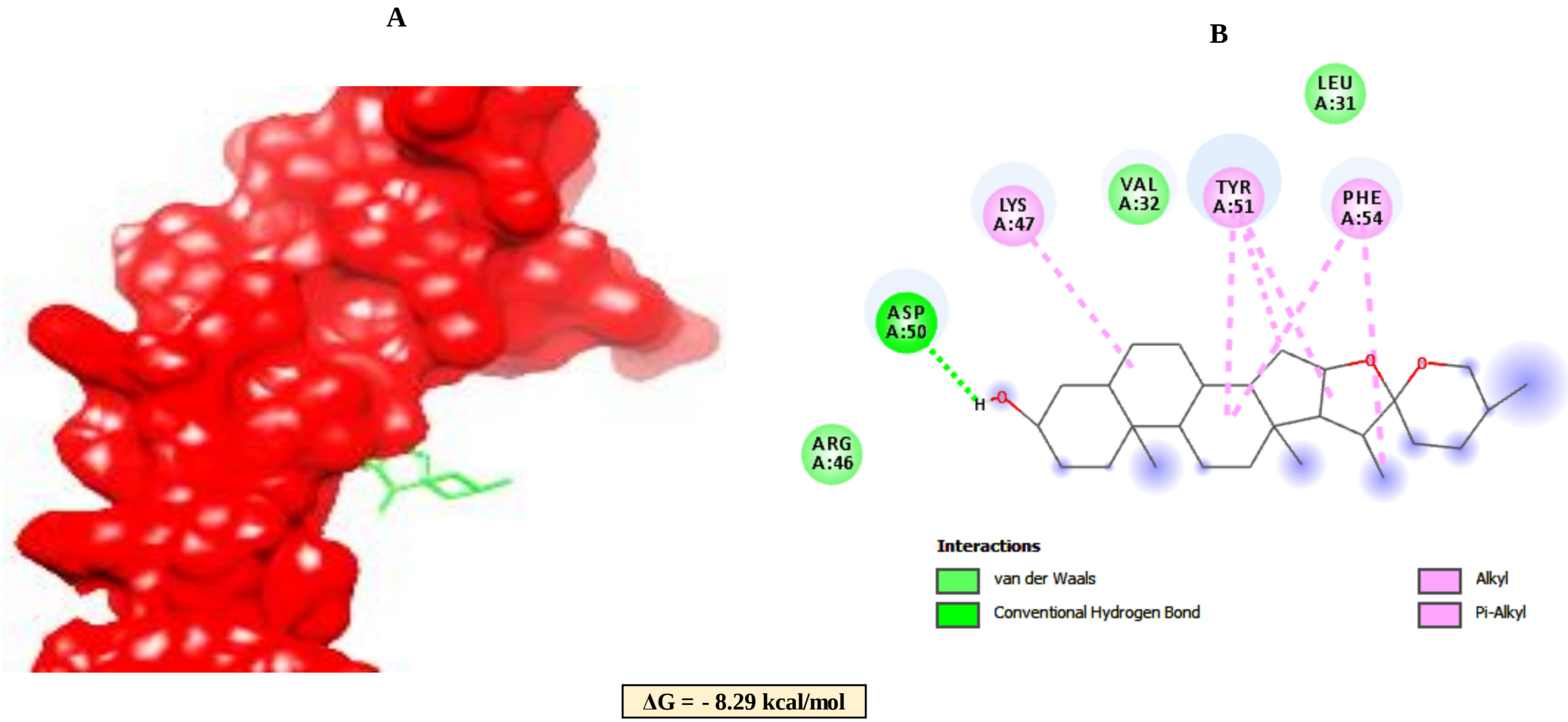


Figure 4. SREBP1a–Smilagenin complex. A) A 3D image of smilagenin (green stick) linked to SREBP1a. B) A 2D representation of the smilagenin residues that bind to SREBP1a. The bond type is color-coded on the inner annotation. The number shows the location within the chain, while the capital letters identify the chain to which the residue belongs.

MD simulation

- The stability assessment was conducted through Molecular Dynamics Simulations (MDS) with a substantial duration of 100 nanoseconds.
- Simulations provided valuable insights into the long-term stability and behavior of these complexes, shedding light on their potential as promising candidates for further study.

RMSD & RMSF

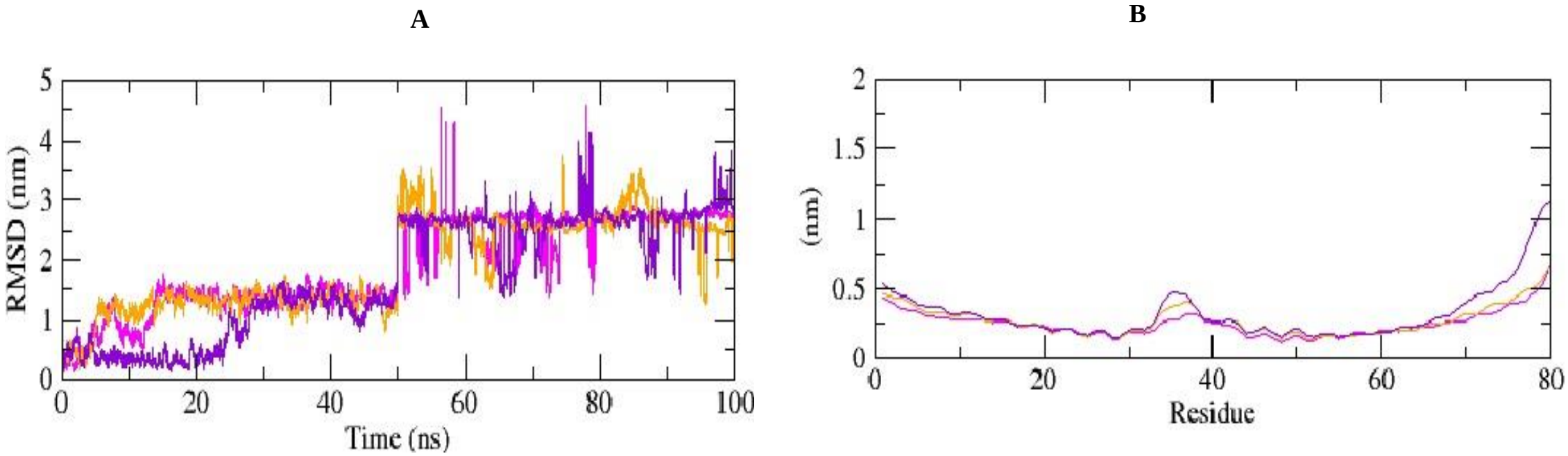


Figure 5: A) RMSD plot as a function of time. magenta, orange, and violet colors represent values obtained for betulin-SREBP1a, diosgenin-SREBP1a, and smilagenin-SREBP1a complexes respectively. B) RMSF plot as a function of time. magenta, orange, and violet colors represent values obtained for betulin-SREBP1a, diosgenin-SREBP1a, and smilagenin-SREBP1a complexes respectively.

SASA & ΔGsolv

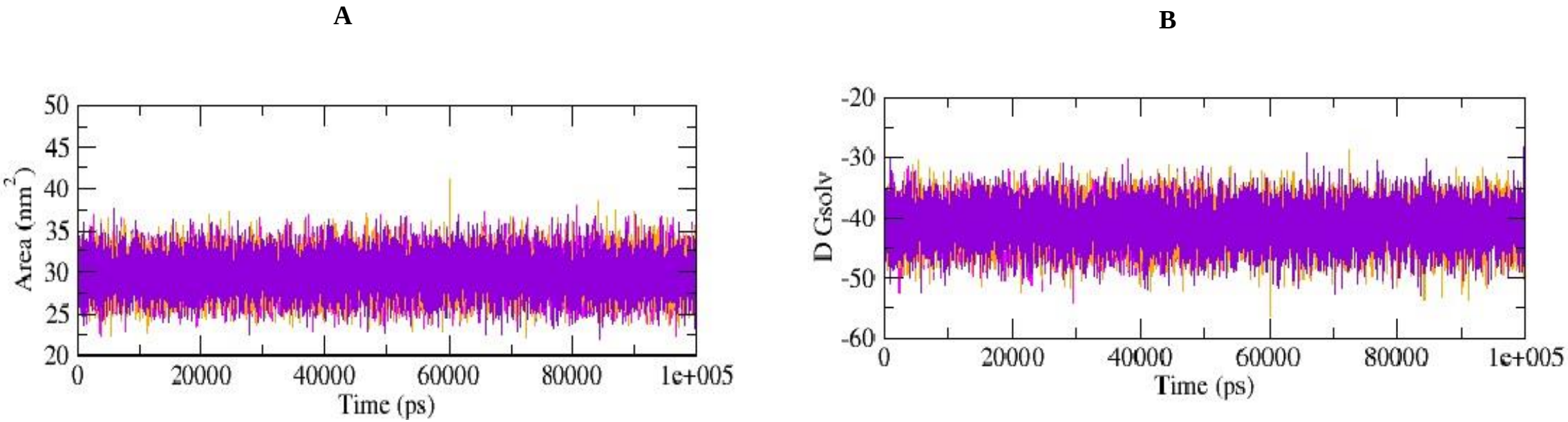


Figure 6: A) SASA plot as a function of time. magenta, orange, and violet colors represent values obtained for betulin-SREBP1a, diosgenin-SREBP1a, and smilagenin-SREBP1a complexes respectively. B) ΔGsolv plot as a function of time. magenta, orange, and violet colors represent values obtained for betulin-SREBP1a, diosgenin-SREBP1a, and smilagenin-SREBP1a complexes respectively.

Rg plot

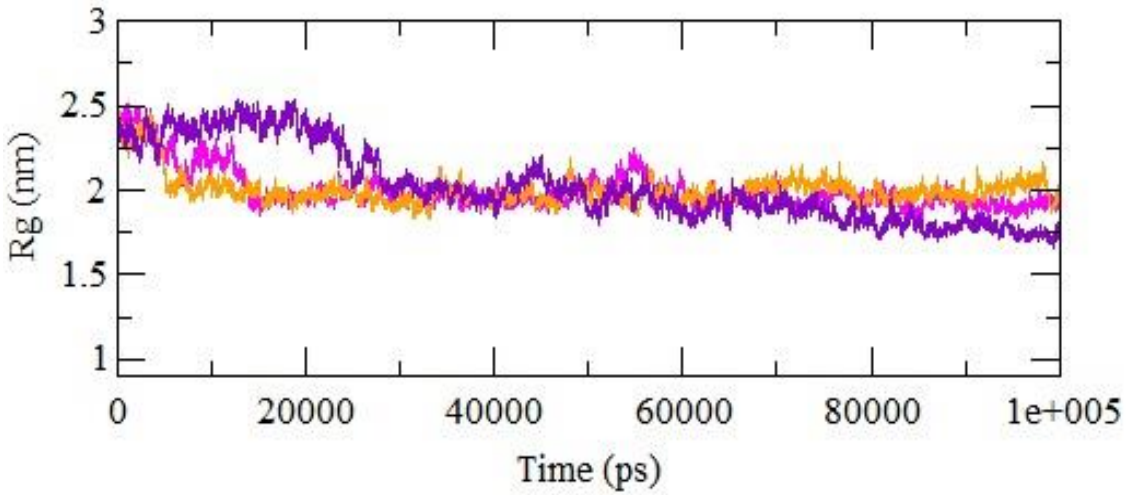


Figure 6: Rg plot as a function of time. Magenta, orange, and violet colors represent values obtained for betulin-SREBP1a, diosgenin-SREBP1a and smilagenin-SREBP1a complexes respectively.

MMPBSA calculations

Polar solvation energy (kJ/mol)				Vacuum MM energy (kJ/mol)			Average binding energy (kJ/mol)		
Complexes	**Protein PB energy**	**LIG PB energy**	**Protein-LIG PB energy**	**Protein-LIG VdW energy**	**Protein-LIG Elec. energy**	**Protein-LIG total energy**	**van der Waals energy**	**Electrostatic energy**	**Binding energy**
SREBP1a-Betulin	-6500	-188	-6253	-150	-325	-475	-148	-325	-165
SREBP1a-Diosgenin	-6805	-250	-6318	-163	-596	-759	-165	-586	-268
SREBP1a-Smilagenin	-5832	-178	-4978	-135	-230	-365	-137	-215	-158

PRINCIPAL COMPONENT ANALYSIS

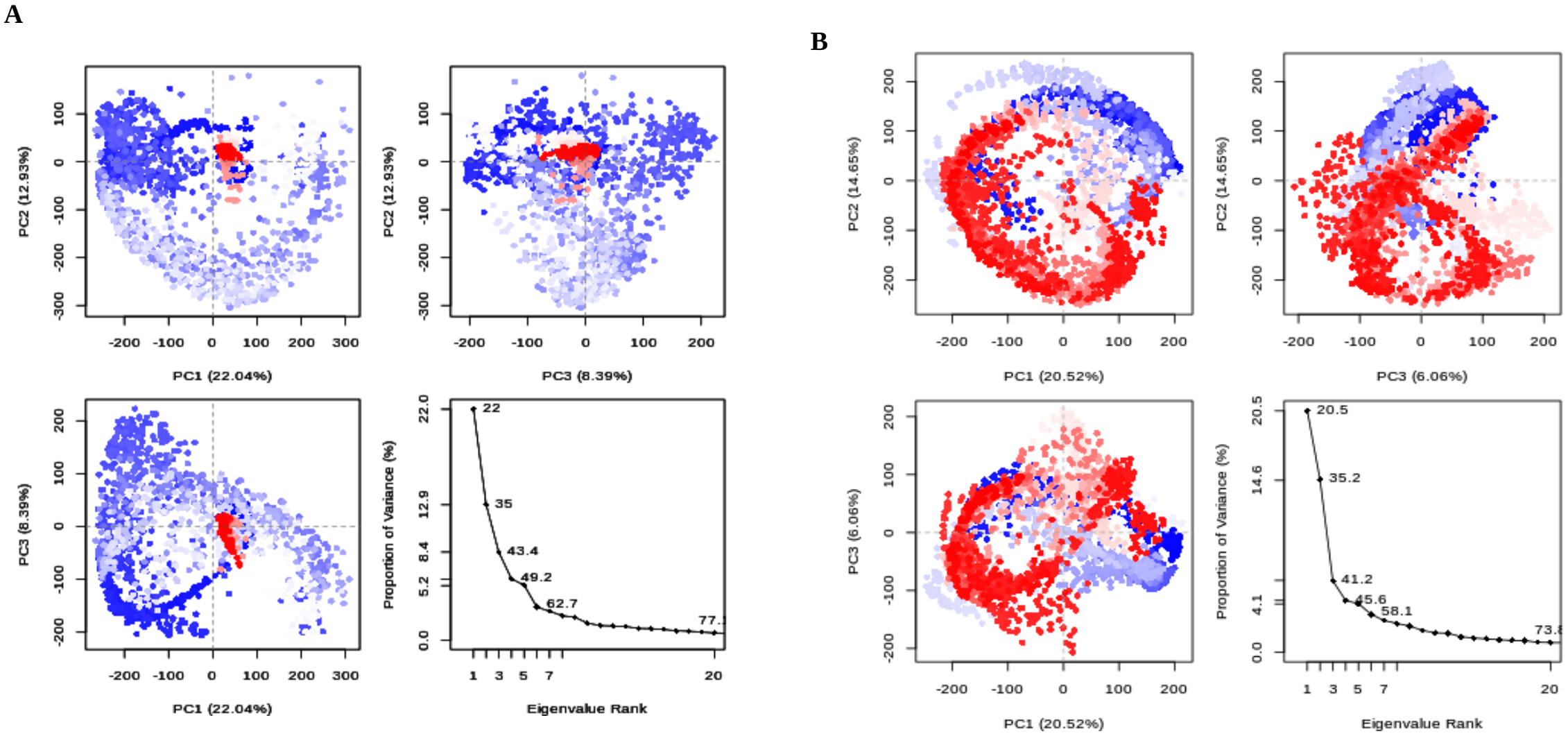


Figure 7: PCA analysis of protein with A) betulin B) diosgenin

CONCLUSION

An extensive assessment of various factors, including toxicity, lipophilicity, solubility, pharmacokinetics, drug-like characteristics, medicinal chemistry attributes, average potential energy, RMSD, RMSF, SASA, ΔGsolv, Rg, and PCA findings, indicates that diosgenin holds promise as a superior inhibitor of SREBP in comparison to smilagenin.

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ACKNOWLEDGEMENTS

- Organizing Committee members of BCADD-2023.
- Supervisor, Department of Bioengineering.
- ACBB
- IIRC
- BRTF

THANKYOU