HOW FLAVONOID PARAMETERIZATION DETERMINES DRUG-INDECED MEMBRANE BIOPHYSICAL OUTCOMES

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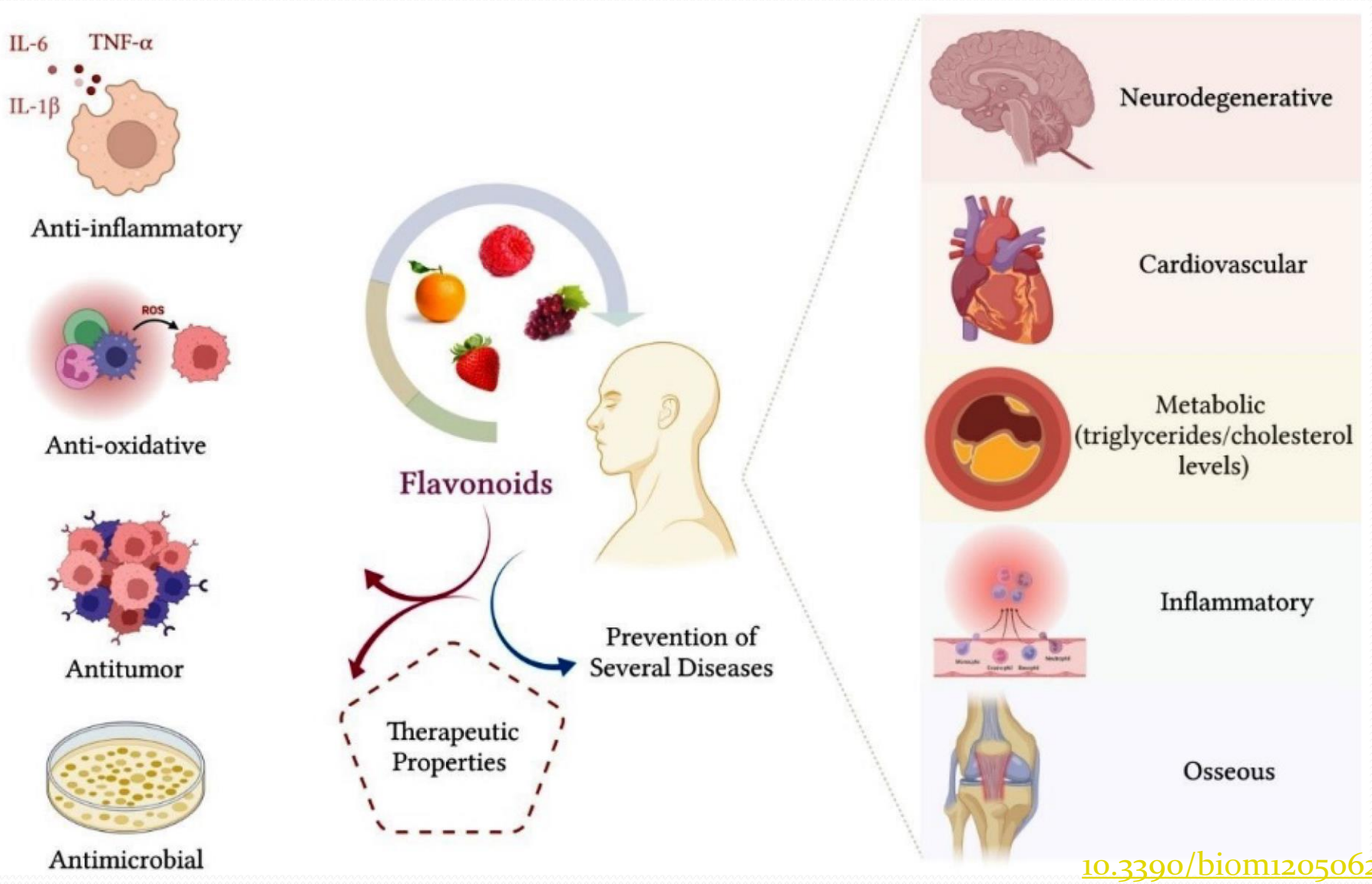
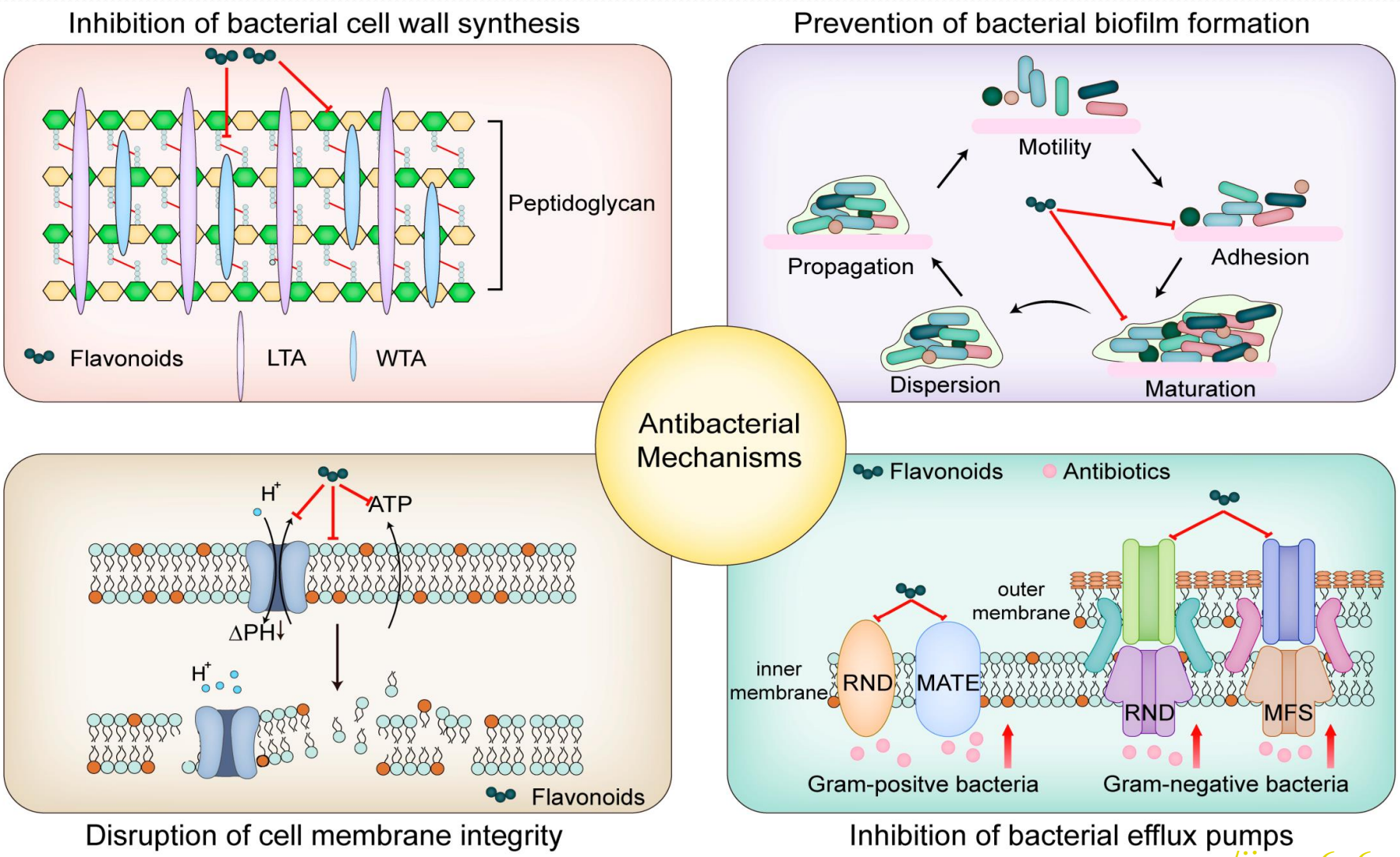
Flavonoids therapeutic effects



10.3390/biom12050626

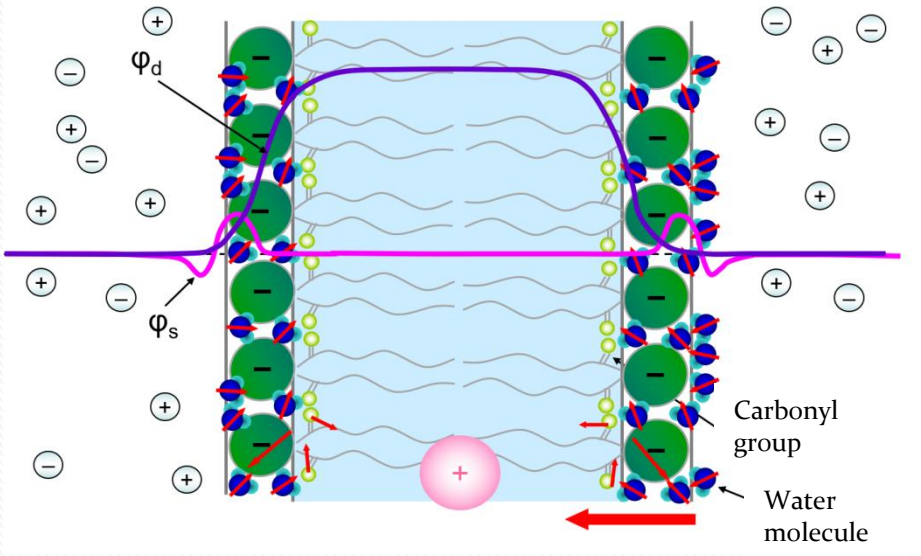
Membrane associated activity



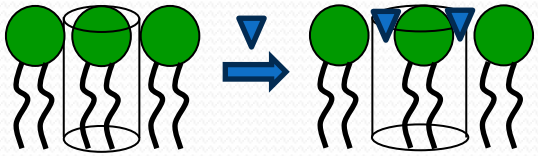
10.3390/ijms26062455

Key membrane properties

- **Transmembrane distribution of electric potential (dipole potential)**



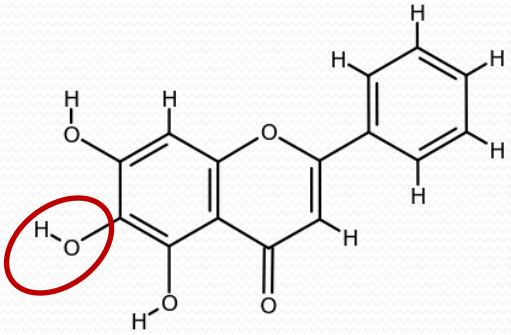
- **Transmembrane distribution of lateral pressure (lipid packing)**



Changes in these properties cause the membrane-mediated action of small molecules.

Can molecular dynamics simulations predict biophysical changes in membrane?

Studied flavonoids

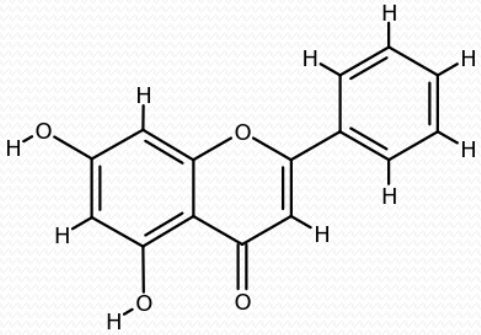


Baicalein

Roots of *Scutellaria baicalensis*

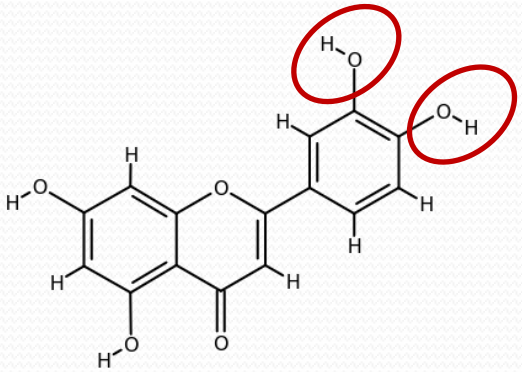
Dipole potential ↑

Passion flower



Chrysin

Dipole potential ↓



Luteolin

Celery

Dipole potential ↓↓↓

Methodology

Parametrization in CHARMM force field

Automated CGenFF v.4 **QC-based ffTK v.2.1**

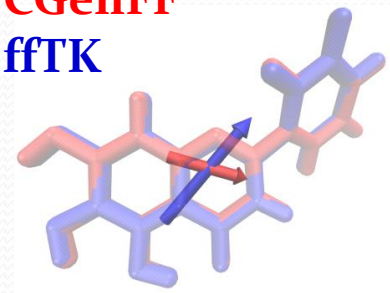
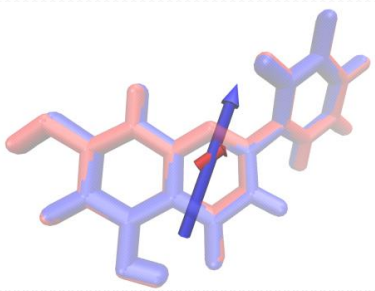
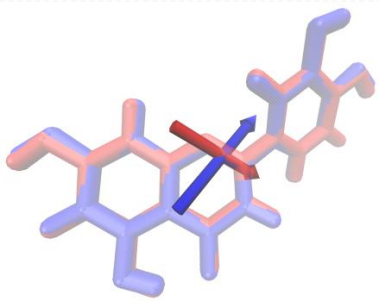
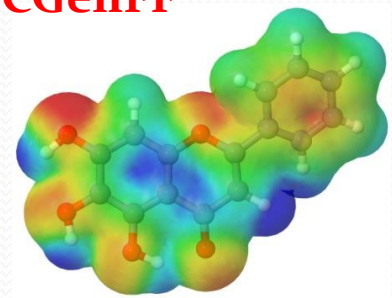
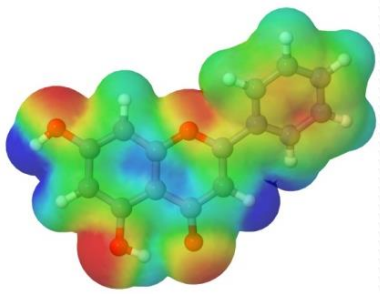
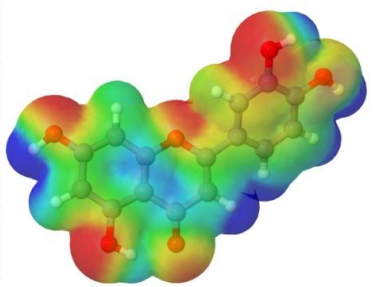
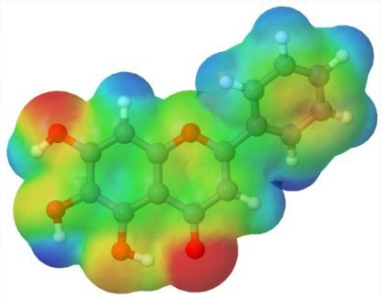
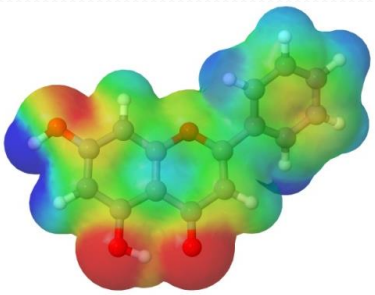
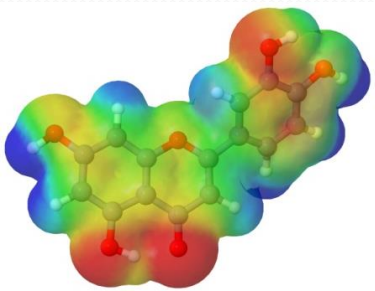
12 or 24 flavonoid molecules inserted
in lipid headgroups of DOPC membrane (120 lipids)

Gromacs v.2023.2
Energy minimization → 6 steps equilibration → 200ns simulation

Analysis of membrane potential

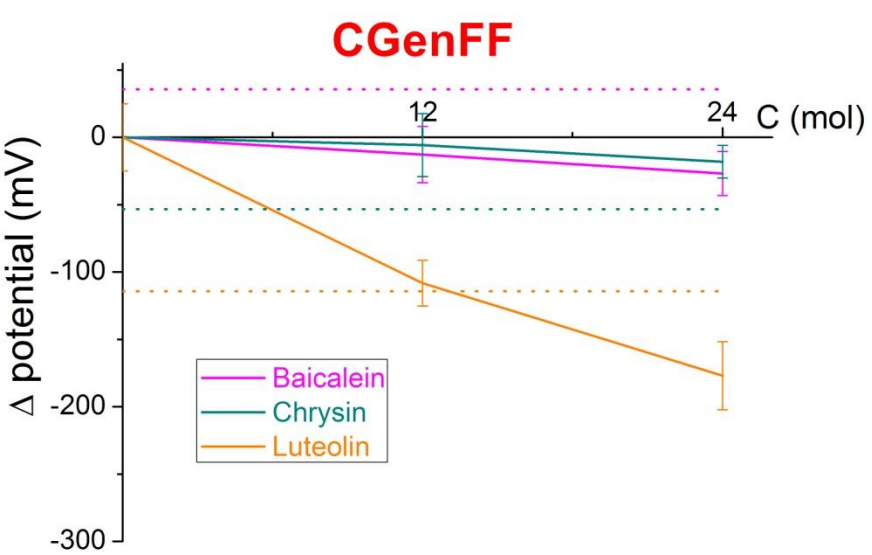
DOPC – dioleoylphosphatidylcholine

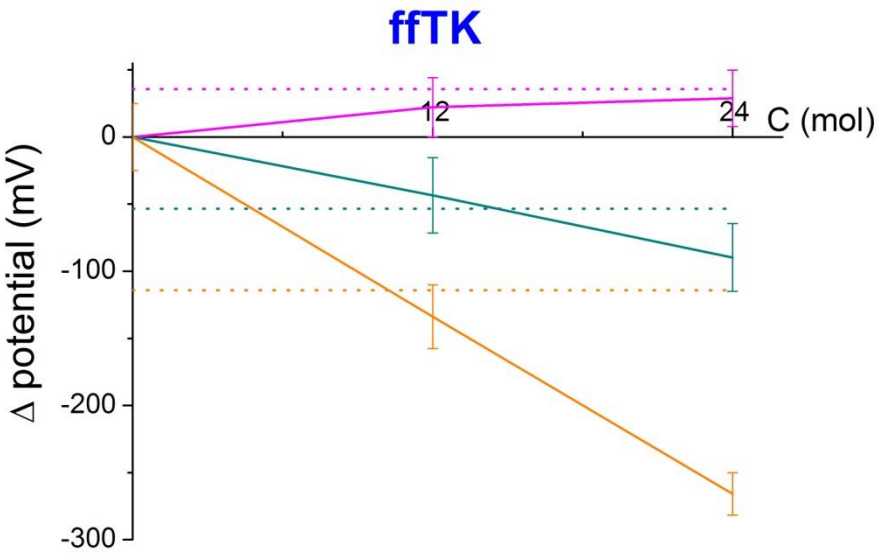
Parameterization results

	Baicalein	Chrysin	Luteolin
Dipole moment	CGenFF ffTK 		
Partial charge distribution	CGenFF 		
	ffTK 		

Bonds, angles, dihedrals comparison: torsion coefficient was generally lower in ffTK

Membrane potential



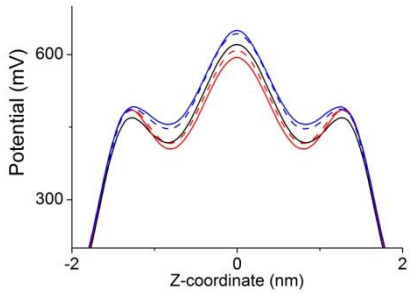
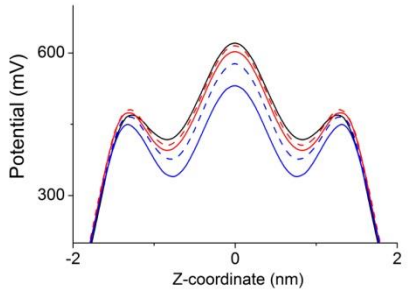
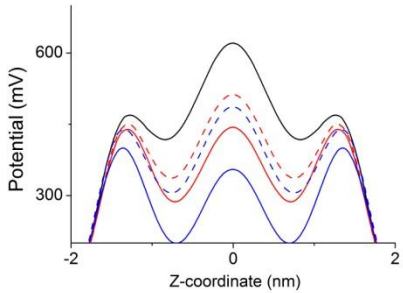
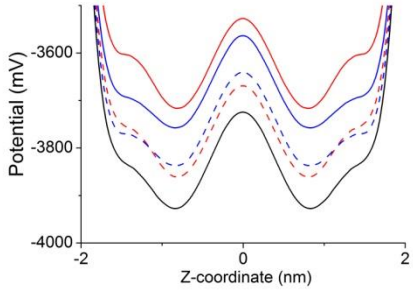
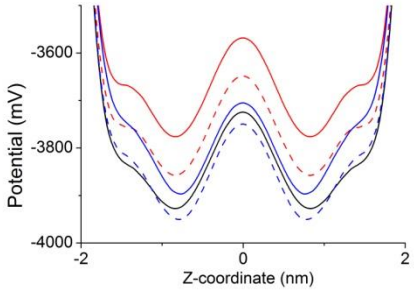
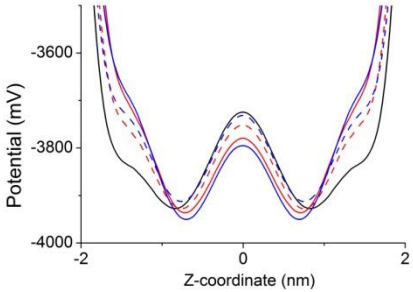
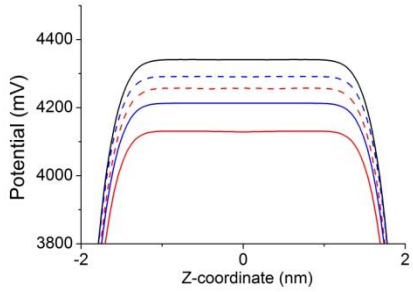
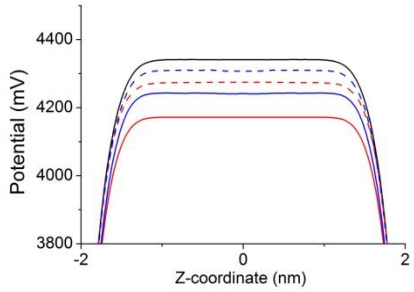
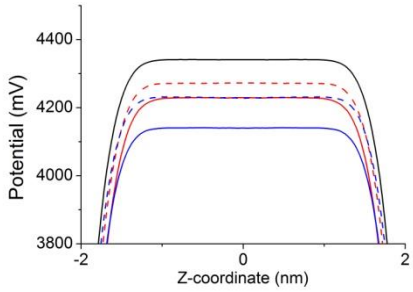


····· *in vitro* data

——— MD data

- ffTK-parameterized molecules reproduces *in vitro* data for all 3 flavonoids
- CGenFF-parameterized molecules reproduces *in vitro* data only for luteolin

Detailed analysis

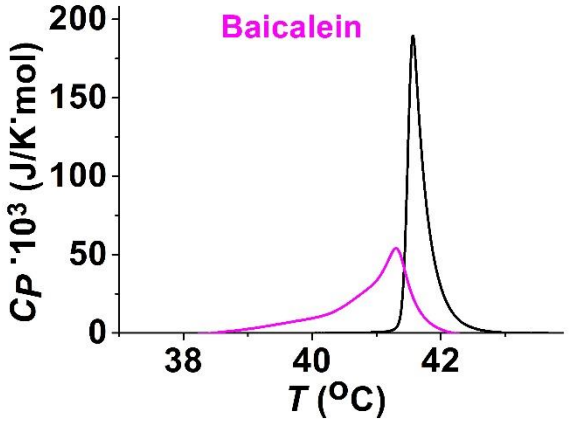
	Baicalein	Chrysin	Luteolin
System			
Membrane + drug			
Solvent			

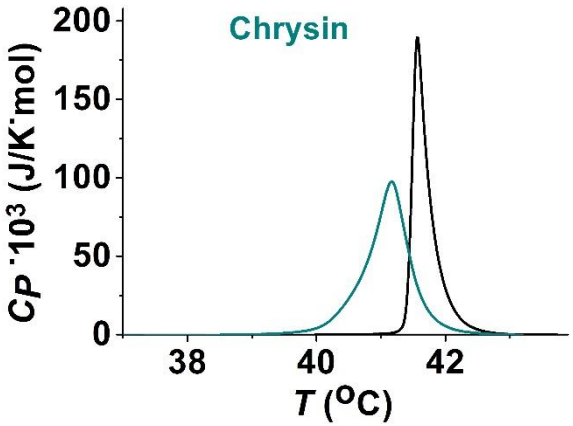
Pre-membrane water defines membrane potential

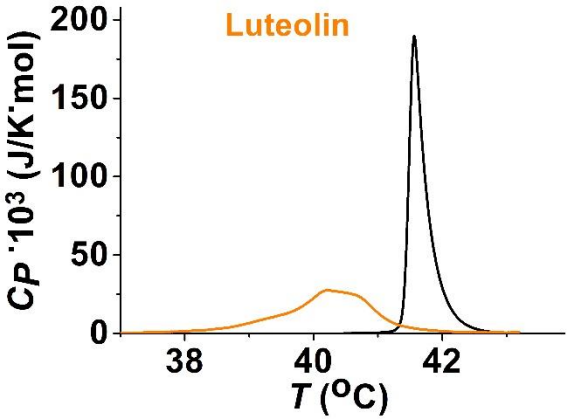
In agreement with ***10.1021/acs.jpcb.4c04469***

Lipid packing assessment

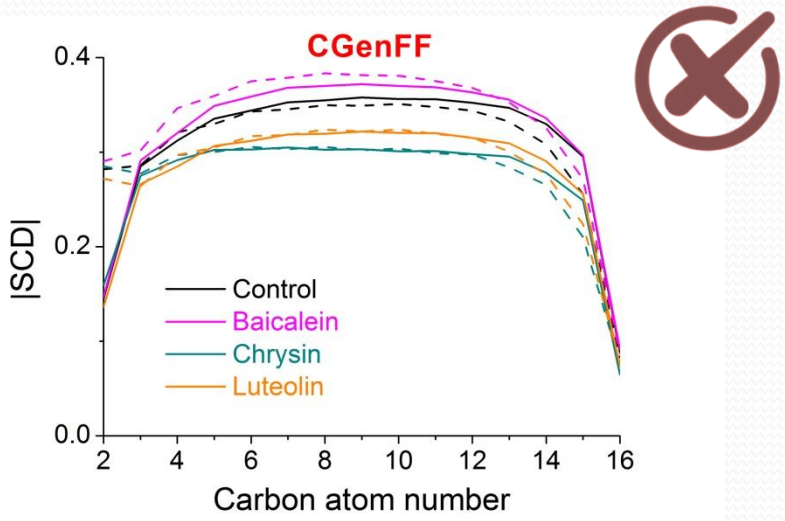
Differential scanning microcalorimetry data

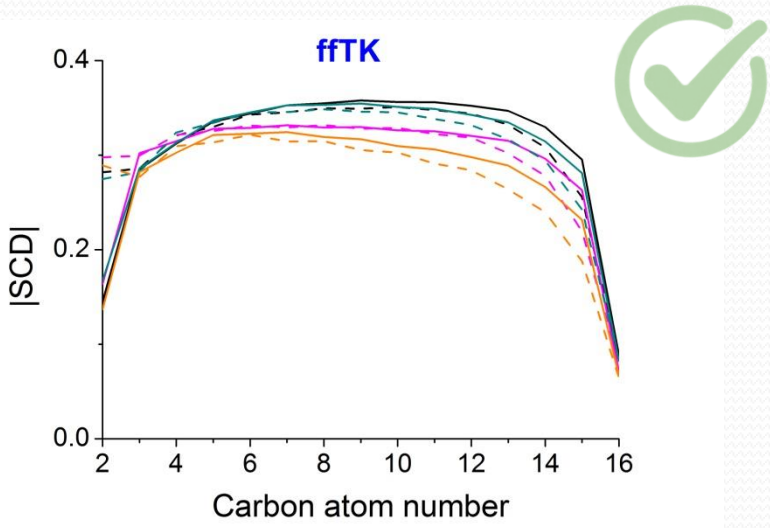






Lipid tail order parameter (MD data)





Conclusions

- The choice of molecular parameterization of drug critically determines the accuracy of MD simulations for predicting the biophysical effects of flavonoids on lipid membranes
- QM-based ffTK parameterization reproduced *in vitro* data for membrane dipole potential changes and bilayer packing density across all three flavonoids tested: baicalein, chrysin, and luteolin.
- Automated CGenFF parametrization reproduced *in vitro* data for luteolin, but not chrysin or baicalein.
- *In vitro* change in dipole potential might be used as parameterization validation assessment?

How Flavonoid Parameterization Determines Membrane Biophysical Outcomes?

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Thank you for your attention