Unveiling the Structural Interplay: investigating the interaction of halogenated flavonoids with liposomes as biomembrane models

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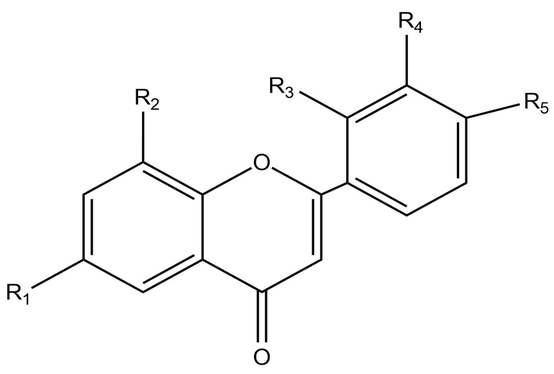
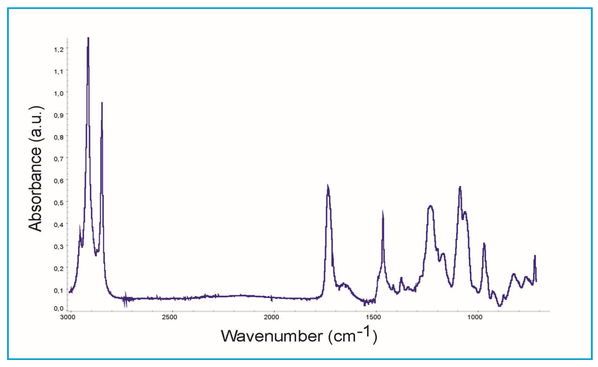
INTRODUCTION

Halogenated flavonoids have garnered attention among polyphenolic compounds due to their unique chemical structures and potential biological activities. The primary objective of this study is to clarify **the interaction of six distinct halogenated flavonoids and biological membranes, MODEL membrane (DPPC/20% cholesterol) as well as the membrane of cancer cells (MIMIC).** These interactions have the potential to affect the fluidity, structure, and stability of membranes, thereby influencing vital cellular processes and the biological activity of the compounds. Gaining insights into these interactions is essential for comprehending the mode of operation of this compound group and their potential application in therapeutics.

MATERIALS AND METHODS

COMPOUND	R1	R2	R3	R4	R5
D1	-H	-H	-Cl	-H	-H
D2	-H	-H	-H	-Cl	-H
D3	-H	-H	-H	-H	-Cl
D4	-Cl	-H	-H	-H	-H
D5	-Cl	-Cl	-H	-H	-H
D6	-Cl	-Br	-H	-H	-H





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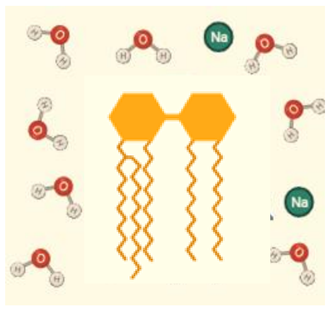

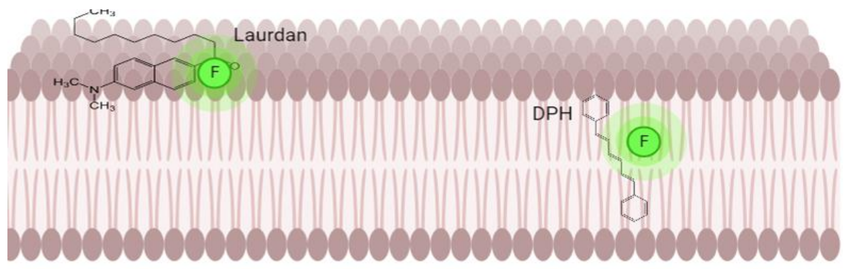

Fluorimetric techniques

Molecular dynamics simulations (MD)

RESULTS

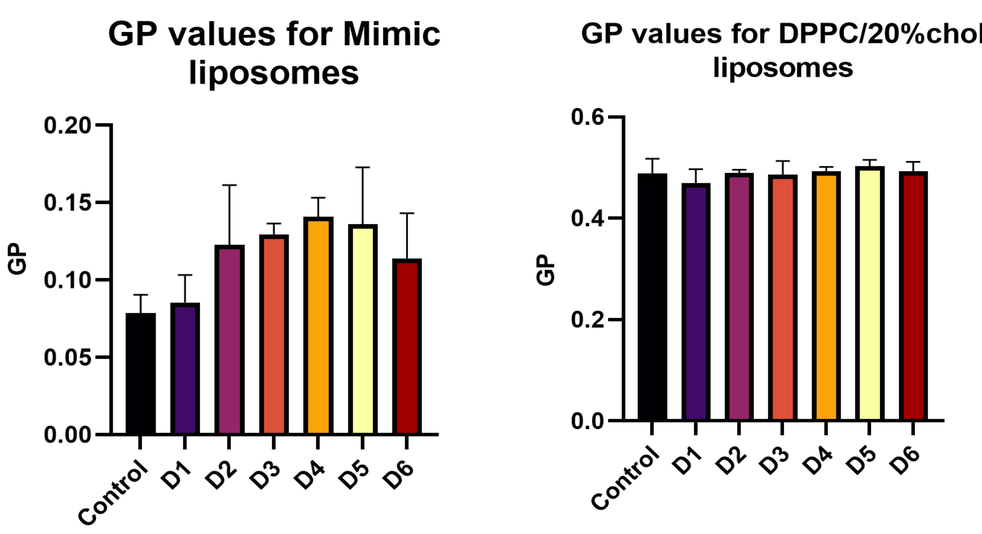

Fig.1 Values of the GP coefficient of the Laurdan probe for MIMIC and DPPC/chol liposomes modified with flavonoids at a concentration of 10 μM.

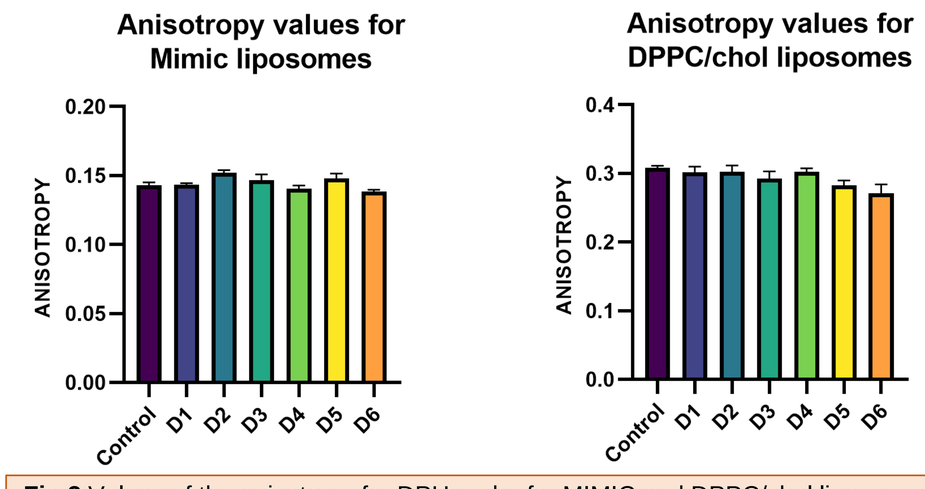

Fig.2 Values of the anisotropy for DPH probe for MIMIC and DPPC/chol liposomes modified with flavonoids at a concentration of 30 μM.

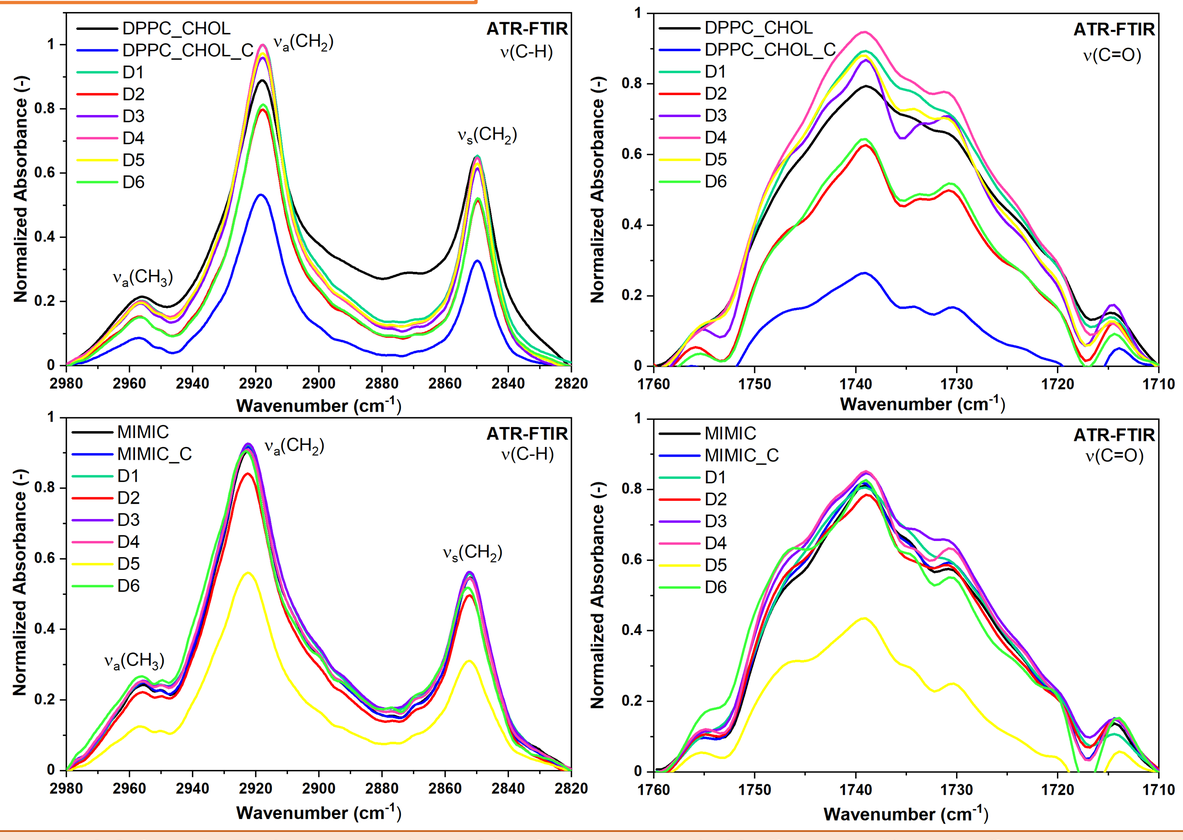

Fig.3 Selected ATR-IR spectra of DPPC/chol bilayer and MIMIC bilayer modified with flavonoids at concentration of 30 μM in the hydrocarbon chains (C-H) and carbonyl groups (C=O) region at temperatures 37°C.

Table 1. Characteristics of the liposomes in the presence of flavonoids at 30 μM concentration: size, polydispersity index (PDI) and Zeta potential (ζ potential).

	MIMIC			DPPC/20%chol		
	SIZE (nm)	PDI	ζ potential (mV)	SIZE (nm)	PDI	ζ potential (mV)
CONTROL	116.80 ±2.91	0.2940±0.0536	11.917±1.2700	195.51±3.82	0.3511±0.0353	-0.2847±0.1208
D1	88.52 ±1.21	0.3371±0.0527	11.883±1.0206	195.27±7.01	0.3843±0.0384	-0.1707±0.0602
D2	104.50 ±1.91	0.2875±0.0708	13.083±0.5981	200.80±2.97	0.4147±0.0616	-0.1854±0.1053
D3	117.18 ±1.44	0.3281±0.0558	12.717±0.5456	229.70±6.65	0.4262±0.0883	0.8040±0.1187
D4	109.73 ±2.53	0.2659±0.0140	12.183±1.1312	239.48±9.09	0.4537±0.0231	0.3150±0.0450
D5	105.02 ±1.33	0.4071±0.0388	12.867±1.0912	177.86±15.85	0.6576±0.0833	0.5027±0.0492
D6	233.75 ±15.08	0.3382±0.0344	12.433±0.9832	239.83±3.40	0.5067±0.0630	0.3845±0.0967

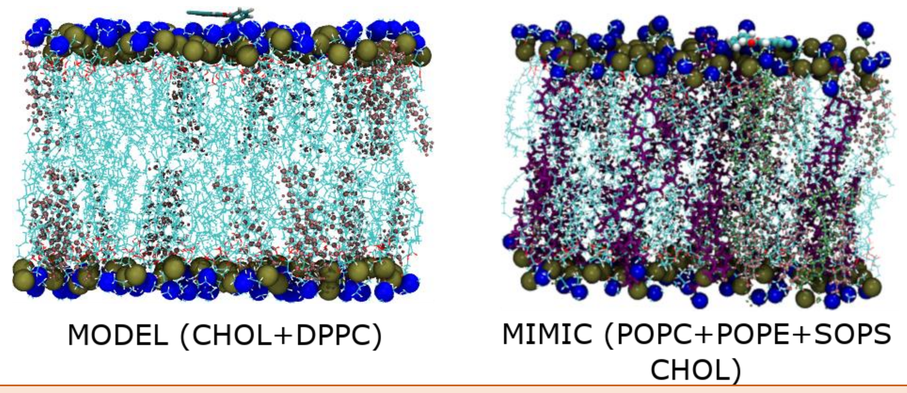

Fig. 4 MD simulations of D6 compound placed above model and MIMIC lipid membrane. The lipid head groups phosphorus P (gold) and nitrogen N (blue) are drawn as small spheres. The acyl chains of the lipids are in blue, lines representation, cholesterol in CPK representation, in pink. POPE drawn in licorice representation, in purple and SOPE in CPK representation, in lime color, D6 in licorice representation. Water is omitted for clarity.

CONCLUSIONS

Flavonoids, in particular D5 and D6, affect the physicochemical properties of liposomes, causing a change in the fluidity of the surface region of the MIMIC membrane which may suggest a decrease in the fluidity of the surface membrane region. D5 compound resulted in an increase in liposome size however, the PDI index and ζ potential remained similar compared to controls without the presence of the flavonoids.
The slight decrease in anisotropy for the DPPC/20%chol membrane can indicate an increase in membrane fluidity in the hydrocarbon chain region in the presence of compound D5 and D6. All compounds tested influence the higher PDI index of DPPC/20%chol liposomes. Moreover, compounds such as D3-D6 led to changes in ζ potential from negative to slightly positive. Based on MD simulations, the compound D6 interacted more prominently with the lipid head groups in the MIMIC lipid membrane compared to the MODEL membrane. The interaction was weaker in the case of the MODEL membrane.

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