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POLYPHENOL-MEDIATED MODULATION OF AMYLOID-LIPID INTERACTIONS

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Förster resonance energy transfer (FRET) between the membrane fluorescent probes pyrene and TDV was employed to investigate the modulation of amyloid-lipid interactions by polyphenols. The effects of various polyphenols, including quercetin, curcumin, gallic and salicylic acids, on the complexation between the amyloid fibrils derived from N-terminal fragment of apolipoprotein A-I (ApoA-IF) and insulin (InsF), and liposomes composed of phosphatidylcholine (PC) and its mixtures with cardiolipin (CL), cholesterol (Chol), or phosphatidylglycerol (PG) were investigated. The incorporation of polyphenols resulted in decreased energy transfer efficiency, indicating a significant alteration in the spatial relationship between amyloid fibrils and lipid membranes. The magnitude of this effect was found to be dependent on lipid bilayer composition, the chemical nature of the polyphenols, and the type of amyloidogenic protein. Notably, curcumin exhibited the most pronounced impact across all systems, with a particularly strong effect on ApoA-IF compared to InsF. This differential response suggests protein-specific mechanisms of interaction and highlights the potential for targeted therapeutic approaches. Our findings provide novel insights into the intricate interplay between polyphenols, amyloid fibrils, and lipid membranes, contributing to the fundamental understanding of amyloid-related pathologies and opening new avenues for the development of polyphenol-based therapeutic strategies in amyloid-associated disorders.
Key words: *Amyloid fibrils; Lipid bilayer; Polyphenols; Förster resonance energy transfer*
PACS: 87.14.C++c, 87.16.Dg

Amyloid-membrane interactions are pivotal in the pathogenesis of numerous neurodegenerative diseases, including Alzheimer's and Parkinson's diseases [1,2]. These interactions can lead to membrane disruption, altered cellular homeostasis, and ultimately, cell death. The amyloid fibrils, which are the aggregates of misfolded proteins, can insert into lipid bilayers, causing structural perturbations that compromise membrane integrity. This disruption is often accompanied by the formation of ion-permeable pores, which can lead to dysregulated ion homeostasis and trigger apoptotic pathways [3]. Understanding the mechanisms underlying amyloid-membrane interactions is crucial for developing therapeutic strategies aimed at mitigating the amyloid toxicity. Various factors and substances can influence the complexation of lipids with fibrillar species, including lipid composition, membrane fluidity, and the presence of small molecules such as polyphenols. Lipid composition, for instance, can significantly affect the binding affinity and insertion depth of amyloid fibrils into the membrane. Cholesterol, a major component of cell membranes, has been shown to either stabilize or destabilize amyloid fibrils depending on its concentration and distribution within the bilayer [4,5]. Polyphenols (PF), which are abundant in various fruits and vegetables, have garnered attention for their potential to modulate these interactions [6,7]. These compounds can interact with both amyloid fibrils and lipid bilayers, altering their structural and functional properties. The consequences of these interactions may be profound, as they can affect membrane integrity, ion channel function, and cellular signaling pathways, thereby contributing to the progression of amyloid-related diseases. A wide arsenal of experimental techniques is employed to analyze biomolecular interactions, each offering unique insights into the dynamics and mechanisms at play. Among these techniques, fluorescence spectroscopy stands out due to its high sensitivity, specificity, and ability to provide real-time data on molecular interactions [8,9]. Fluorescence spectroscopy allows for the detection of subtle changes in the environment of fluorescent probes, making it an invaluable tool for studying complex biological systems. In the present study, we utilized one of the fluorescence spectroscopy modalities, Förster resonance energy transfer (FRET), to investigate the impact of different polyphenols on amyloid-lipid interactions. FRET is a powerful technique that enables the measurement of distances between two fluorophores in the range of 1-10 nm, making it ideal for studying interactions at the molecular level. The aim of the present study was to ascertain whether the efficiency of the Förster resonance energy transfer between the membrane fluorescent probes pyrene and TDV can serve as an indicator of polyphenol effects on fibril-lipid interactions. The lipid bilayers employed in our experiments were composed of distinct combinations of phosphatidylcholine (PC), cholesterol (Chol), cardiolipin (CL), and phosphatidylglycerol (PG). Amyloid fibrils were prepared from apolipoprotein A-I (Apo-IF) and insulin (InsF). This methodological approach enabled elucidation of the modulatory role of polyphenols on amyloid-membrane interactions, thereby providing significant insights into their potential therapeutic applications.

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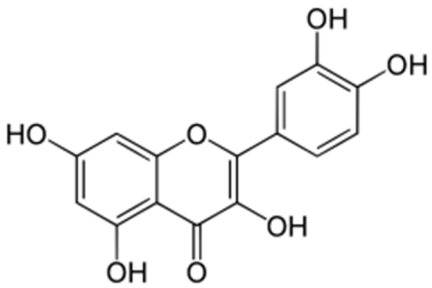
METHODS

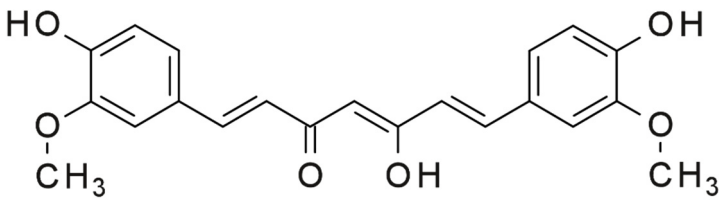
The bovine insulin, Tris, thioflavin T (ThT), cholesterol (Chol), quercetin (QR), curcumin (CR), salicylic (SA) and gallic acids (GA) were purchased from Sigma-Aldrich (St. Louis, MO, USA). The phosphonium dye TDV was kindly provided by Professor Todor Deligeorgiev (University of Sofia, Bulgaria). The N-terminal (1-83) fragment of apolipoprotein A-I with amyloidogenic mutation G26R was kindly provided by Professor Hiroyuki Saito (Kyoto Pharmaceutical University, Japan). All other reagents were of analytical grade and used without further purification.

The insulin amyloid fibrils were prepared by incubation of the protein solution (10 mg/ml) in 10 mM glycine buffer (pH 2.0) 24 hours at 37 ºC under continuous orbital shaking. The fibrillization of N-terminal fragment of apolipoprotein A-I was conducted at 37 °C with constant agitation on an orbital shaker after the protein dialysis from 6M guanidine hydrochloride solution into 10mM Tris-HCl buffer, 150 mM NaCl, 0.01% NaN_3, pH 7.4. The fibril growth was monitored through measuring the intensity of ThT fluorescence at excitation and emission wavelengths of 440 and 484 nm, respectively. Hereafter, the fibrillar forms of insulin and N-terminal fragment of apolipoprotein A-I are referred to as InsF and ApoA-IF, respectively. The large unilamellar vesicles were prepared from egg yolk phosphatidylcholine (PC) and its mixtures with beef heart cardiolipin (CL), cholesterol and phosphatidylglycerol (PG) in different molar proportions: neat PC, 11 mol% CL (CL11), 30 mol% cholesterol (Chol30), 11 mol% CL, 30 mol% Chol (CL11Chol30) and 20 mol% PG (PG20). The thin lipid films were obtained by evaporation of appropriate lipid solutions in ethanol, then hydrated with 1.2 ml of 10 mM Tris-HCl buffer (pH 7.4) and extruded through a 100 nm pore size polycarbonate filter. The concentration of lipids in the stock liposomal suspensions was 10 mM. The fluorescence measurements were carried out in 10 mM Tris-HCl buffer (pH 7.4) with a Shimadzu RF-6000 spectrofluorimeter (Shimadzu, Japan) using the 10 mm path-length quartz cuvettes. In the FRET measurements the fibril-liposome mixtures containing pyrene in concentration 5.1 μM were sequentially titrated with TDV solution in buffer. The fluorescence spectra were recorded from 360 to 640 nm with the excitation wavelength 340 nm. The excitation and emission band passes were set at 5 nm. The ratio of vibronic bands in the pyrene fluorescence spectra (I_1/I_3) was calculated from the intensities at 374 nm (peak 1) and 383 nm (peak 3). The excimer-to-monomer fluorescence intensity ratio (E/M) was determined by measuring fluorescence intensity at the monomer (391 nm) and excimer (474 nm) peaks.

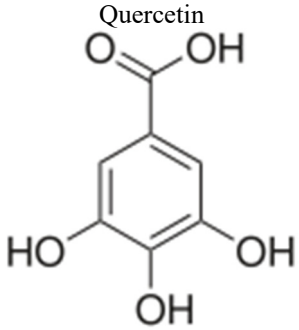
The stock solutions of polyphenols, *viz.* quercetin, curcumin, salicylic and gallic acids (Fig. 1), were prepared in dimethylsulfoxide in concentration 620 μM.



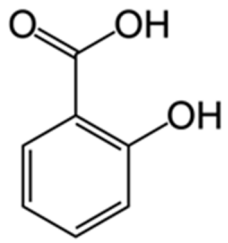
Quercetin



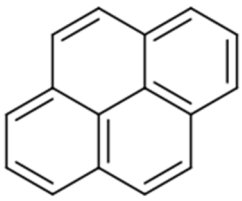
Curcumin (enol form)



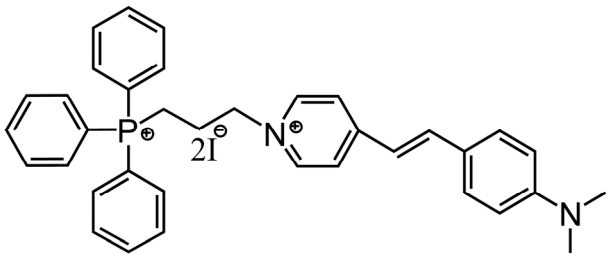
Gallic acid



Salicylic acid



Pyrene



TDV

Figure 1. Chemical structure of the examined polyphenols and fluorescent probes

RESULTS AND DISCUSSION

Figs. 2 and 3 illustrate the pyrene emission spectra in amyloid-lipid systems in the presence and absence of polyphenols at increasing concentrations of TDV. The data clearly demonstrate that as the concentration of TDV increases, there is a corresponding decrease in the fluorescence intensity of pyrene. This inverse relationship is indicative of the Förster resonance energy transfer occurring between the two membrane fluorescent probes, since TDV absorption spectrum strongly overlaps with the emission spectrum of pyrene excimers (Fig. 2, F).

The introduction of various polyphenols into the system significantly influenced the energy transfer process. The extent of this influence varied depending on several factors, including the chemical nature of the polyphenols, the specific composition of the liposomes, and the type of protein involved in the amyloid formation.

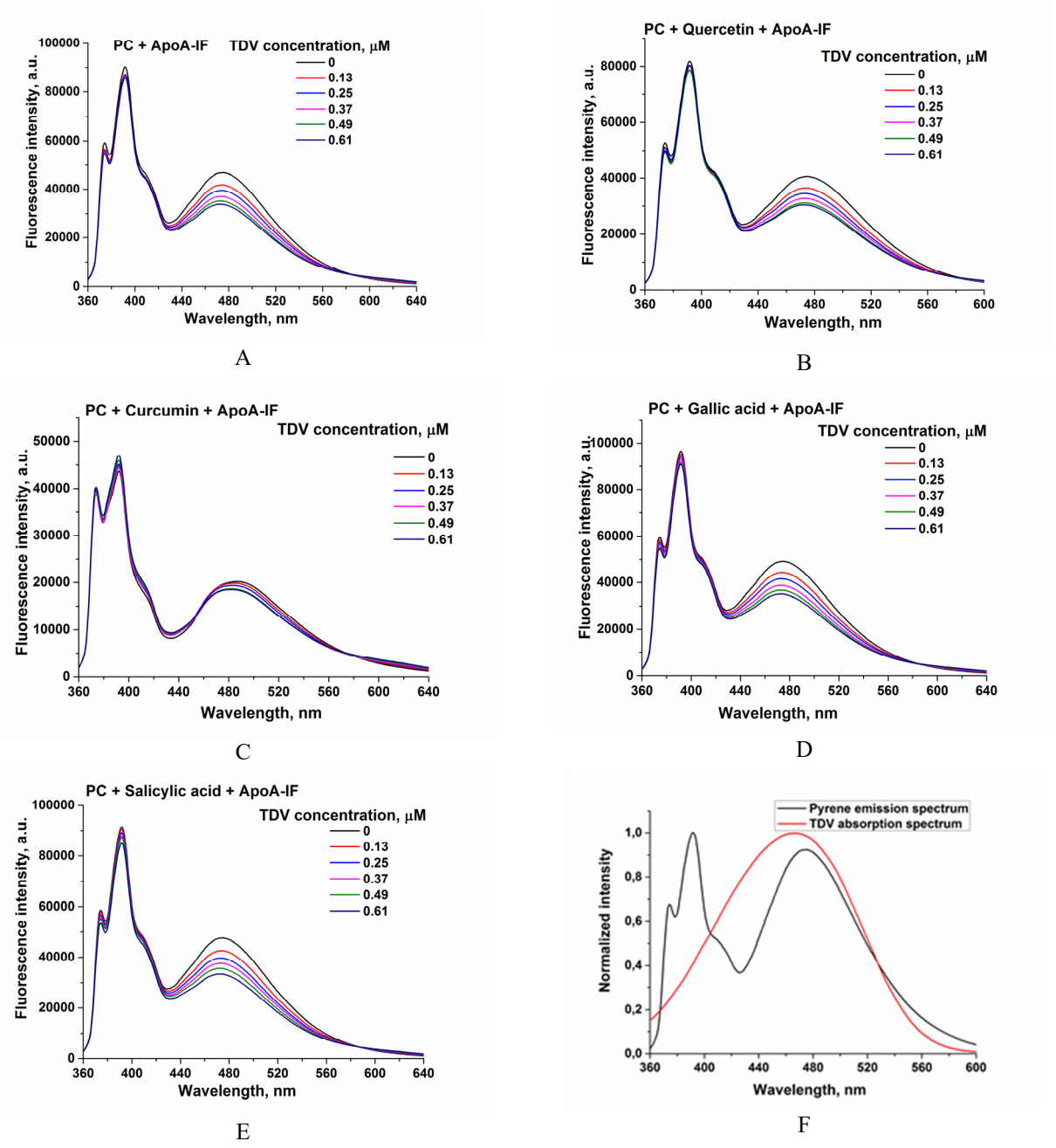


Figure 2. Pyrene fluorescence spectra in the systems PC+ApoA-IF+TDV (A) and PC+ApoA-IF+PF+TDV (B-E) measured at different concentrations of TDV. The overlap between pyrene emission and TDV absorption spectra (F). Lipid concentration was 67 μM, Pyrene concentration was 5.1 μM. ApoA-IF concentration was 1.1 μm. PF concentrations were – quercetin/curcumin – 2 μM, gallic acid/ salicylic acid – 20 μM

To assess the impact of polyphenols quantitatively, the energy transfer efficiency was calculated in all systems under study (Figs. 4, 5). The results reveal a notable influence of liposome composition on FRET efficiency between pyrene and TDV in amyloid-liposome systems.

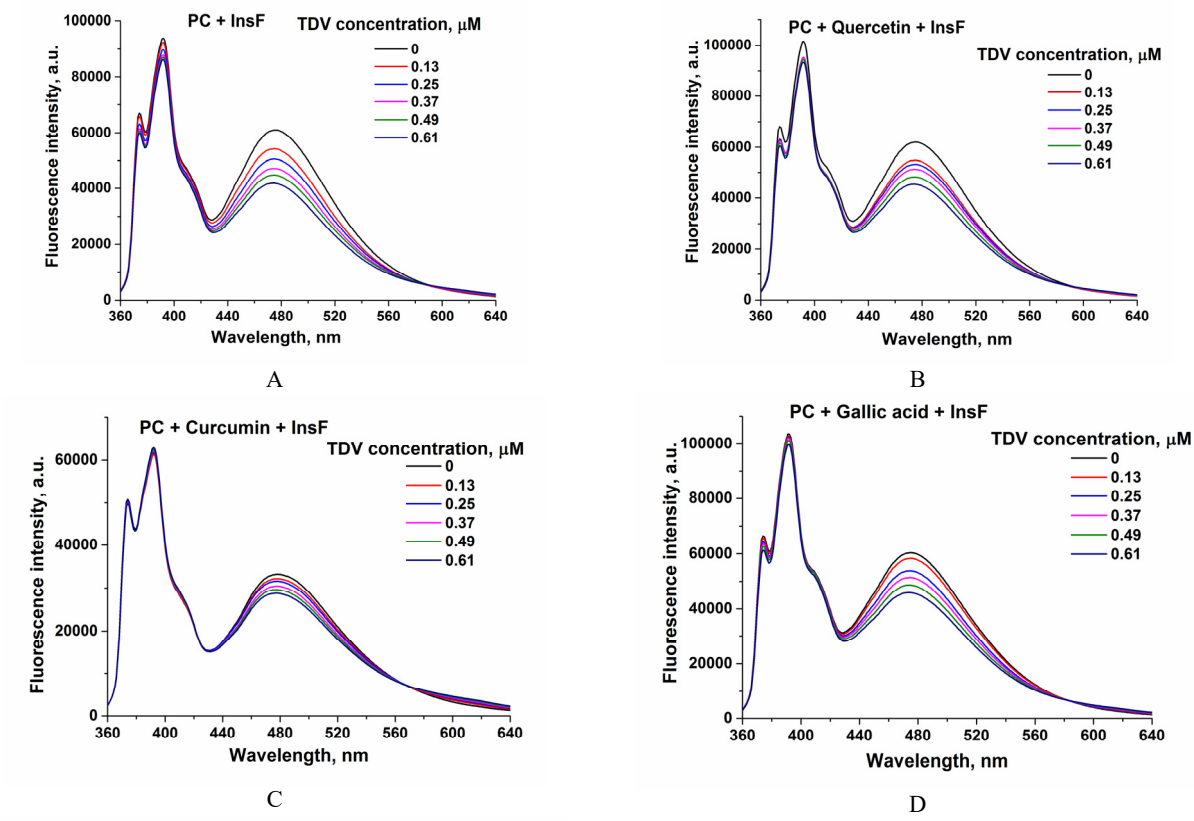


Figure 3. Pyrene fluorescence spectra in the systems PC+InsF+TDV (A) and PC+InsF+PF+TDV (B-E) measured at different concentrations of TDV. Lipid concentration was 67 μM. Pyrene concentration was 5.1 μM. InsF concentration was 13 μm. PF concentrations were – quercetin/curcumin – 2 μM, gallic acid/ salicylic acid – 20 μM

Interestingly, the FRET efficiency remained virtually consistent regardless of the amyloid fibril type, whether derived from apolipoprotein A-I or insulin, suggesting that the specific protein composition of the fibrils does not significantly affect energy transfer in these systems.

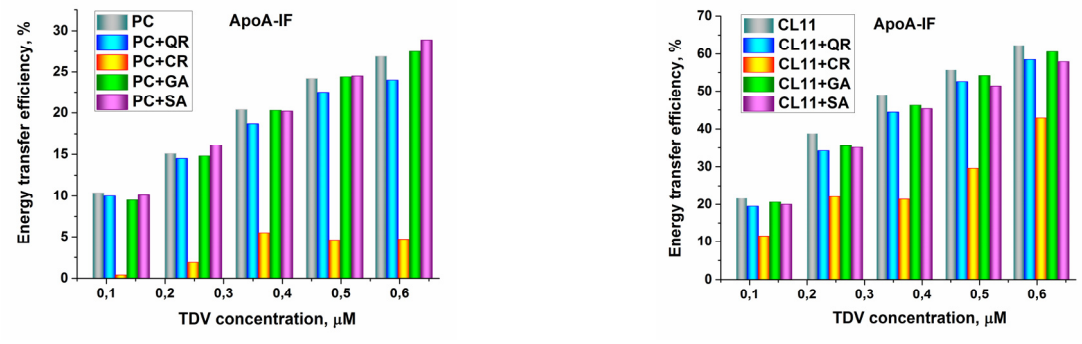


Figure 4. The efficiencies of the Förster resonance energy transfer between pyrene excimers and TDV observed in the systems PC+ApoA-IF+PF+TDV (A), CL11+ApoA-IF+PF+TDV (B), Chol30+ApoA-IF+PF+TDV (C), CL11Chol30+ApoA-IF+PF+TDV (D), PG20+ApoA-IF+PF+TDV (E)

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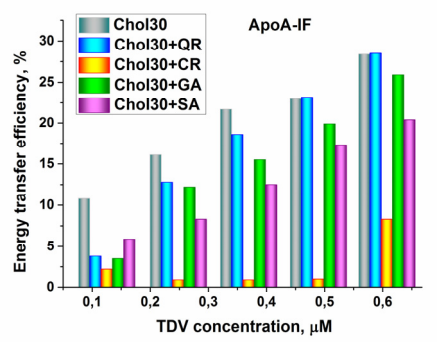

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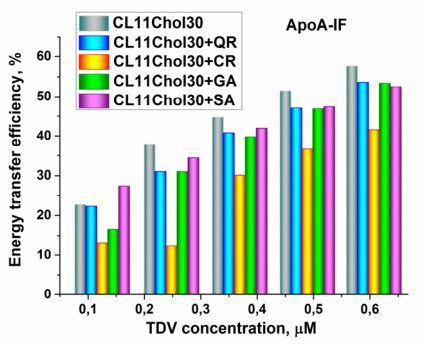

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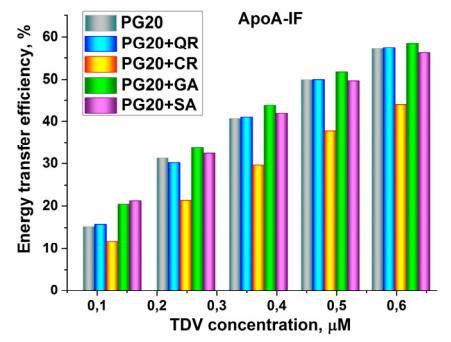
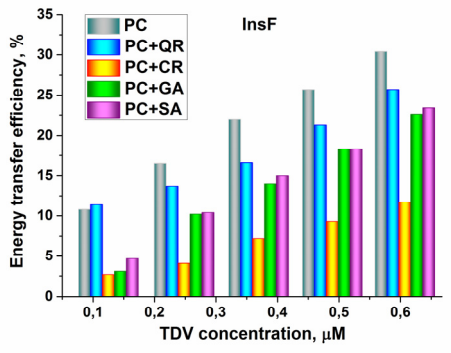


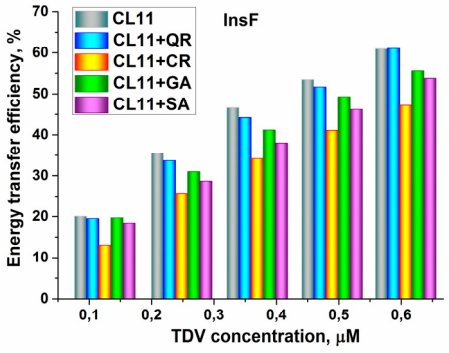
E

Figure 4. The efficiencies of the Förster resonance energy transfer between pyrene excimers and TDV observed in the systems PC+ApoA-IF+PF+TDV (A), CL11+ApoA-IF+PF+TDV (B), Chol30+ApoA-IF+PF+TDV (C), CL11Chol30+ApoA-IF+PF+TDV (D), PG20+ApoA-IF+PF+TDV (E)

The most striking observation was the marked variation in FRET efficiency across different lipid compositions. Neat PC bilayers exhibited a baseline FRET efficiency of ~30%, which served as a reference point for comparison with more complex lipid mixtures. The incorporation of cardiolipin (CL) into PC bilayers resulted in a dramatic increase in FRET efficiency to 60%, representing a two-fold enhancement compared to pure PC systems. This substantial increase may be attributed to CL unique molecular structure and its ability to alter membrane curvature and fluidity [10], potentially facilitating closer proximity or more favorable orientation between the donor and acceptor fluorophores.



A



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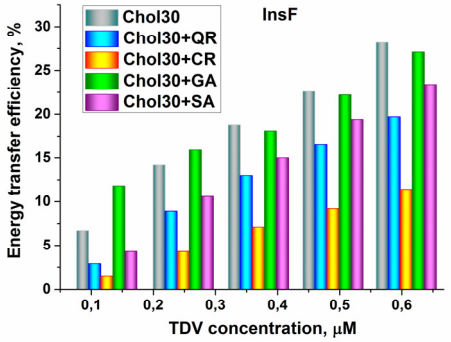

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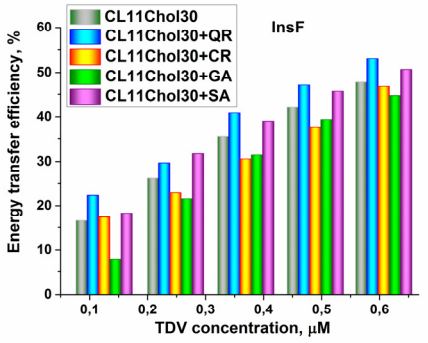

D

Figure 5. The efficiencies of the Förster resonance energy transfer between pyrene excimers and TDV observed in the systems PC+InsF+PF+TDV (A), CL11+InsF+PF+TDV (B), Chol30+InsF+PF+TDV (C), CL11Chol30+InsF+PF+TDV (D), PG20+InsF+PF+TDV (E).

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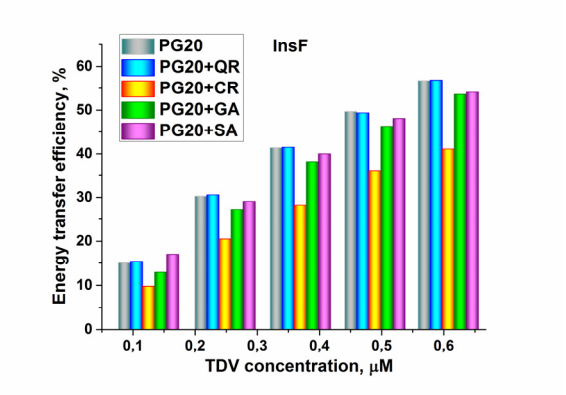

E

Figure 5. The efficiencies of the Förster resonance energy transfer between pyrene excimers and TDV observed in the systems PC+InsF+PF+TDV (A), CL11+InsF+PF+TDV (B), Chol30+InsF+PF+TDV (C), CL11Chol30+InsF+PF+TDV (D), PG20+InsF+PF+TDV (E).

Conversely, the addition of Chol to PC bilayers did not affect FRET efficiency. This observation suggests that well-known membrane-ordering effect of the sterol does not significantly influence the spatial relationship or energy transfer dynamics between pyrene and TDV in this context. However, the combination of PC, Chol, and CL yielded an intermediate FRET efficiency of ~50%, indicating a complex interplay between these lipid components. This result implies that while cholesterol alone does not enhance FRET efficiency, it does not completely negate the positive effect of cardiolipin when both are present in the membrane. The inclusion of PG into PC bilayers also led to a substantial increase in FRET efficiency, reaching ~55%. This enhancement, albeit slightly less pronounced than that observed with CL, suggests that negatively charged lipids generally promote more efficient energy transfer in these amyloid-liposome systems. The observed findings can be interpreted through several mechanistic lenses. First, the increased FRET efficiency in CL- and PG-containing bilayers may be due to electrostatic interactions between the negatively charged lipids and the amyloid fibrils, potentially altering the fibril orientation or proximity to the membrane surface. Second, changes in membrane fluidity and curvature induced by these lipids could modify the distribution or mobility of the fluorophores within the bilayer, thereby affecting their average separation distance and, consequently, FRET efficiency. Furthermore, the differential effects of various lipid compositions on FRET efficiency may reflect alterations in the membrane physical properties, such as thickness, lateral pressure profile, or phase behavior. These changes could indirectly influence the interaction between amyloid fibrils and the liposome surface, thus modulating the spatial relationship between the donor and acceptor molecules.

Next, we evaluated the impact of different polyphenols on amyloid-lipid complexation. To this end, the changes in the systems liposomes+amyloid+PF were calculated relative to the systems without PF (Figs. 6, 7).

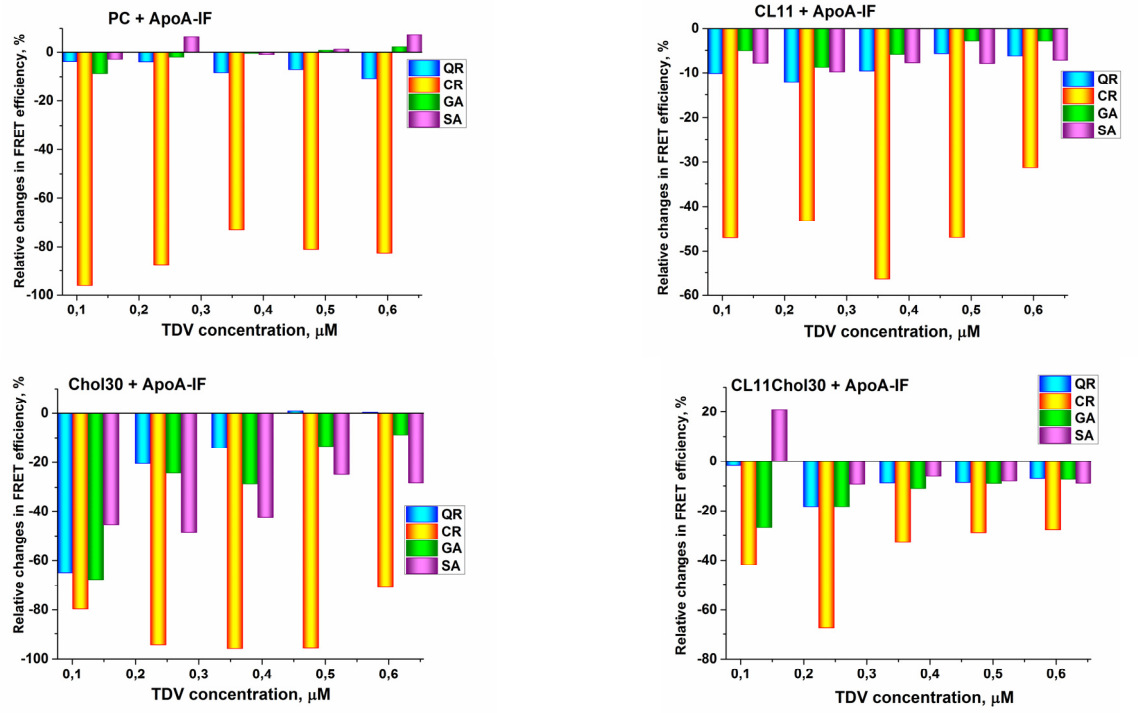

Figure 6. The changes in FRET efficiency relative to control without PF in the systems PC+ApoA-IF+PF+TDV (A), CL11+ApoA-IF+PF+TDV (B), Chol30+ApoA-IF+PF+TDV (C), CL11Chol30+ApoA-IF+PF+TDV (D), PG20+ApoA-IF+PF+TDV (E)

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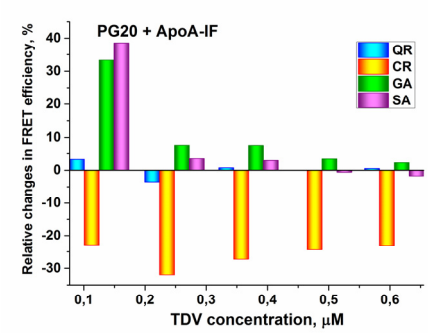

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Analyzing these results, the following tendencies emerged: i) the incorporation of polyphenols into amyloid-lipid systems resulted in decrease of energy transfer efficiency, ii) the effect of polyphenols on amyloid-lipid interactions depends on lipid bilayer composition, chemical nature of polyphenols and the type of the protein, iii) for all systems there is no correlation between the increase in TDV concentration and the magnitude of polyphenols impact, iv) curcumin induced the changes in energy transfer efficiency in all systems under consideration. Furthermore, in the case of ApoA-IF in all types of lipid membranes except Chol30, the influence of quercetin, salicylic and gallic acids were within the experimental error, and only in Chol30 the changes in the efficiency of energy transfer were noticeable not only for curcumin but also for gallic and salicylic acids. In turn, in the presence of InsF, the statistically significant effect of polyphenols was observed for all polyphenols. Finally, the impact of curcumin on amyloid-lipid interactions is more pronounced in the case of ApoA-IF.

The most salient finding is the observed decrease in energy transfer efficiency upon incorporation of PF into the amyloid-lipid systems. This reduction in FRET efficiency suggests that polyphenols may modulate the spatial relationship between the amyloid fibrils and the lipid membranes, potentially altering the proximity or orientation of the fluorophores within the system. Several mechanisms may account for this phenomenon. First, PF are known to interact directly with amyloid fibrils, potentially inducing conformational changes or disrupting fibril structure [11]. Such interactions could lead to a reorganization of the amyloid-lipid interface, thereby increasing the average distance between the FRET donor (pyrene) and acceptor (TDV) molecules. This increased separation would result in reduced energy transfer efficiency, as FRET is highly sensitive to the distance on the nanometer scale. Furthermore, PF may exert their effects by modulating the properties of the lipid membranes themselves. Many polyphenolic compounds have been shown to interact with lipid bilayers, altering membrane fluidity, curvature, or lateral organization [12,13]. These changes in membrane properties could indirectly affect the binding or orientation of amyloid fibrils at the lipid interface, again leading to altered FRET efficiency.

The magnitude of the polyphenol-induced effect was found to be dependent on a complex interplay of factors, including the lipid bilayer composition, the chemical nature of the polyphenols, and the type of amyloidogenic protein. This multifactorial dependence underscores the intricate nature of these interactions and suggests that the modulation of amyloid-lipid complexation by polyphenols is not a simple, uniform process but rather a nuanced phenomenon influenced by the specific molecular characteristics of all components involved.

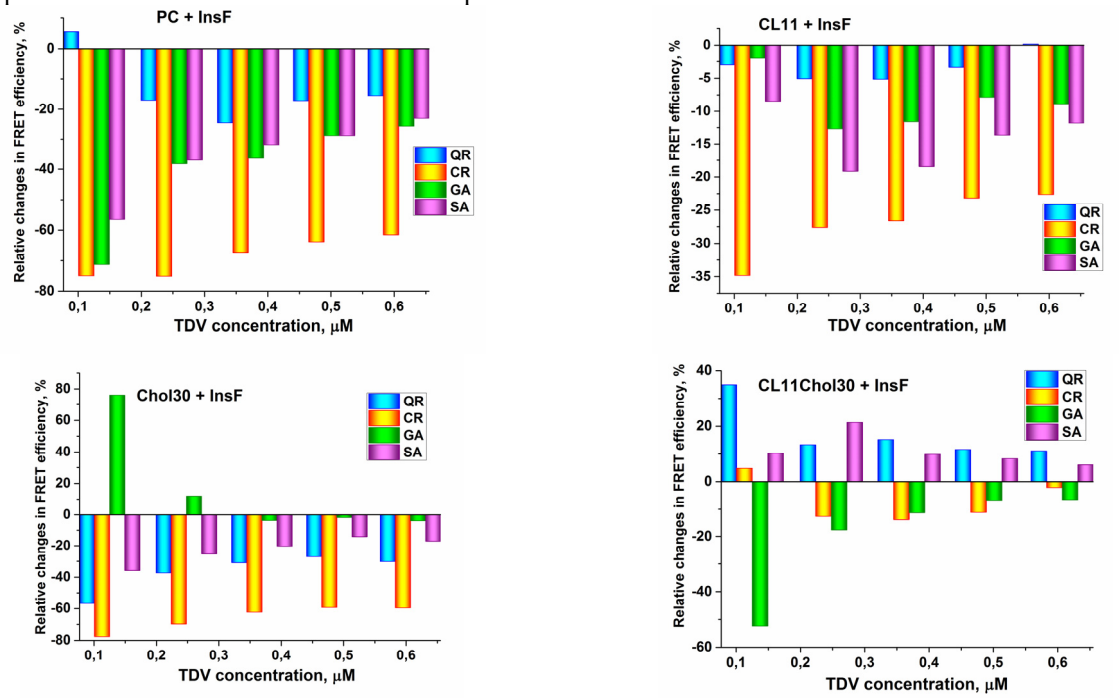

Figure 7. The changes in FRET efficiency relative to control without PF in the systems PC+InsF+PF+TDV (A), CL11+InsF+PF+TDV (B), Chol30+InsF+PF+TDV (C), CL11Chol30+InsF+PF+TDV (D), PG20+InsF+PF+TDV (E)

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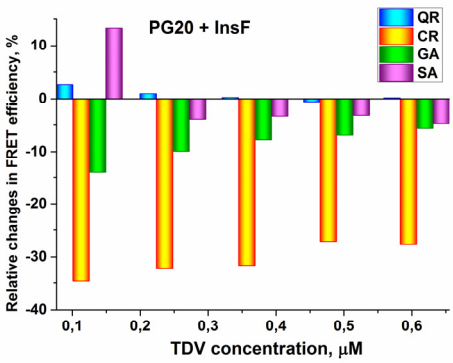

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Among the polyphenols studied, CR demonstrated the most pronounced and consistent effect across all systems under consideration, exhibiting a remarkable ability to reduce FRET efficiency. This observation not only aligns with previous studies highlighting curcumin potent ability to interact with amyloid fibrils and modulate their behavior but also extends our understanding of its effects in complex, membrane-associated systems [14]. The superior efficacy of curcumin in reducing FRET efficiency may be attributed to its unique molecular structure, which includes two aromatic rings connected by a flexible linker region, conferring both hydrophobic and hydrophilic properties. This amphipathic nature could allow CR to interact more effectively with both the amyloid fibrils and the lipid membranes, potentially disrupting their association or altering their relative orientations through multiple mechanisms. Furthermore, CR ability to modulate oxidative stress and inflammation, processes often associated with amyloid pathology, may contribute to its pronounced effects in these systems [15].

The dependence of polyphenol effects on lipid bilayer composition suggests that the membrane environment plays a crucial and multifaceted role in mediating amyloid-lipid interactions. Different lipid compositions may alter a myriad of physical properties of the membrane, such as fluidity, curvature, surface charge, and lateral organization, which in turn could affect the binding of amyloid fibrils and the distribution of polyphenols within the system in complex and potentially synergistic ways. For instance, the presence of negatively charged lipids like CL or PG might enhance electrostatic interactions between the membrane and positively charged regions of the amyloid fibrils, potentially influencing the ability of polyphenols to disrupt these associations. Additionally, the incorporation of cholesterol could modulate membrane fluidity and the formation of lipid rafts, potentially creating specialized microenvironments that influence the interaction of both amyloid fibrils and polyphenols with the membrane.

Of particular interest is the observation that CR exerts a more pronounced impact on amyloid-lipid interactions in the case of ApoA-IF compared to InsF.This differential effect can be attributed to several factors related to the structural and physicochemical properties of these amyloidogenic proteins. ApoA-I, being an amphipathic protein with a high α-helical content, possesses a unique structural plasticity that allows it to interact with lipids and undergo conformational changes. This inherent flexibility might render ApoA-IF more susceptible to CR-induced perturbations. Curcumin, with its amphipathic nature and ability to intercalate into lipid bilayers, may disrupt the delicate balance of hydrophobic and hydrophilic interactions that stabilize ApoA-IF, leading to more pronounced effects on fibril structure and stability. The pronounced effect of curcumin on ApoA-IF may also be attributed to its ability to modulate lipid-protein interactions. Curcumin has been shown to alter membrane fluidity and organization, which could indirectly affect the binding of ApoA-IF to lipid surfaces. Given that ApoA-I plays a crucial role in lipid metabolism and transport, its interaction with lipid membranes is likely more sensitive to curcumin-induced changes in membrane properties compared to insulin. The observed differences in CR impact on ApoA-IF and InsF interactions with lipid membranes may also have implications for understanding the role of these amyloidogenic proteins in their respective pathological contexts. ApoA-I is associated with atherosclerosis and cardiovascular diseases, while insulin is linked to type 2 diabetes. The enhanced susceptibility of ApoA-IF to CR-mediated modulation suggests that curcumin or its derivatives might be particularly effective in targeting ApoA-I-related amyloidoses.

CONCLUSIONS

In summary, our findings indicate that the efficiency of FRET between pyrene as a donor and TDV as an acceptor is sensitive to the variables such as i) lipid composition of the model membranes; ii) the structural peculiarities of amyloid fibrils; and iii) the chemical nature of polyphenolic compounds. The observed reduction in FRET efficiency upon polyphenol incorporation suggests a significant and nuanced modulation of amyloid-lipid interactions, which could have important implications for understanding and potentially mitigating the membrane-mediated toxicity of amyloid species in various pathological conditions. These findings not only expand our fundamental understanding of the biophysical principles governing amyloid-membrane interactions but also open new avenues for the development of targeted therapeutic strategies in amyloid-related disorders.

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ВПЛИВ ПОЛІФЕНОЛІВ НА ВЗАЄМОДІЮ АМІЛОЇДНИХ ФІБРИЛ З ЛІПІДНИМИ МЕМБРАНАМИ

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Метод Фьорстерівського резонансного переносу енергії (ФРПЕ) між мембранними флуоресцентними зондами піреном та TDV був застосований у якості аналітичного інструменту для дослідження модулюючого впливу поліфенолів на взаємодію амілоїдних фібрил з ліпідними мембранами. Було вивчено ефекти різних поліфенолів, включаючи кверцетин, куркумін, галову та саліцилову кислоти, на комплексоутворення між амілоїдними фібрилами, отриманими з N-термінального фрагменту аполіпопротеїну A-I (ApoA-IF) та інсуліну (InsF), і ліпосомами, що складалися з фосфатидилхоліну (ФХ) та його сумішей з кардіоліпіном (КЛ), холестерином (Хол) або фосфатидилгліцеролом (ФГ). Включення поліфенолів призвело до зниження ефективності переносу енергії, що вказує на зміну просторового розташування амілоїдних фібрил та ліпідних мембран. Величина цього ефекту залежала від складу ліпідного бішару, хімічної природи поліфенолів та типу амілоїдогенного білка. Особливо виражений вплив мав куркумін, який демонстрував найсильніший ефект у всіх системах, зокрема у присутності ApoA-IF порівняно з InsF. Цей диференційований відгук свідчить про білок-специфічні механізми взаємодії та вказує на можливість розробки цілеспрямованих терапевтичних підходів. Отримані результати надають нові уявлення про складну взаємодію між поліфенолами, амілоїдними фібрилами та ліпідними мембранами, що сприяє фундаментальному розумінню амілоїдогенезу та відкриває нові шляхи для створення терапевтичних стратегій на основі поліфенолів у лікуванні амілоїд-асоційованих захворювань.

Ключові слова: *амілоїдні фібрили; ліпідний бішар; поліфеноли; Фьорстерівський резонансний перенос енергії*