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THE POTENTIAL OF PURPLE CABBAGE (*BRASSICA OLERACEA* L. VAR. *CAPITATA F. RUBRA*) CHEMICAL CONSTITUENTS AS ANTIHYPERTENSIVE: *IN SILICO* AND ADMET APPROACH

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BACKGROUND

Purple cabbage

Carotenoid

Anthocyanin

Vitamin

Polyphenol

Flavonoid

Antioxidant

Anti-inflammatory

Antihypertensive

eNOS enzyme

OBJECTIVE

This study aims to determine the effectiveness of compounds from purple cabbage as antihypertensive and pharmacokinetic predictions.

METHODOLOGY

Prediction of constituent interactions from purple cabbage with eNOS enzyme using AutoDock Tools 1.5.6. Then, the potency of constituents based on molecular docking was tested for pharmacokinetic properties with the pkCSM ADMET descriptors algorithm protocol.

RESULTS AND DISCUSSION

1. Molecular Docking Validation

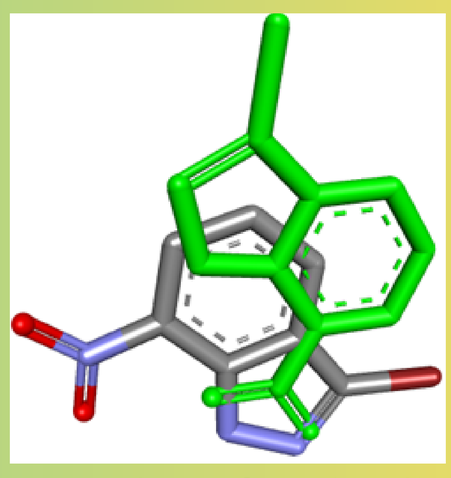

Figure 1. Overlap of native ligand between *co*-crystal (green) and *re*-docking (gray)

The docking parameter in this study was declared valid because it has an RMSD of 3.077 Å. It shows that the position of the native ligand as a result of *re*-docking after being superimposed was getting closer to the *co*-crystal results (Jain and Nicholls, 2008).

2. Receptor-Ligands Interaction and Visualization

Compounds	Amino Acid Residue Interactions: Hydrogen Bonds	Amino Acid Residue Interactions: Van der Waals Bonds (Hydrophobic)	ΔG (kcal/mol)	Ki (nM)
Test ligands				
Cyanidin-3-diglucoside-5-glucoside	Glu465, His463, Ala448, Asp446, Met466, and Trp76	Ser104, Asn468, and Ala445	-7.85	1770
α-carotene	-	Glu465 and Gln464	-7.94	1510
β-carotene	-	Gly103, Asp446, Asn468, Ala445, Gln464, Glu465, Phe462, and Glu77	-9.91	54.21
α-tocopherol	-	Gln464, Glu465, Met466, and Glu77	-6.18	29560
γ-tocopherol	Met466	Gln464, Glu465, and Arg72	-5.94	44180
Ascorbic acid	Trp447, His463, and Trp76	Gln464, Glu465, and Phe462	-3.83	1570
Vitamin A	Trp447 and Ala445	His463, Gln464, Glu465, Met466, Asp446, and Asn468	-7.06	6630
Quercetin	Met466, Trp447, Trp76 and Phe462	Glu462, Gln464, and His463	-6.87	9290
Kaemferol	Met466, His463, and Trp447	Glu465, Gln464, and Phe462	-6.89	8880
Lutein	-	Glu465, Gln464, and Glu77	-8.40	695.27
Reference ligand				
Captopil	His463, Gln464, and Trp447	Phe462, Met466, and Glu465	-4.02	1130000

In silico molecular docking, results show that β-carotene, lutein, and α-carotene (carotenoid group), as well as cyanidin-3-diglucoside-5-glucoside (anthocyanin group), have very high binding affinities with ΔG (kcal/mol) and Ki values (nM), -9.91; 54.21, -8.40; 695.27, -7.94; 1510, and -7.85; 1770, respectively compared to captopril (-4.02; 1130000) as a drug. The purple color caused by this group of compounds is helpful for therapeutic effects, such as degenerative diseases.

3. Prediction of Pharmacokinetic Properties

Properties	β-carotene	Lutein	α-carotene
Absorption			
Water solubility (log mol/L)	-7.252	-6.822	-7.39
Caco2 permeability (log Papp in 10^{-6} cm/s)	1.239	1.251	1.262
Intestinal absorption (human) (% absorbed)	90.393	89.781	92.061
P-glycoprotein substrate	No	Yes	No
P-glycoprotein I inhibitor	No	No	No
P-glycoprotein II inhibitor	Yes	Yes	Yes
Distribution			
VDss (human, log L/kg)	0.202	-0.23	0.264
Fraction unbound (human) (Fu)	0	0	0
BBB permeability (log PS)	0.92	-0.215	0.945
CNS permeability (log PS)	-1.074	-1.144	-1.094
Metabolism			
CYP2D6 substrate	No	No	No
CYP3A4 substrate	Yes	Yes	Yes
CYP1A2 inhibitor	No	No	No
CYP2C19 inhibitor	No	No	No
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
Excretion			
Total clearance (log mL/min/kg)	1.061	0.924	0.947
Renal OCT2 substrate	No	No	No
Toxicity			
AMES toxicity	No	No	Yes
hERG I inhibitor	No	No	No
hERG II inhibitor	Yes	Yes	Yes
Hepatotoxicity	No	No	No

Properties	Cyanidin-3-diglucoside-5-glucoside	Vitamin A	Kaemferol
Absorption			
Water solubility (log mol/L)	-2.88	-6.415	-3.04
Caco2 permeability (log Papp in 10^{-6} cm/s)	-1.604	1.516	0.032
Intestinal absorption (human) (% absorbed)	0	92.218	74.29
P-glycoprotein substrate	Yes	No	Yes
P-glycoprotein I inhibitor	No	No	No
P-glycoprotein II inhibitor	No	No	No
Distribution			
VDss (human, log L/kg)	0.263	0.5	1.274
Fraction unbound (human) (Fu)	0.276	0.066	0.178
BBB permeability (log PS)	-2.779	0.644	-0.939
CNS permeability (log PS)	-5.754	-2.036	-2.228
Metabolism			
CYP2D6 substrate	No	No	No
CYP3A4 substrate	No	Yes	No
CYP1A2 inhibitor	No	Yes	Yes
CYP2C19 inhibitor	No	No	No
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
Excretion			
Total clearance (log mL/min/kg)	-0.354	1.531	0.477
Renal OCT2 substrate	No	No	No
Toxicity			
AMES toxicity	No	No	No
hERG I inhibitor	No	No	No
hERG II inhibitor	Yes	Yes	No
Hepatotoxicity	No	Yes	No

Properties	Quercetin	α-tocopherol	γ-tocopherol
Absorption			
Water solubility (log mol/L)	-2.925	-6.901	-7.602
Caco2 permeability (log Papp in 10^{-6} cm/s)	-0.229	1.345	1.458
Intestinal absorption (human) (% absorbed)	77.207	89.782	90.043
P-glycoprotein substrate	Yes	No	No
P-glycoprotein I inhibitor	No	No	Yes
P-glycoprotein II inhibitor	No	Yes	Yes
Distribution			
VDss (human, log L/kg)	1.559	0.709	0.732
Fraction unbound (human) (Fu)	0.206	0	0
BBB permeability (log PS)	-1.098	0.876	0.739
CNS permeability (log PS)	-3.065	-1.669	-1.669
Metabolism			
CYP2D6 substrate	No	No	No
CYP3A4 substrate	No	Yes	Yes
CYP1A2 inhibitor	Yes	No	No
CYP2C19 inhibitor	No	Yes	No
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	No	No	No
CYP3A4 inhibitor	No	No	No
Excretion			
Total clearance (log mL/min/kg)	0.499	0.794	0.821
Renal OCT2 substrate	No	No	No
Toxicity			
AMES toxicity	No	No	No
hERG I inhibitor	No	No	No
hERG II inhibitor	No	Yes	Yes
Hepatotoxicity	No	No	No

ADMET predictions show that only α-carotene and vitamin A meet the predictions of absorption (Caco2, 1.262 and 1.516 × 10-6 cm/s and intestinal absorption, 92.061 and 92.218%), distribution (BBB permeability, 0.945; 0.644), metabolism (cytochrome P450), excretion (total clearance, 1,531 log mL/min/kg vitamin A only), and toxicity (vitamin A that is not toxic in AMES test).

CONCLUSION

The carotenoid and vitamin group from purple cabbage have the potential to be antihypertensive.

REFERENCES

Jain, A. N., and Nicholls, A. (2008). Recommendations for evaluation of computational methods. *Journal of Computer-Aided Molecular Design*, 22(3–4),133–139.