Berry and citrus phenolic compounds can bind to hepatocyte nuclear factor-1 alpha

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Introduction

- Hepatocyte nuclear factor-1 alpha (HNF-1A) has shown to increase the expression of the enzyme dipeptidyl peptidase IV (DPP-IV).[1]
- HNF-1A is a transcription factor with three domains and a linker that interacts with the dimerization cofactor of hepatocyte nuclear factor-1 (DCoH).[2]
- DPP-IV is a new target in the treatment of type 2 diabetes as it degrades insulin releasing hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[3]
- It has been shown that phenolic compounds present in many berries and citrus fruits can inhibit DPP-IV activity. [3]

Objective

To investigate if the flavonoids apigenin, luteolin, cyanidin-3-glucoside, delphinidin-3-arabinoside, malvidin-3-galactoside, and malvidin-3-glucoside and the stilbenoid resveratrol can bind to the dimerization domain, homodimer of the dimerization domain, and the DNA domain of hepatocyte nuclear factor-1 alpha using computational modeling.

Methodology

Preparation of Ligands

Structure files obtained from Chemical Book or created using Marvin Sketch

↓

Chlorine atoms deleted if present and hydrogen atoms added

↓

CHARMm22 force field and DreidingMinimize function applied

↓

Non-rotatable bonds in flavonoids designated

↓

AutoDock PDBQT files created

Preparation of Macromolecules

Protein Data Bank (PDB) files obtained (PDB ID: 1G39, 1IC8, & 1JB6)

↓

Water molecules and unnecessary amino acids and residues deleted

↓

Hydrogen atoms added

↓

Flexible residues designated in macromolecules with dimerization domain

↓

Flexible and rigid AutoDock PDBQT files created

Performing Computational Dockings

Grid parameters determined in AutoDockTools[4]

↓

Configuration files created with macromolecule and ligand files

↓

Ran AutoDock Vina[5] dockings

↓

Analyzed results in Accelrys Discovery Studio 3.5

Results

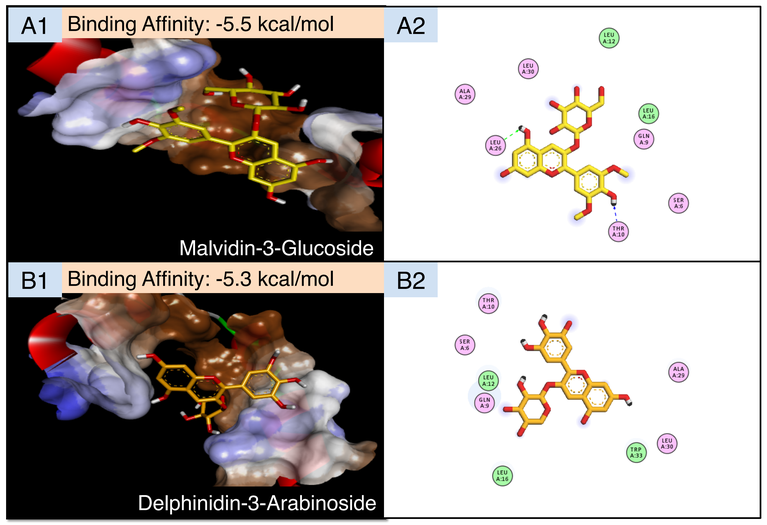

Figure 1. The lowest (A1, A2) and second lowest (B1, B2) binding affinity conformations are shown for the dimerization domain of hepatocyte nuclear factor-1 alpha. A molecular graphic of each interaction is displayed (A1, B1). Amino acids that interacted with each ligand (A2, B2) are presented with pink for being involved in hydrogen-bonding, ionic, or polar interactions or with green for having Van der Waals interactions. Dashed arrows indicate hydrogen bonds to side chain amino acids when blue and to backbone amino acids when green.

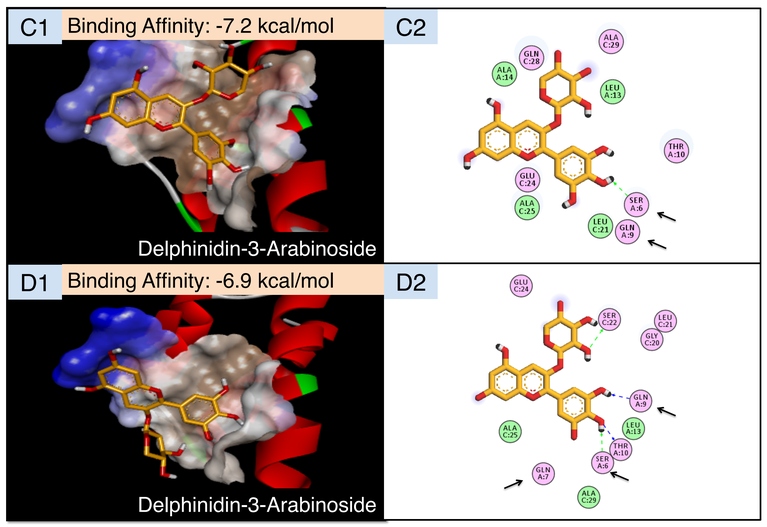

Figure 2. The lowest (C1, C2) and second lowest (D1, D2) binding affinity conformations are shown for the homodimer of the dimerization domain of hepatocyte nuclear factor-1 alpha. A molecular graphic of each interaction is displayed (C1, D1). Amino acids that interacted with each ligand (C2, D2) are presented with pink for being involved in hydrogen-bonding, ionic, or polar interactions or with green for having Van der Waals interactions. Dashed arrows indicate hydrogen bonds to side chain amino acids when blue and to backbone amino acids when green. Black arrows indicate target amino acids that bind to the dimerization coactivator of hepatocyte nuclear factor-1 (DCoH).

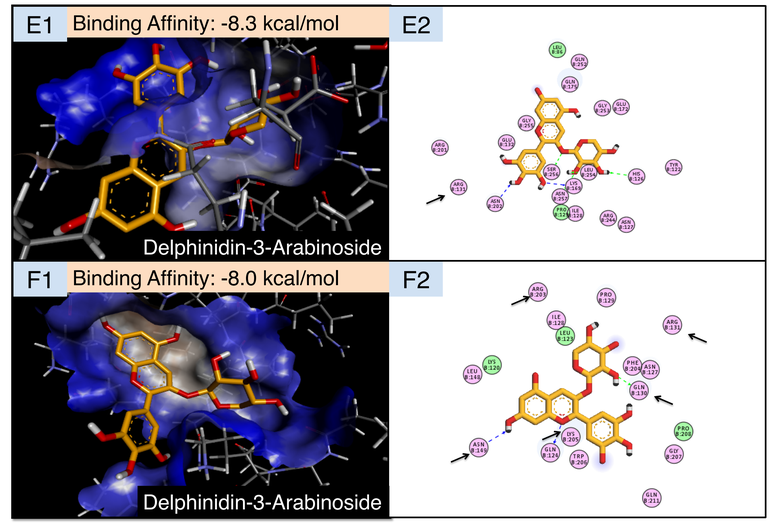

Figure 3. The lowest (E1, E2) and the second lowest (F1, F2) binding affinity conformations are shown for the DNA domain of hepatocyte nuclear factor-1 alpha. A molecular graphic of each interaction is displayed (E1, F1). Amino acids that interacted with each ligand (E2, F2) are represented with pink for being involved in hydrogen-bonding, ionic, or polar interactions or with green for having Van der Waals interactions. Dashed arrows indicate hydrogen bonds to side chain amino acids when blue and to backbone amino acids when green. Black arrows indicate target amino acids that specifically bind to DNA.

Conclusions

- Berry and citrus phenolic compounds, especially delphinidin-3-arabinoside, can bind to hepatocyte nuclear factor-1 alpha (HNF-1A).
- Berry and citrus phenolic compounds can bind to target amino acids that bind to the dimerization cofactor of hepatocyte nuclear factor-1 (DCoH) and DNA.
- The phenolic compounds tested could be possible inhibitors of HNF-1A activity and decrease the expression the of DPP-IV gene. This could allow for normal function of insulin releasing hormones in patients with type 2 diabetes.

Acknowledgments

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References

(1) Gu et al. Biochem Biophys Res Commun 2006; 346(3): 1016-1023. doi: 10.1016/j.bbrc.2006.06.010 **(2)** Narayana et al. J Mol Biol 2001; 310(3): 635-658. **(3)** Fan et al. Evid Based Complement Alternat Med (in press). **(4)** Morris et al. J Comput Chem 2009; 30(16): 2785–2791. doi: 10.1002/jcc.21256 **(5)** Trott & Olson. J Comput Chem 2010; 31(2): 455-461. doi: 10.1002/jcc.21334