6th International Electronic Conference on Medicinal Chemistry
1-30 November 2020
sciforum.net/conference/ECMC2020
sponsored by pharmaceuticals

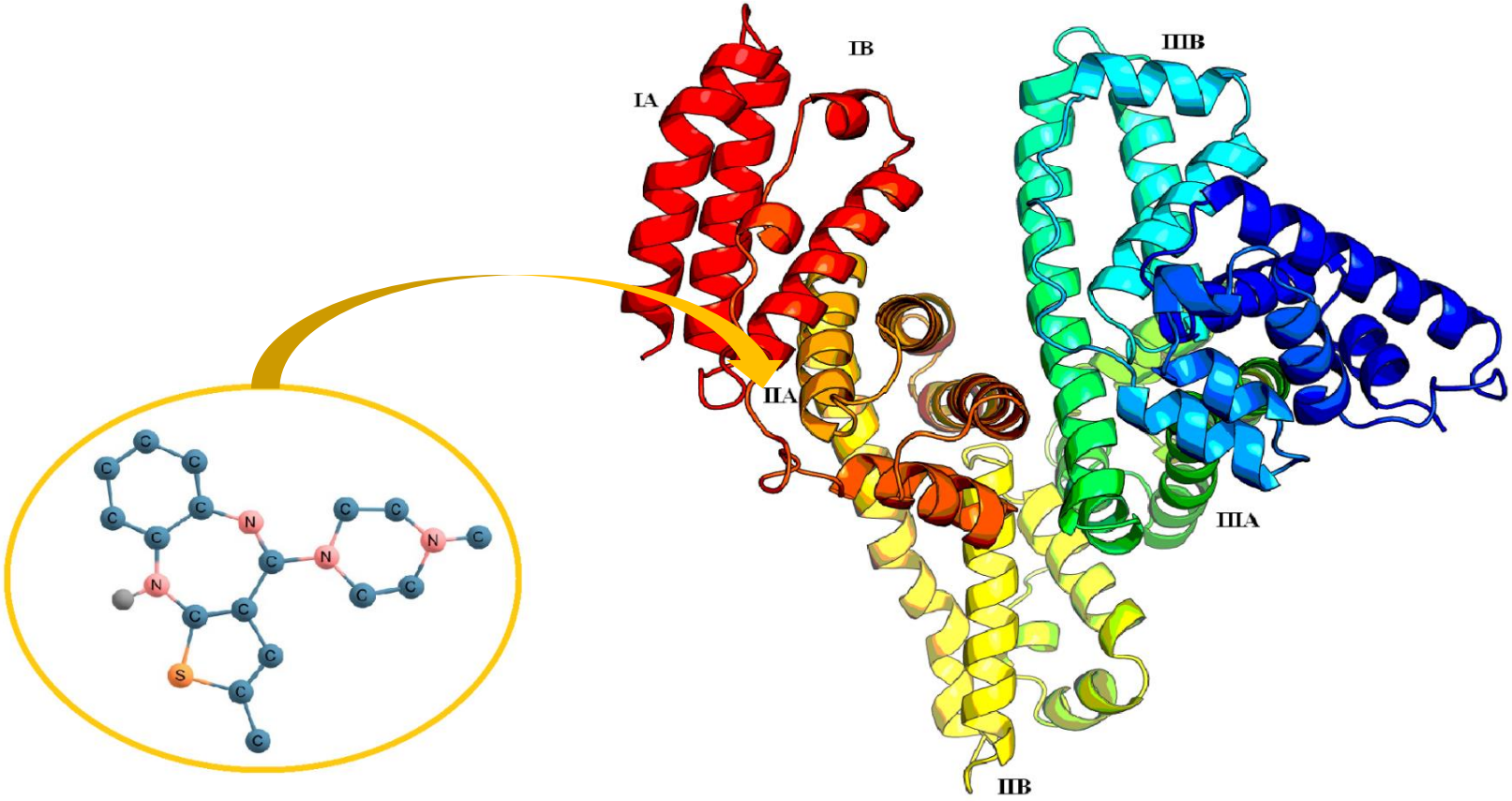
Interaction between olanzapine and human serum albumin and effect of flavonoids on the binding: A spectroscopic study

Emina Mrkalić [1,*], Ratomir Jelić [2], Stefan Stojanović [2], Miroslav Sovrlić [2]

[1] University of Kragujevac, Institute for Information Technologies, Department of Science, Jovana Cvijića bb, Kragujevac 34000, Serbia;
[2] University of Kragujevac, Faculty of Medical Sciences, Department of Pharmacy, Svetozara Markovića 69, Kragujevac 34000, Serbia.

* emina.mrkalic@pmf.kg.ac.rs

Interaction between olanzapine and human serum albumin and effect of flavonoids on the binding: A spectroscopic study



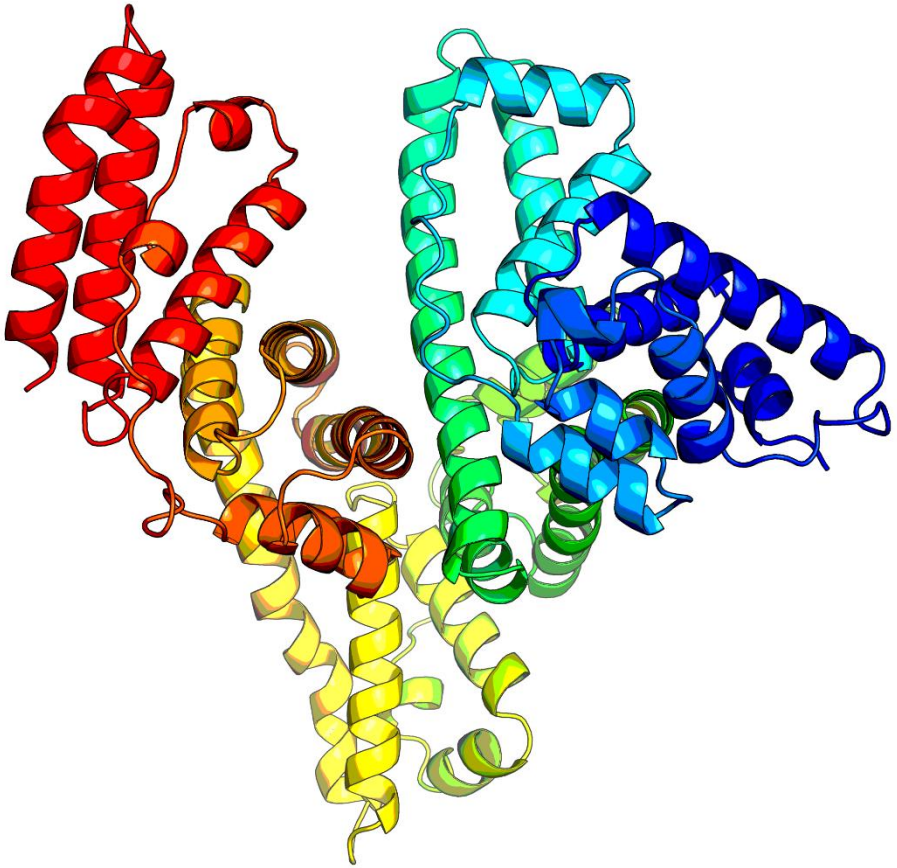
Abstract:

The aim of this study was to investigate the binding properties of OLZ to HSA and its competitive binding to HSA with flavonoids - diosmin (DIO), quercetin (QUE) and catechin (CAT) under the physiological conditions by fluorescence and absorption spectroscopy. Results of fluorescence experiments suggest that OLZ quench the fluorescence of HSA through the mixed quenching mechanism and non-radiation energy transferring because of the HSA–OLZ complex formation. According to thermodynamic parameters, the reaction was spontaneous and mainly driven by hydrogen bonds and van der Waals interactions. The presence of DIO and CAT decreased binding affinity between OLZ and HSA which indicates that they could compete binding OLZ to HSA. Contrary, in the presence of QUE the binding affinity of the HSA-OLZ system enhanced, which may be explained by non-competitive interference. This study may provide a better understanding of OLZ pharmacokinetics and illustrate drug-drug interactions.

Keywords: Olanzapine; HSA; Flavonoids; Competitive binding

Introduction

- Serum albumin (HSA) is the most abundant carrier protein present in the circulatory system [1]
- The drug-serum albumin interaction plays a dominant role in the metabolism of drugs [2]
- Flavonoids belong to a group of phenolic compounds found in fruits and vegetables [3]
- Olanzapine (OLZ) is an atypical antipsychotic drug is widely used for the treatment of psychiatric disorders [4]

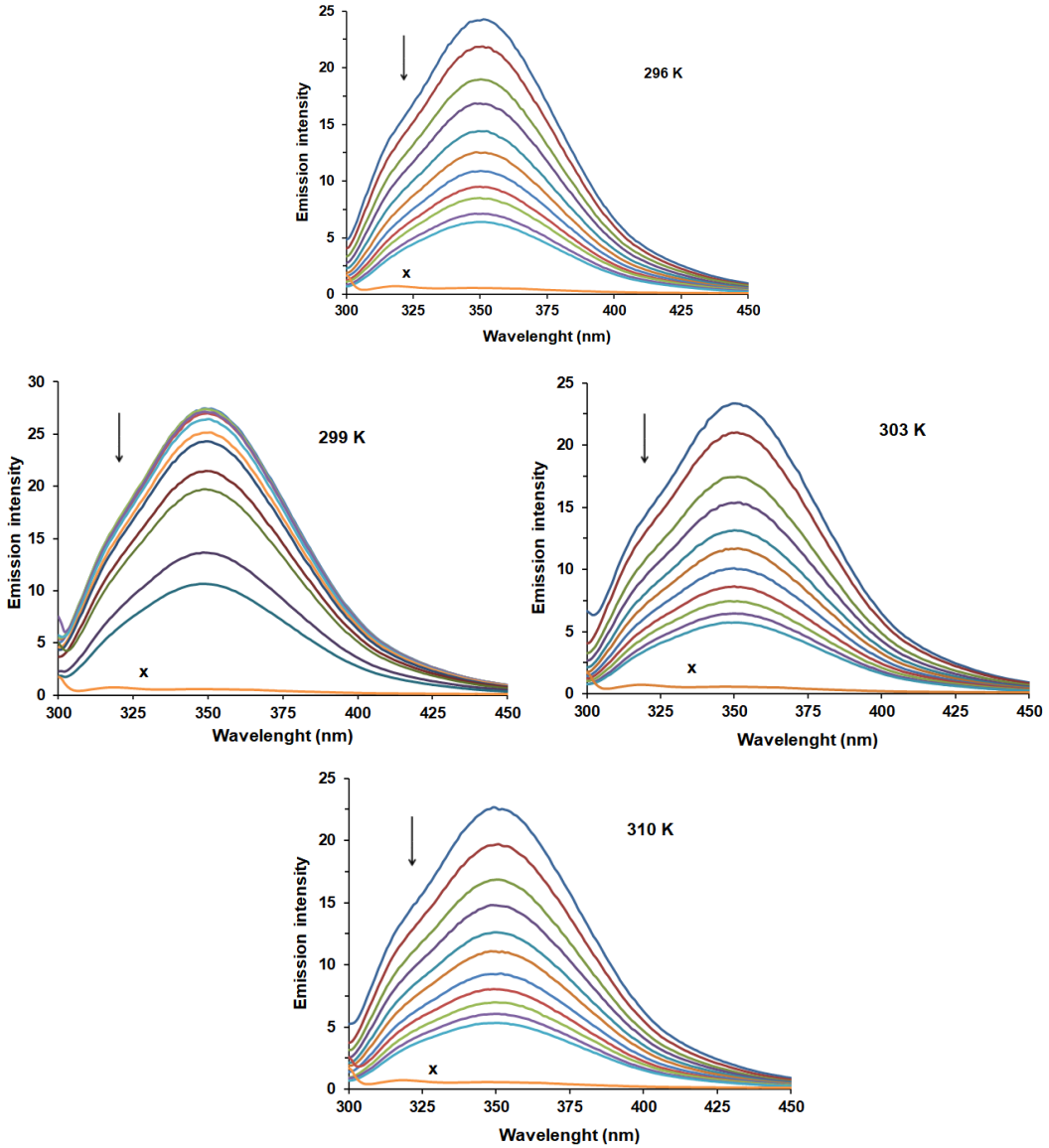


[1] X.M. He. D.C. Carter, Atomic structure and chemistry of human serum albumin, Nature, 358 (1992) 209-215.
[2] A.B. Khan, J.M. Khan, M.S. Ali, R.H. Khan, Kabir-ud-Din, Interaction of amphiphilic drugs with human and bovine serum albumins, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 97 (2012) 119-124.
[3] T.J. Mabry, K.R. Markham, M.B. Thomas, Springer-Verlag, Berlin, Heidelberg, New York. 1970.
[4] S. Leucht, C. Corves, D. Arbter, R.R. Engel, C. Li, J.M. Davis, Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis, Lancet 373 (2009) 31–41.

Results and discussion

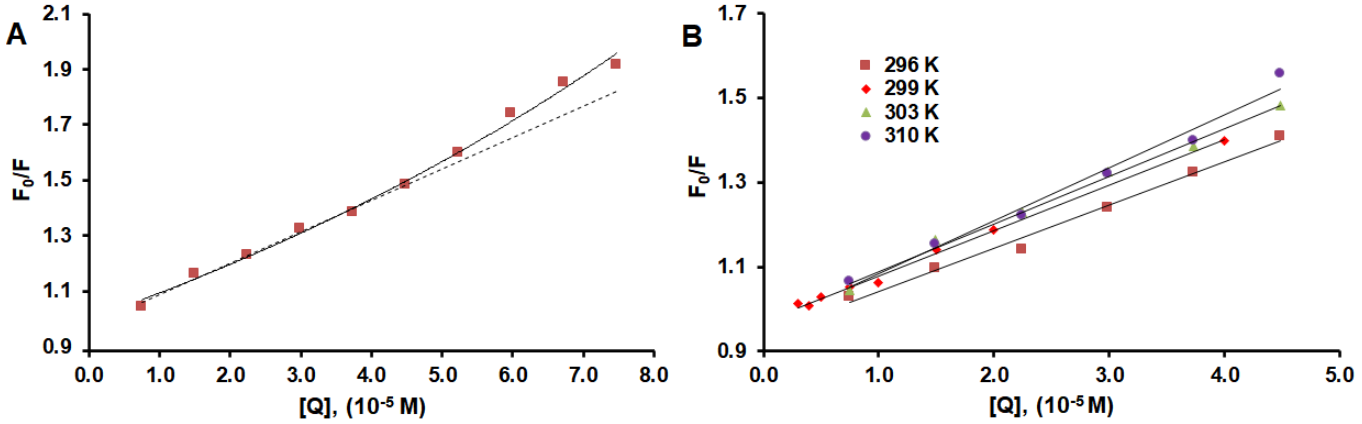
HSA-OLZ system

- *Fluorescence measurements*

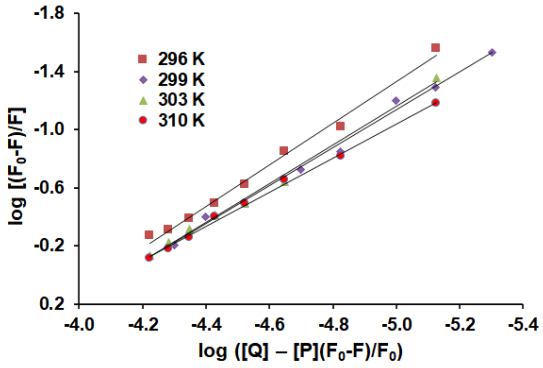


Emission spectra of HSA in the presence of various concentrations of OLZ at different temperatures. ***x*** *represents 2 µM OLZ only.*

Results and discussion



*(**A**) The Stern-Volmer plot for HSA induced by OLZ at 303 K. (**B**) The Stern-Volmer plots of the fluorescence quenching of HSA by OLZ at different temperatures.*



Logarithmic plots of the fluorescence quenching of HSA by OLZ at different temperatures

Table 1

Stern–Volmer quenching constants (K_{SV}), quenching rate constants (k_q), binding constants (K_b) and number of binding sites (n) for the interaction of OLZ with HSA at lower complex concentrations

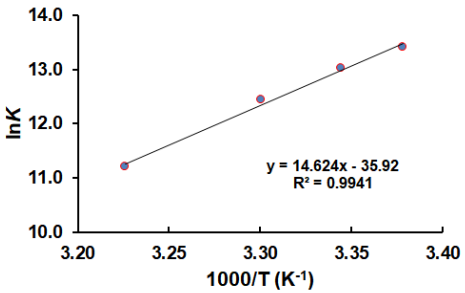
T (K)	K_{SV} x 10^{-4} (M^{-1})	k_q x 10^{-12} (M^{-1} s^{-1})	R^{2a}	K_b x 10^{-5} (M^{-1})	n	R^{2a}
296	1.03	1.03	0.9942	7.10	1.42	0.9931
299	1.07	1.07	0.9964	4.78	1.36	0.9924
303	1.13	1.13	0.9928	2.56	1.31	0.9942
310	1.26	1.26	0.9820	0.73	1.18	0.9975

[a] R is the correlation coefficient

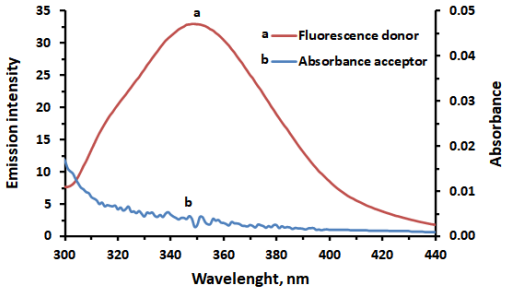
Results and discussion

HSA-OLZ system

- *Thermodynamics of HSA-OLZ interaction*
- *Energy transfer from HSA to OLZ*



Van't Hoff plot of the interaction between HSA and OLZ at 296, 299, 303 and 310 K.



The overlap of the fluorescence spectrum of HSA (a) and the absorption spectrum of OLZ (b) (pH = 7.40; T = 298 K)

Table 2

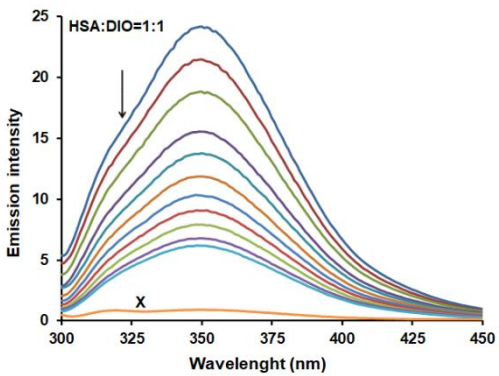
The thermodynamics parameters of the HSA-OLZ systems at different temperatures

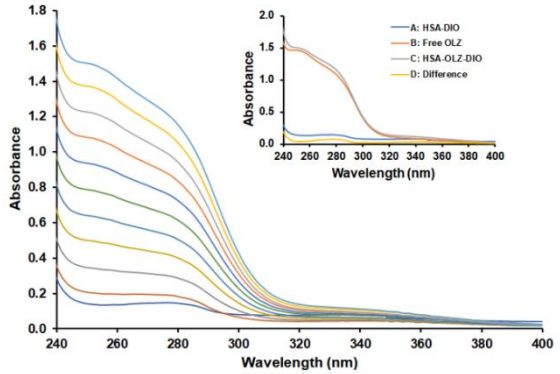
System	T (K)	ΔH^0 (KJmol^{-1})	ΔS^0 (Jmol^{-1}K^{-1})	ΔG^0 (KJmol^{-1})
HSA-OLZ	296	-124.96	-309.56	-33.33
	299			-32.40
	303			-31.16
	310			-29.00

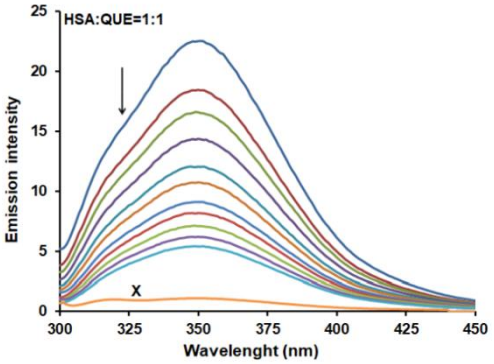
Results and discussion

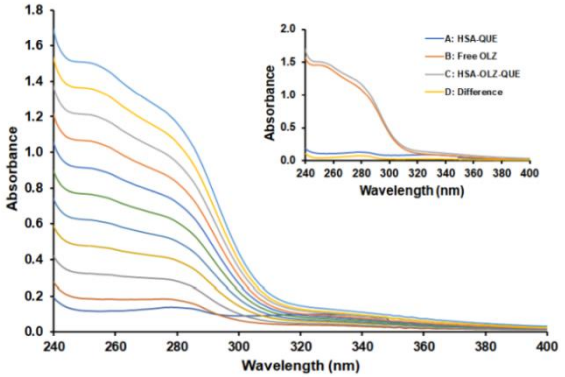
HSA-OLZ-flovonoid systems

- *Fluorescence measurements*
- *UV-vis measurements*









Fluorescence emission spectra of HSA-OLZ in the presence of DIO (QUE) (T = 296 K, pH = 7.4). ***x*** *represents OLZ (2 μM) only.*

UV–Vis absorption spectra of HSA-DIO (QUE) (1:1) in the absence and presence of increasing amounts of OLZ (T = 296 K, pH = 7.4).

Table 4

The interaction parameters of the binary (HSA-OLZ) and ternary (HSA-OLZ-L, HSA:L = 1:1) systems at 296 K

System	K_{SV} x 10^{-4} (M^{-1})	R^2	K_b x 10^{-5} (M^{-1})	n	R^2
HSA-OLZ	1.03	0.9942	7.10	1.42	0.9931
HSA-OLZ-DIO	1.19	0.9944	2.77	1.32	0.9888
HSA-OLZ-QUE	1.17	0.9951	9.82	1.47	0.9888
HSA-OLZ-CAT	1.15	0.9931	2.34	1.33	0.9958

[a] R is the correlation coefficient

Conclusions

- ✓ Fluorescence experiments suggest that OLZ interact with HSA through the mixed quenching process.
- ✓ The values of K_b indicate that OLZ strong binds to HSA. Increasing temperature causing a decrease in the binding affinity of OLZ to HSA which may increase the free concentration of unbound OLZ in circulating plasma and improve its pharmacological effects.
- ✓ According to thermodynamic parameters ($\Delta H^0<0$ and $\Delta S^0<0$) the main interaction forces in OLZ-HSA system were van der Waals interactions and hydrogen bonds.
- ✓ The negative value of Gibb's free energy indicated that the interaction process is spontaneous.

Conclusions

- ✓ The obtained binding distance (r < 7 nm) for tested system confirmed that non-radiation energy transfer from HSA to OLZ occurred with high probability.
- ✓ Competitive interference - the presence of DIO and CAT caused decrease in the binding constant of the HSA-OLZ system which leads to an increase free concentrations of OLZ in plasma and improve its maximum effectiveness.
- ✓ Non-competitive interference - calculated values of K_b indicate that the binding affinity of the HSA-OLZ system is enhanced in the presence of QUE which leads to the decreasing concentration of free OLZ in plasma and reduce its maximum effectiveness.
- ✓ Combined actions of olanzapine and flavonoids may lead to further changes in HSA conformation.

Acknowledgments

This work was supported by the Ministry of Education, Science and Technological Development of the Republic of Serbia (Agreement No. 451-03-68/2020-14/200122).