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Binding of tigecycline to human serum albumin in the presence of catechin

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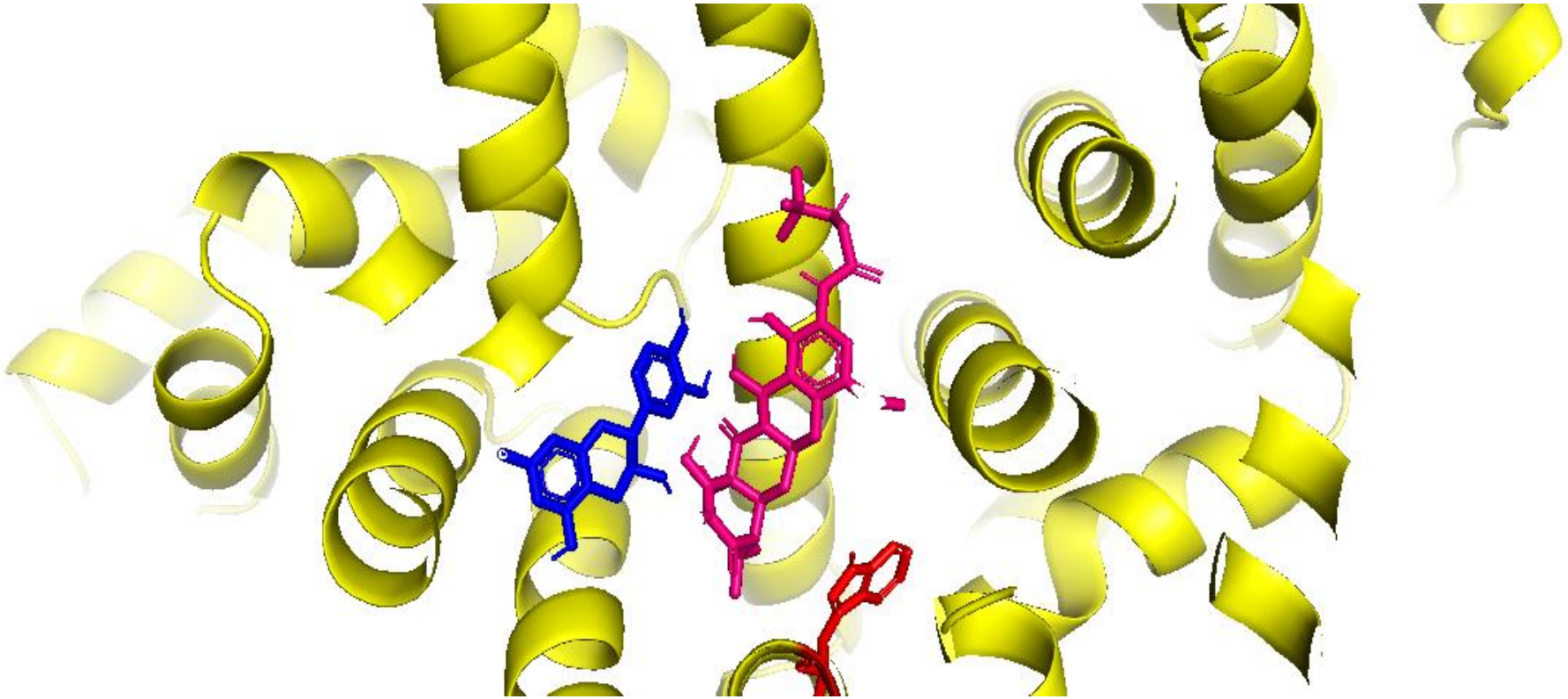


Abstract:

In the presented work, the binding affinity of tigecycline, tetracycline antibiotic, to HSA in the presence of catechin has been investigated by fluorescence and UV–Vis absorption spectroscopy under simulated physiological conditions (pH 7.4) and using molecular docking simulations. The main objective of the study was to reveal the mechanism of interactions and evaluate influence of catechin to HSA-drug binding. The presented study contributes to improve the current knowledge about pharmacology of TGC in presence of food components. The studies showed that the effect of catechin has a positive influence on binding TGC to HSA in simulated physiological conditions by multiple spectroscopic methods. Also, fluorescence quenching measurements reveal that catechin share IIA subdomain in HSA with TGC drug. Also, docking experiments toward HSA protein have been done, indicating a good correlation with experimental results.

Keywords: catechin, human serum albumin, tigecycline

Introduction

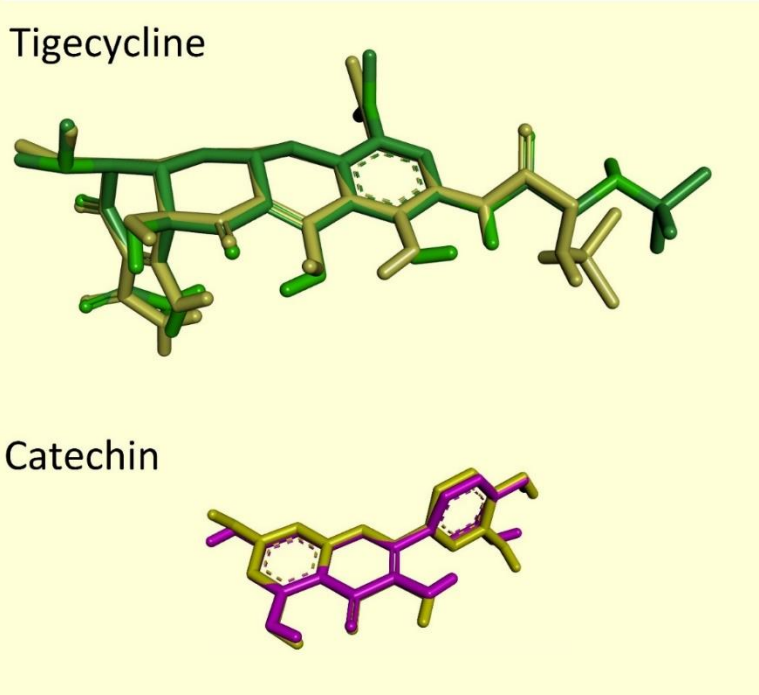


Figure 1. Structures of tigecycline and catechin

Tigecycline

- the first of a new class of antimicrobials
- possesses better activity than other tetracyclines[1]
- has similar mechanism of action to tetracyclines[2,3]

Catechins

- significant antioxidant properties[4]
- numerous applications in the pharmaceutical, agricultural and food industries[5]
- showed negative effects, such as prooxidative, cytotoxic and phytotoxic activities[6,7]

[1] N. Scheinfeld, J. Dermatolog. Treat 16 207 (2005)
[2] G.G. Zhanel, K. Homenuik, K. Nichol, A. Noreddin, L. Vercaigne, J. Embil, A. Gin, J.A. Karlowsky, D.J. Hoban, Drugs 64 63- (2004)
[3] G. Fey, M. Reiss, H. Kersten, Biochemistry 12 1160- (1973)
[4] M. Peng, S. Shi, Y. Zhang, Spectrochim. Acta Part A 85 190– (2012)
[5] S. B. Jadhav, R. S. Singhal, L. Gum, Food Chem. 150 9- (2014)
[6] C. Cabrera, R. Artacho, R. Giménez, J. Am. Coll. Nutr. 25 79– (2006)
[7] T. Ishii, T. Mori, T. Ichikawa, M. Kaku, K. Kusaka, Y. Uekusa, M. Akagawa, Y. Aihara, T. Furuta, T. Wakimoto, T. Kan and T. Nakayama, Bioorg. Med. Chem. 18 4892– (2010)

Introduction

Human serum albumin

- the most abundant protein in plasma
- contains three homologous domains (I, II and III)
- each domain includes A and B subdomains
- plays a central role in the transportation and deposition of many endogenous and exogenous ligands present in the blood

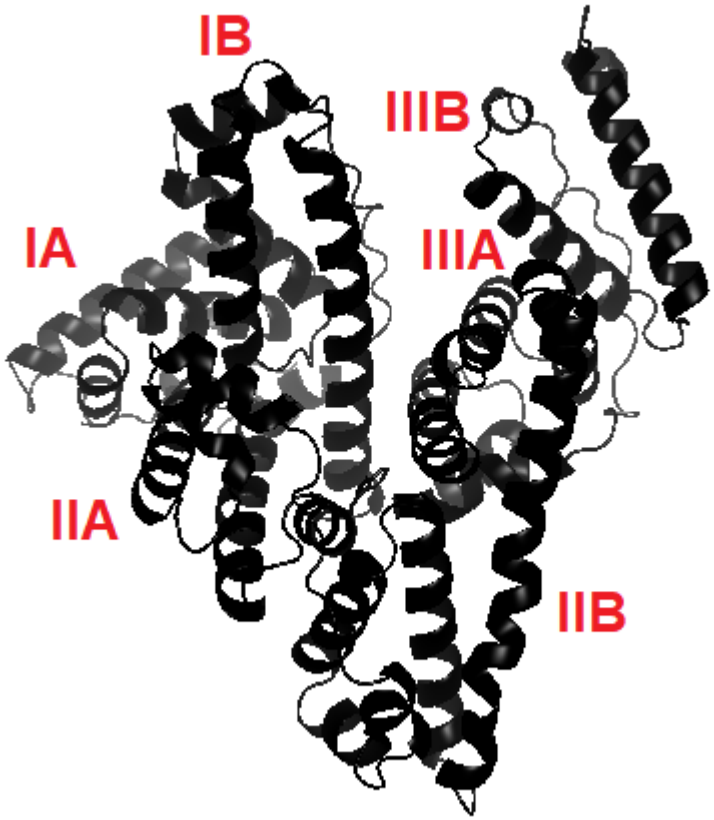


Figure 2. Structure of human serum albumin

Results and discussion

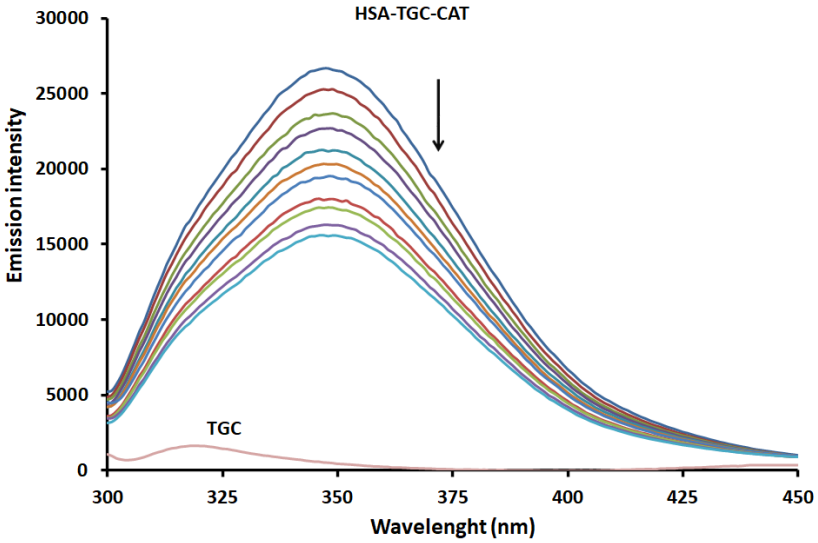


Figure 3. Fluorescence emission spectra of HSA-TGC in the presence of CAT (T = 298 K, pH = 7.4). [HSA] = 2 µM and [CAT] = 2 µM and [TGC] = 0 to 1 x 10^{-5} M.

$$F_{cor} = F_{obs} \times 10^{\frac{A_{ex} + A_{em}}{2}}$$

$$\frac{F_0}{F} = 1 + K_q \tau_0 [Q] = 1 + K_{SV}[Q]$$

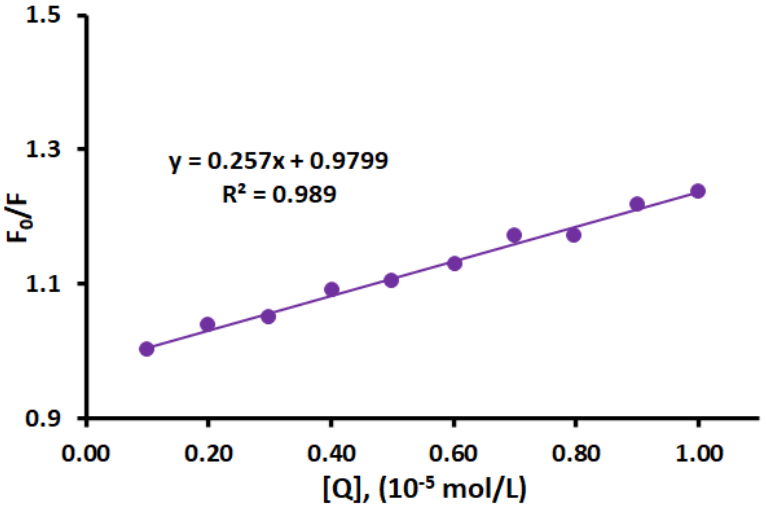
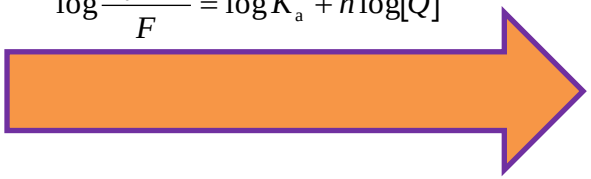


Figure 4. Stern-Volmer plots of the fluorescence quenching of HSA-TGC system by CAT at 298 K[8]

[8] J.R. Lakowicz, Principles of fluorescence spectroscopy, 3rd ed. Springer, New York, (2006)

Results and discussion

$$\log\frac{F_0 - F}{F} = \log K_a + n\log[Q]$$



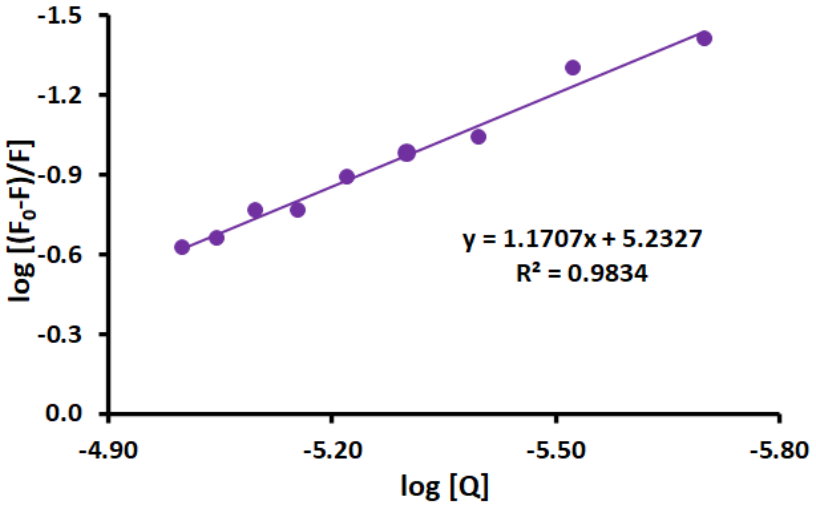


Figure 5. Logarithmic plots of the fluorescence quenching of HSA by TGC in the presence of CAT at 298 K

Table 1. The interaction parameters of the binary (HSA-TGC) and ternary (HSA-TGC-CAT, HSA : CAT = 1 : 1) systems

System [a]	K_{SV} x 10^{-4} [b]	k_q x 10^{-12} [c]	R^2 [d]	K_a x 10^{-5} [b]	n	R^2
HSA-TGC	5.00	5.00	0.996	0.18	0.9	0.991
HSA-TGC-CAT	2.57	2.57	0.9890	1.71	1.17	0.9834

[a] 298 K; [b] M^{-1}; [c] $M^{-1}s^{-1}$; [d] R is the correlation coefficient

Results and discussion

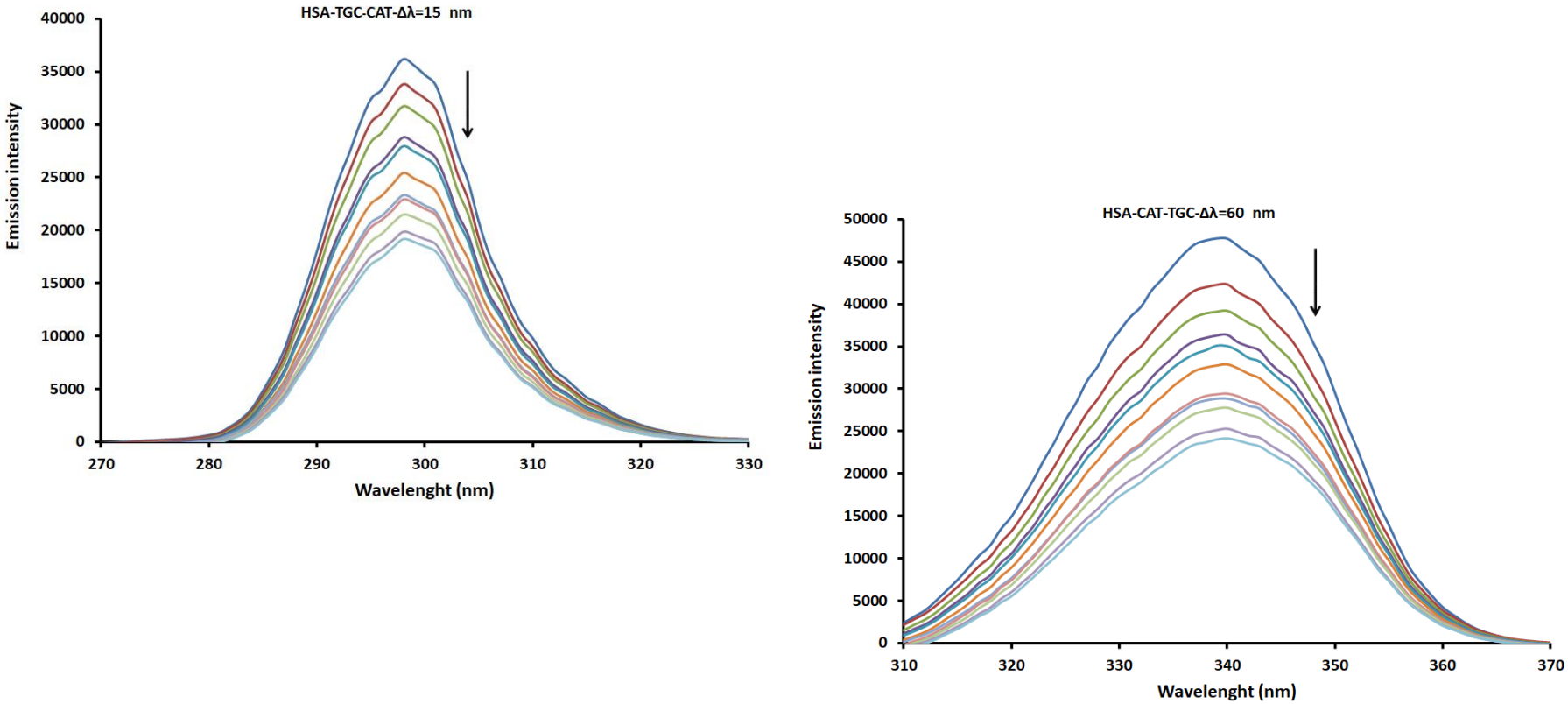


Figure 6. The effect of CAT on the synchronous fluorescence emission spectra of HSA-TGC system (T = 298 K, pH = 7.4). [HSA] = 2 µM, [CAT] = 2 µM and [TGC] = 0 to 1 x 10^{-5} M.

Results and discussion

Table 2. ΔG[a] values of site I (subdomain IIA) versus site II (subdomain IIIA)

System[b]	Autodock		Ref.
	Site I	Site II	
HSA-TGC	-24.36	-14.60	[9]
HSA-TGC-CAT	-25.60	-16.65	This work

[a] kJ·mol^{-1}; [b] 298 K.

Table 3. Energies and inhibition constants of site I (subdomain IIA)

	Autodock		Ref.
System[a]	ΔG[b]	Ki[c]	
HSA-TGC	-24.36	5.44 x 10^{-5}	[9]
HSA-TGC-CAT	-25.60	3.27 x 10^{-5}	This work

[a] 298 K; [b] kJ·mol^{-1}; [c] mol·dm^{-3}.

[9] S.D. Stojanovic, S.M. Jankovic, Z.D. Matovic, I.Z. Jakovljevic, R.M. Jelic, Monatsh Chem 146 399- (2015)

Results and discussion

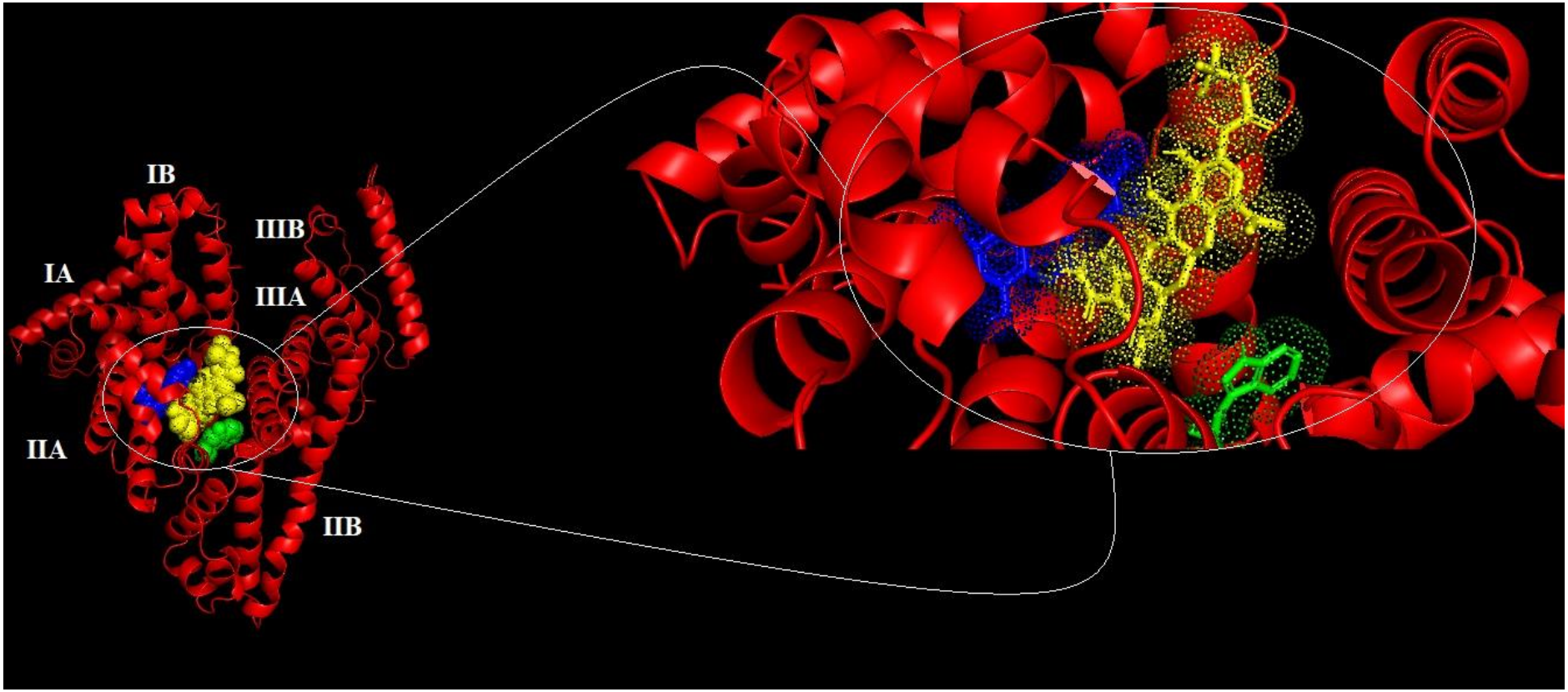


Figure 7. HSA-TGC-CAT system (CAT colored blue, TGC colored yellow and TRP214 colored green).

Results and discussion

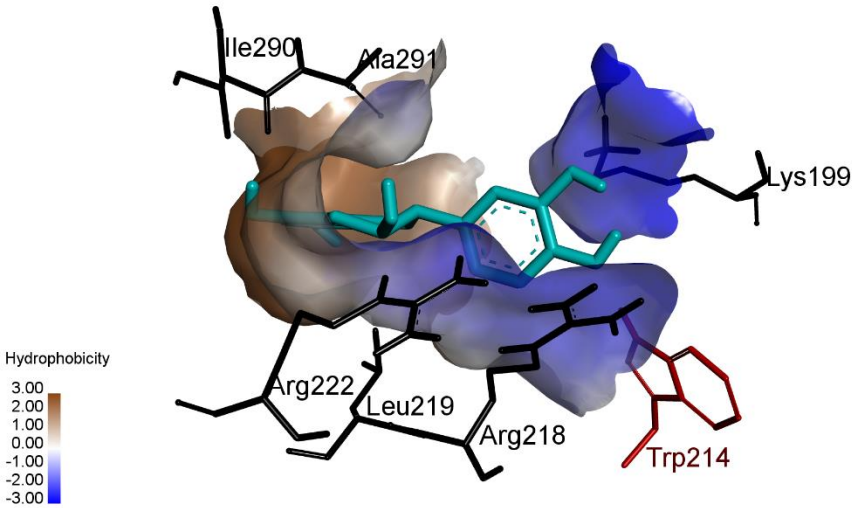


Figure 8. Hydrophobic contributions in HSA-TGC-CAT

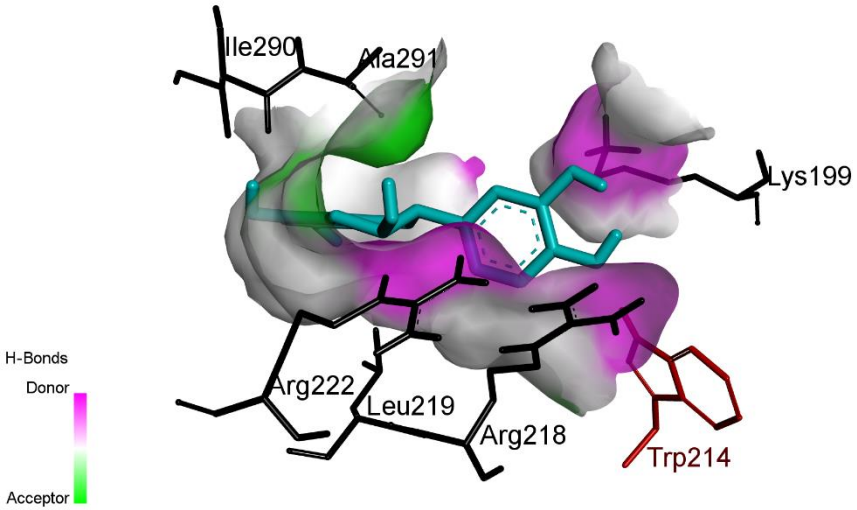


Figure 9. Contribution of H-bonds in HSA-TGC-CAT

Conclusions

- ✓ Catechin has a positive influence on binding tigecycline to HSA in simulated physiological conditions
- ✓ The fluorescence quenching measurements showed that catechin share IIA subdomain in HSA with tigecycline drug
- ✓ There is no significant change in the microenvironment on the Trp residues in the IIA subdomain and there is hydrophilicity or hydrophobicity around it
- ✓ Docking experiments toward HSA protein indicate a good correlation with experimental results
- ✓ Computational work confirmed that catechin bind preferentially to sub-domain IIA of HSA and affinities of triple systems are higher than a double one
- ✓ Sequential docking predicts that subdomain IIA is large enough to accommodate multiple ligands at the same time
- ✓ The hydrogen bonds and hydrophobic interactions are responsible for the relatively strong binding between tested compounds and the HSA receptor.

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