

Email ID: nkchopra.pharm@gmail.com; priyanagupharma@gmail.com; vineet.mehta20@gmail.com

METHODOLOGY

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graph LR; A[NETWORK PHARMACOLOGY] --> B[ML-QSAR (RANQSAR)]; B --> C[MOLECULAR DOCKING (AUTODOCK VINA)];
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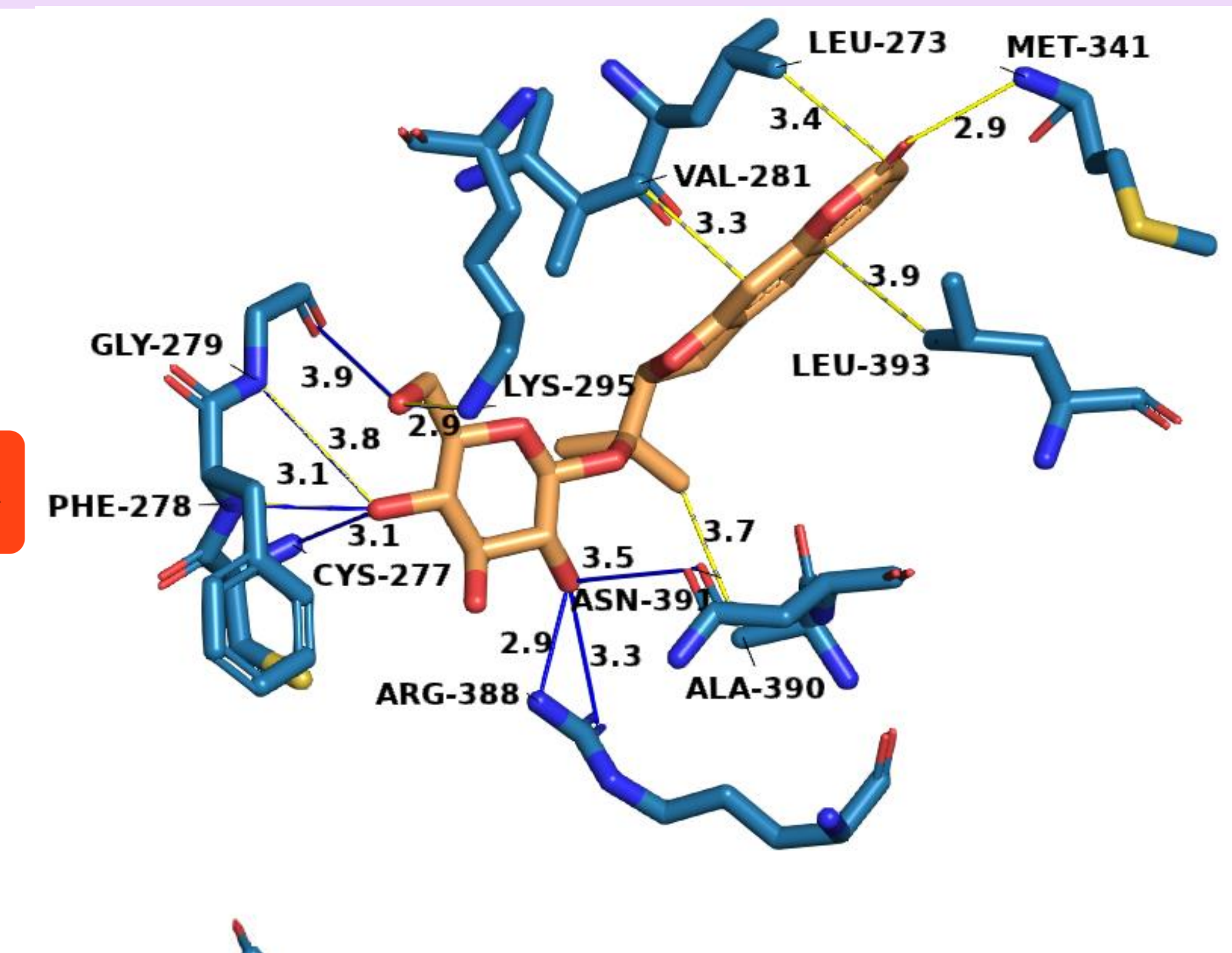
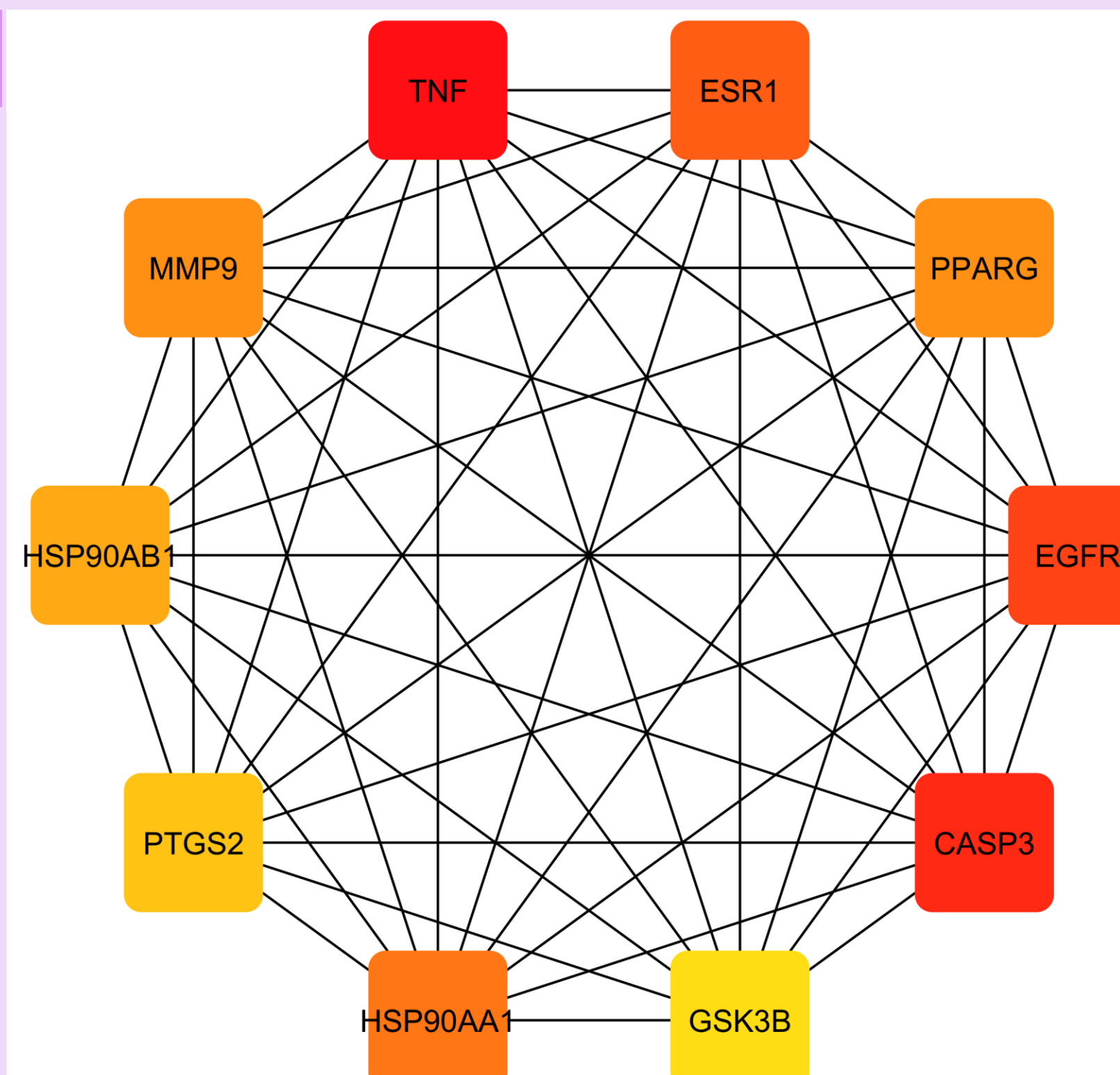
NETWORK PHARMACOLOGY

ML-QSAR (RANQSAR)

MOLECULAR DOCKING (AUTODOCK VINA)

Shramahara Mahakasya is an ayurvedic formulation consisting of 10 plants which could be beneficial in management of AD. Out of 596 bioactive molecules, a total of 134 molecules were screened on the basis of Lipinski's rule of 5. Our results showed that these 134 molecules have a total of 410 non-repetitive targets out of which 162 works in AD. The top 10 target proteins identified for these bio-actives are namely **TNF**, **CASP3**, **EGFR**, **ESR1**, **HSP90AA1**, **MMP9**, **PPARG**, **HSP90AB1**, **PTGS2** & **GSK3B** which works on AD by various pathways. These 134 molecules were further screened based on predicted biological activity by using ML-based QSAR platform (RANQSAR). The top 20 molecules were further subjected to molecular docking studies to analyze their binding affinity and poses.

Plant Name	Useful Part
<i>Vitis vinifera</i> L.	Fruit
<i>Phoenix dactylifera</i> L.	Fruit
<i>Buchanania lanzan</i>	Seed kernel
<i>Ziziphus mauritiana</i>	Fruit
<i>Punica granatum</i> L.	Fruit
<i>Ficus carica</i> L.	Fruit
<i>Grewia asiatica</i> L.	Fruit
<i>Saccharum officinarum</i>	Stem juice (Internode)
<i>Hordeum vulgare</i>	Grain
<i>Oryza sativa</i> L.	Grain



- ❖ To identify the potential bioactive molecules of AM and predict pathways to inhibit neurodegeneration using NP.
- ❖ To validate the results of NP using MD.
- ❖ To provide an experimental justification for the traditional use of AM in Ayurveda for CNS complications.

S.No.	Molecule	Predicted IC50 (uM)			Binding affinity (kCal/mol)		
		ACHE	BCHE	BACE	ACHE	BCHE	BACE
1	Syringaldehyde	1.340092	1.744281565	2.465233836	-5.3	-5.3	-4.4
2	Quercetin	1.373004	1.508754435	0.755412549	-8.8	-8.9	-6.9
3	Rizolipase	1.726195	1.397800527	1.751962952	-6	-6.3	-6.4
4	Norisoboldine	1.76823	1.760428972	1.799777536	-8.7	-10	-6.7
5	Vanillin	1.796678	1.75163152	1.976204494	-5	-5.8	-4.7
6	Ferulic Acid	1.79887	1.920091434	2.341657431	-5.2	-4.9	-5
7	Zingerone	1.804468	1.718206777	2.190789514	-5	-6.2	-5
8	4-hydroxybenzaldehyde	1.860467	1.910224832	2.821093628	-4.9	-5.5	-4.3
9	Guaiacol	1.893568	1.493639126	1.893551443	-5.3	-5.1	-4.6
10	2,3-dimethoxyphenol	1.902473	1.446605265	1.774081367	-4.9	-5.5	-4.4
11	Donepezil	0.054	2.557	1.413	-8.9	-9.9	-6.7

FUTURE PROSPECTS

- Syringaldehyde, Quercetin, Rizolipase, Norisoboldine are the most promising bioactive molecules present in the ayurvedic formulation “Shramahara Mahakasya”. That could be responsible for the beneficial effects in improving neuronal activity and cognitive functions.
- The major bioactive molecules which played a decisive role in AD by influencing multiple genes such as **AKT1, TNF, SRC, STAT3, EGFR, CASP3** and numerous other genes are involved in the various functions.
- The impact of AM against AD can be attributed to numerous biological processes such as protein phosphorylation, signal transduction and regulation of apoptotic process which influences various pathways involved in AD namely PI3K-Akt signaling pathway, MAPK signaling pathway, and Ras signaling pathway out of which **PI3K-Akt signaling pathway** was most promising pathway identified.

- ❖ Our results guide directions for subsequent *in vivo* **experiments based on the comprehensive investigation** into the pharmacological and molecular mechanism underlying SM in AD management.
- ❖ To conduct **clinical trials** to advance and validate the effectiveness of the ayurvedic polyherbal formulation.

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