

Attenuating Cholinergic Neurotoxicity by an Ayurvedic Formulation: An Integrative Medicine Approach

Poster Number: Tuesday-1182

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- ❖ A widely used ayurvedic polyherbal formulation has neuroprotective activities.
- ❖ *In-silico* approaches reveal that the formulation interacts with key pathological targets: Acetylcholinesterase and GSK-3 β .
- ❖ *In-vitro* activities exhibit promising outcomes when used in combination with a standard drug as an integrative medicine approach.

INTRODUCTION

Alzheimer's disease has a complex etiology involving proteins like amyloid beta and tau. Tau has seen increasing interest in the past decade, and therapeutic strategies targeting it are being investigated. WHO has developed the TCIM Strategy to encourage evidence-based research in traditional medicine. Exploring this opportunity, we have dissected the molecular mechanisms of the neuroprotective activities of a widely used polyherbal formulation – Saraswat churna (SC).

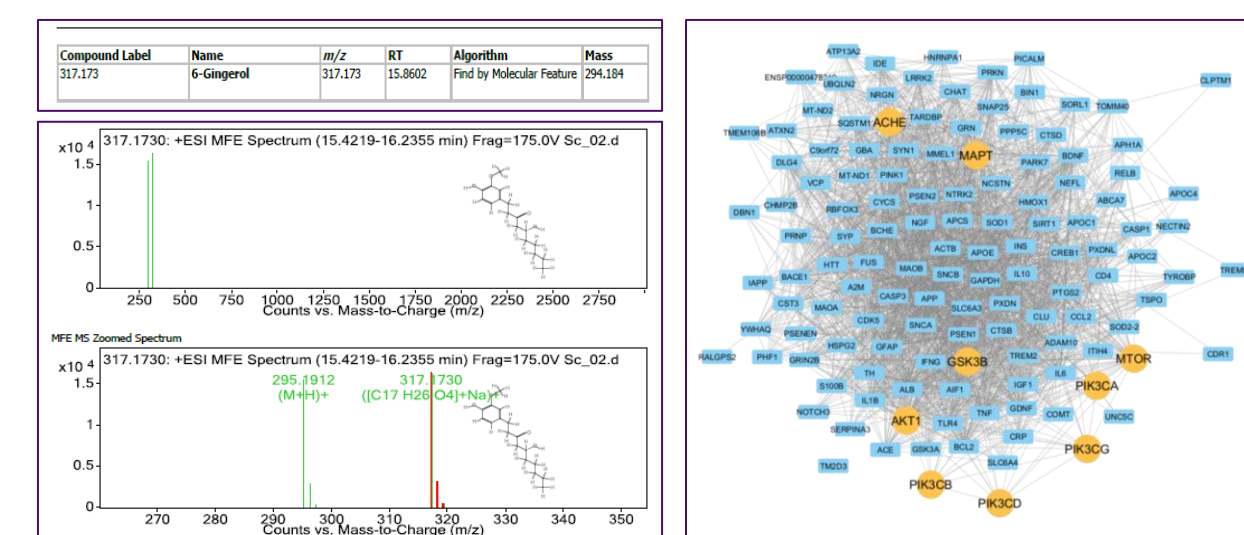
METHODS

1. SC aqueous extract preparation
2. Q-TOF-MS/MS
3. Network pharmacology
4. Molecular docking
5. Molecular Dynamics
6. Cell line investigations (SH-SY5Y model)

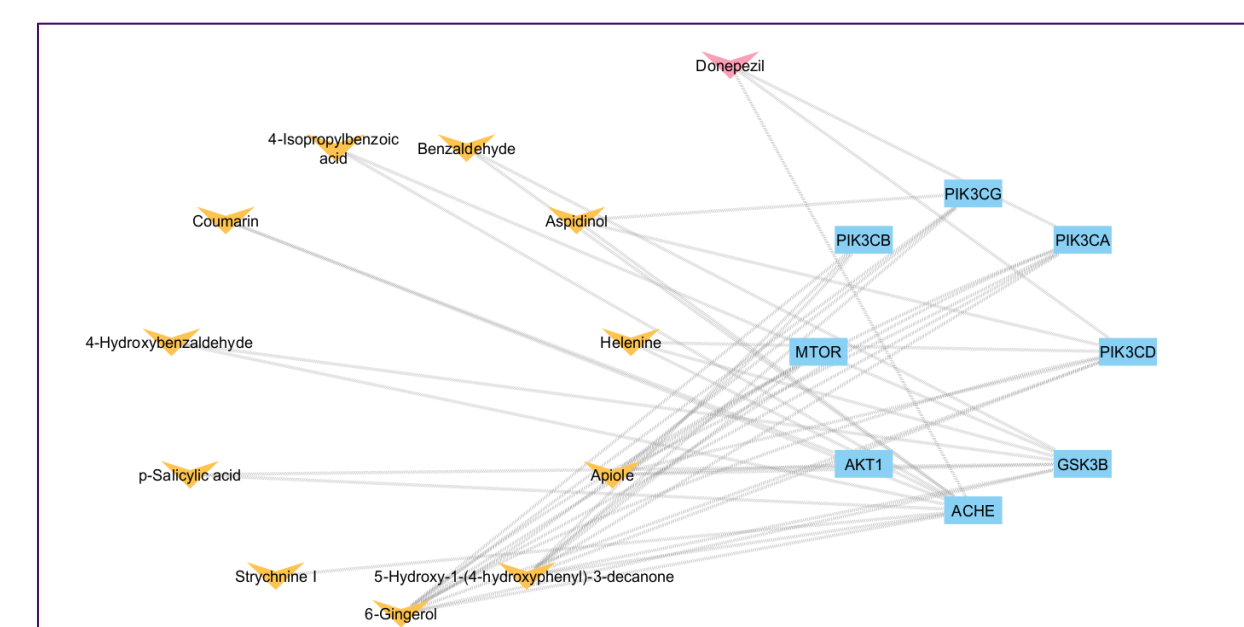
RESULTS

- Q-TOF-MS/MS analysis revealed around 723 compounds in SC.

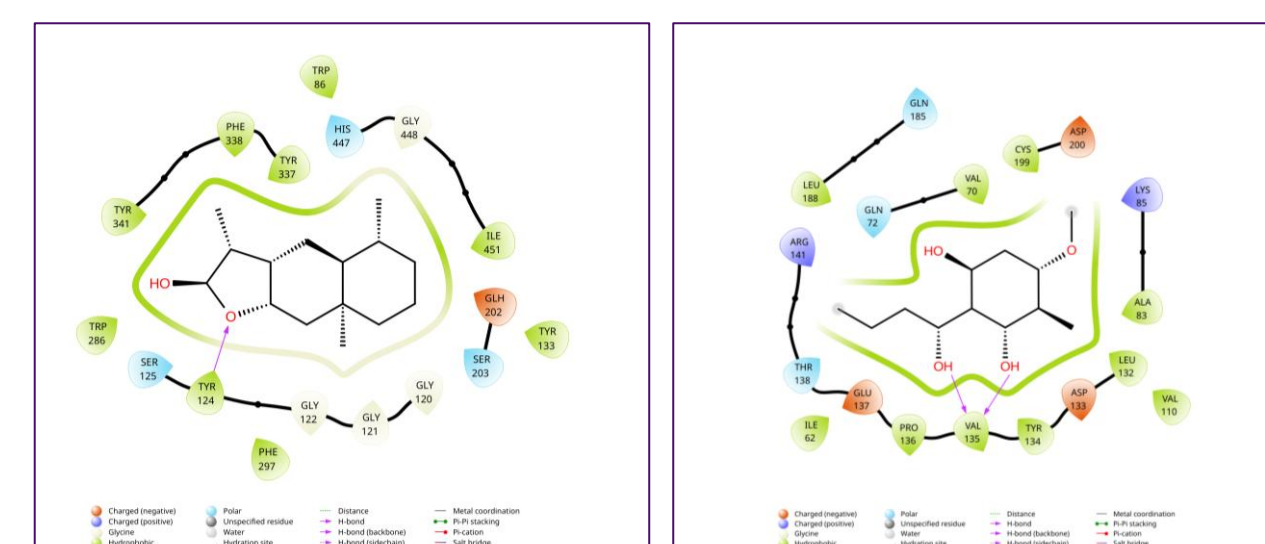
- The protein-protein network acquired from the STRING database shows genes involved in dementia and tau pathology interact with each other.



- Further, target prediction revealed the possible interactions between the genes and the compounds from SC.

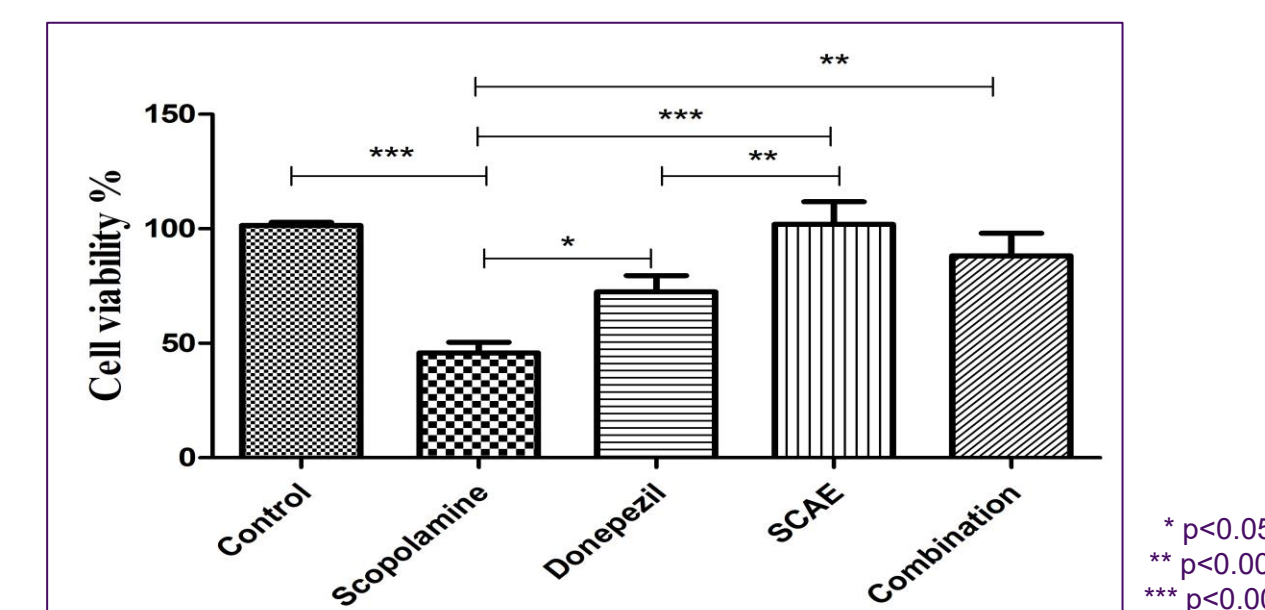


- These interactions, when subjected to molecular docking and MD simulations, reveal important interactions with acetylcholine and GSK-3 β .

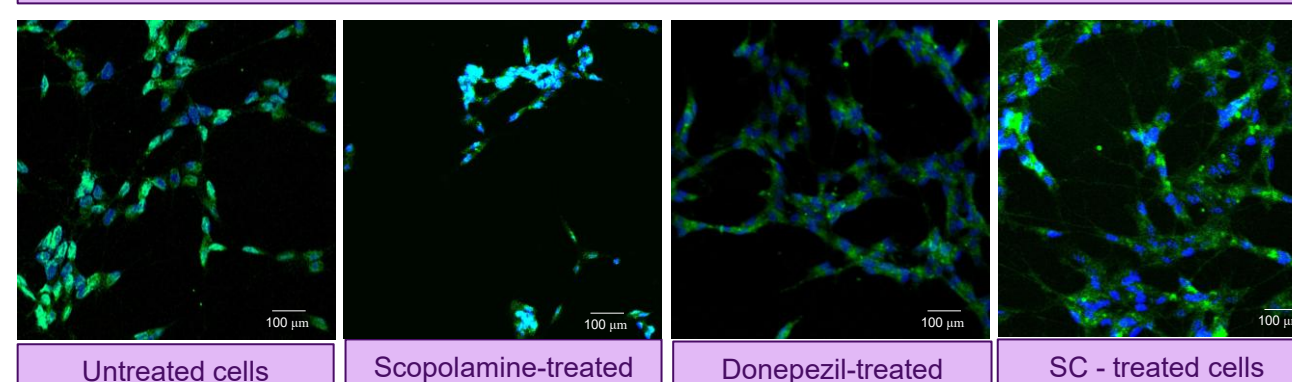


Helenine, a bioactive compound from SC, shows strong molecular interactions with AChE.

Aspidinol, a bioactive compound from SC, shows strong molecular interactions with GSK-3 β .



Differentiated SH-SY5Y cells treated with donepezil (standard drug), SC, and a combination of the two (1:1), exhibit regeneration of neuronal cells following scopolamine-induced neuronal damage.



Differentiated SH-SY5Y stained with Alexa Fluor488-tagged anti-Tau antibody (green) and DAPI (blue) show the morphology of cells under various treatments.

CONCLUSIONS

- The polyherbal formulation has multiple bioactive compounds, thereby providing a multi-target strategy of therapeutic intervention
- This multiple target approach is validated in network pharmacology studies, which show one compound interacting with various disease targets.
- Further, molecular docking and MD simulations show that this interaction with the disease targets is stronger and interacts with amino acids at important sites. This controls the inhibition of AChE and hyperphosphorylation of GSK-3 β .
- Moreover, it is exhibited in cell line models that SC is good at increasing cell viability and protecting synaptic networks after cholinergic damage.
- A combination of SC and Donepezil shows synergistic neuroprotection.

FUTURE PERSPECTIVES

- Gene and protein expression studies to elucidate the pathways involved.

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