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Computational Evaluation of Bioactive Compounds from Vaccinium vitis-idaea L (Ligonberry) for Treating KRAS-associated Lung Cancer

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***In silico* drug design approach** revealed **inhibitors** that could be tested as **potential drug candidates** against KRAS-associated lung cancer

1. Introduction

- Until recently, directly targeting KRAS mutation involved in many cancer types have historically achieved little success due to associated complexities encountered during interaction with ligand.
- KRAS interacts with several proteins including phosphodiesterase 6δ (PDE6D) termed the trafficking chaperone of prenylated proteins.
- Studies (Papke et al. 2016) have shown that the manipulation of PDE6D directly affects the localization and spatial organization of KRAS and this might provide an alternative route for indirectly inhibiting KRAS signaling.

2. Methods

- Considered 39 phenolic bioactive compounds extracted from Lingonberry plant in a recent study (Raudone et al. 2019)
- 3D conformers of ligands and a control were retrieved from PubChem database and the protein from Protein Data Bank
- Phytocompounds were virtually screened using the PyRx software
- Molecular docking and post docking analysis using Maestro-Schrödinger suite and the Desmond program
- Drugability were predicted and conformation to the Lipinski rule of five conventions were pursued using the SwissADME web platform

3. Results

Table 1. *Top four bioactive compounds (including control, Sotorasib) and corresponding binding affinities upon interaction with the target protein.*

COMPOUND	BINDING AFFINITY (Kcal/mol)
(+) – Catechin (Cianidanol)	**-8.1**
Resveratrol	-7.9
Arbutin	-6.6
Sinapic acid	-6.5
Sotorasib	**-5.6**

3. Results

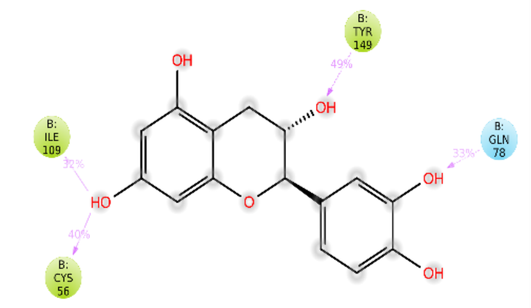

Figure 1. *Structural view of a top compound, (+) – Catechin (Cianidanol)) in interactions with the protein residues.*

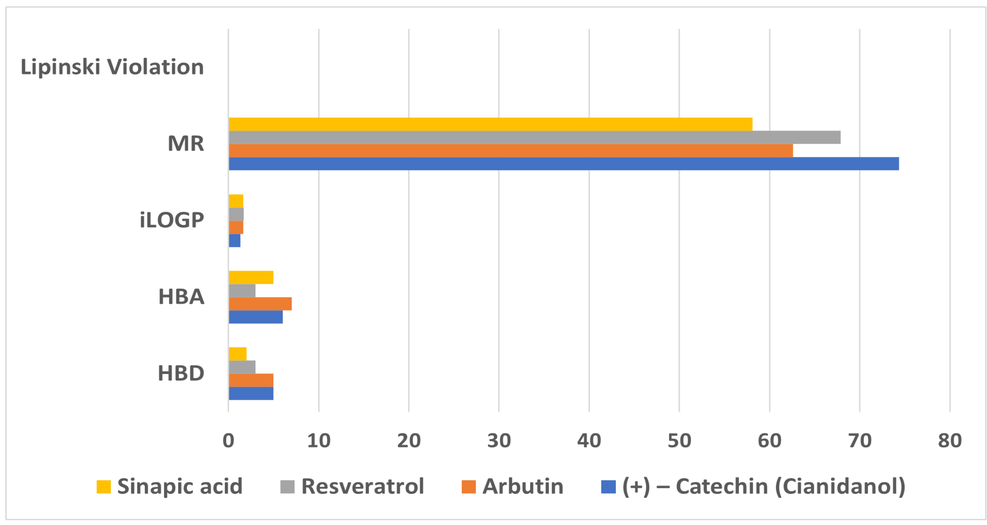

Figure 2. *Drug-likeness prediction of top four bioactive compounds following molecular docking.*

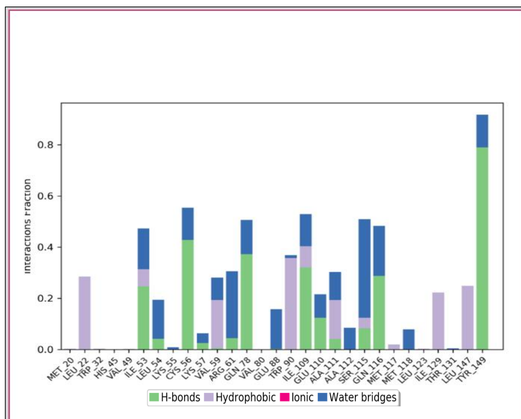

Figure 3. *Stability of docked 4JV8 and (+) – Catechin (Cianidanol) complexes for hydrogen bonds, ionic interactions, hydrophobic contacts, and water bridges*

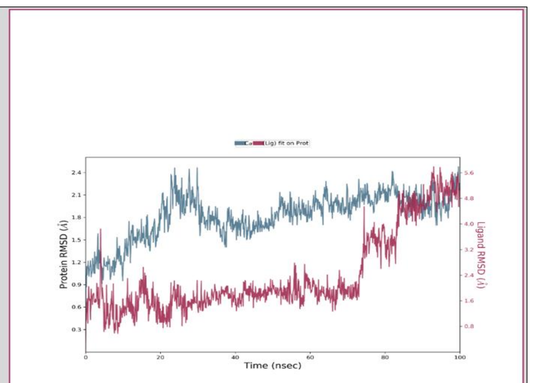

Figure 4. *Molecular dynamics simulation (RMSD) of the protein and (+) – Catechin (Cianidanol).*

4. Take home

- 4 out of 26 bioactive compounds with high binding affinity could be further explored.
- Further (in-vitro) assays are needed to validate the drugability of the top compounds.

References

1. *Papke, Björn, et al. "Identification of pyrazolopyridazinones as PDEδ inhibitors." Nature communications 7.1 (2016): 1-9*
2. *Raudone, Lina, et al. "Antioxidant activities of Vaccinium vitis-idaea L. leaves within cultivars and their phenolic compounds." Molecules 24.5 (2019): 844.*
3. *Zimmermann, Gunther, et al. "Small molecule inhibition of the KRAS–PDEδ interaction impairs oncogenic KRAS signaling." Nature 497.7451 (2013): 638-642.*

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