A molecular docking study on natural compounds as anxiolytics and antidepressants

Maria Mernea[1,*], Maria-Eliza Satmaru[1], Alina-Nicoleta Toma[1], Cristina Doina Nițu[2,3], Dan F. Mihăilescu[1], Speranta Avram[1], Miruna Silvia Stan[4]

[1] Department of Anatomy, Animal Physiology and Biophysics, Faculty of Biology, University of Bucharest, Bucharest, Romania

[2] Doctoral School of Biology, Faculty of Biology, University of Bucharest, Bucharest, Romania

[3] Institute of Oncology "Prof. dr. Al. Trestioreanu", Bucharest, Romania

[4] Department of Biochemistry and Molecular Biology, Faculty of Biology, University of Bucharest, Bucharest, Romania

* e-mail: maria.mernea@bio.unibuc.ro

Introduction

Depression and anxiety are two conditions whose incidence increased in the context of COVID-19. Administration of current therapies based on anxiolytic and antidepressant drugs can result in adverse reactions and even potential dangers in the case of some patients like older adults and elderly patients.

Aim

In order to identify safer treatments, we screened twenty natural compounds reported as beneficial in depression and anxiety against major drug targets in the two conditions - serotonin transporter (SERT) for depression and γ-aminobutyric acid A receptor (GABAA R) for anxiety.

Methods

-The twenty natural compounds were identified from the literature: apigenin, astilbin, astragalin, baicalein, berberine, chrysin, crocin, curcumin, esculin, fisetin, hesperidin, icariin, kaempferitrin, myricetin, kaempferol, luteolin, naringenin, piperine, umbelliferone, vanillin

-Their SMILES structures and 3D structures as SDF files were retrieved from PubChem database

-The compounds docked to:

- SERT - 6VRH structure (Figure 1a)
- GABAA R - 6X3X structure (Figure 1b)

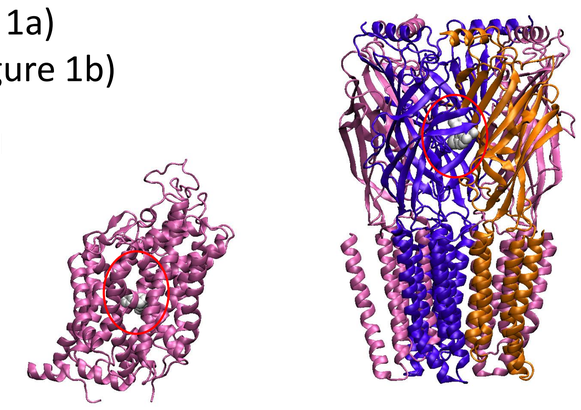


Figure 1. Crystal structures of (a) SERT (PDB id 6VRH) and (b) GABAA R (PDB id 6X3X). The sites considered for molecular docking are circled with red on the figure: (a) the central binding site of SERT and (b) the benzodiazepine binding site of GABAA receptor)

-Molecular docking was performed using Biovia Discovery Studio v16.1.0.15350 (BIOVIA Dassault Systemes, San Diego, CA, USA), by applying the CDOCKER algorithm

-Compounds were ranked according to resulted CDOCKER energies

-Top five compounds identified in the case of SERT and GABAA R were further analyzed by predicting their:

- bioavailability and the drug-likeness profiles using SwissADME
- pharmacokinetic features using pkCSM

Results

-The most favorable CDOCKER energies calculated for the top five compounds docked to SERT and GABAA R are presented in Table 1.

-Luteolin, myricetin and curcumin are common ligands for both targets. Their 2D interaction maps with the proteins are presented in Figures 2 and 3.

Table 1. Docking scores of the most favorable ligands identified in the case of SERT and GABAA R. The three common ligands of the two targets are highlighted.

Compound	-CDOCKER energy (kcal/mol) SERT	-CDOCKER interaction energy (kcal/mol) SERT	Compound	-CDOCKER energy (kcal/mol) GABAA R	-CDOCKER interaction energy (kcal/mol) GABAA R
Myricetin	**43.86**	**49.81**	**Luteolin**	**44.64**	**38.97**
Luteolin	**41.7**	**35.28**	Baicalein	43.7	43.54
Curcumin	**39.19**	**51.19**	**Myricetin**	**43.63**	**50.33**
Apigenin	35.94	36.05	Chrysin	40.89	42.57
Fisetin	34.78	39.85	**Curcumin**	**38.88**	**47.1**

Figure 2. 2D interaction maps of compounds with SERT.

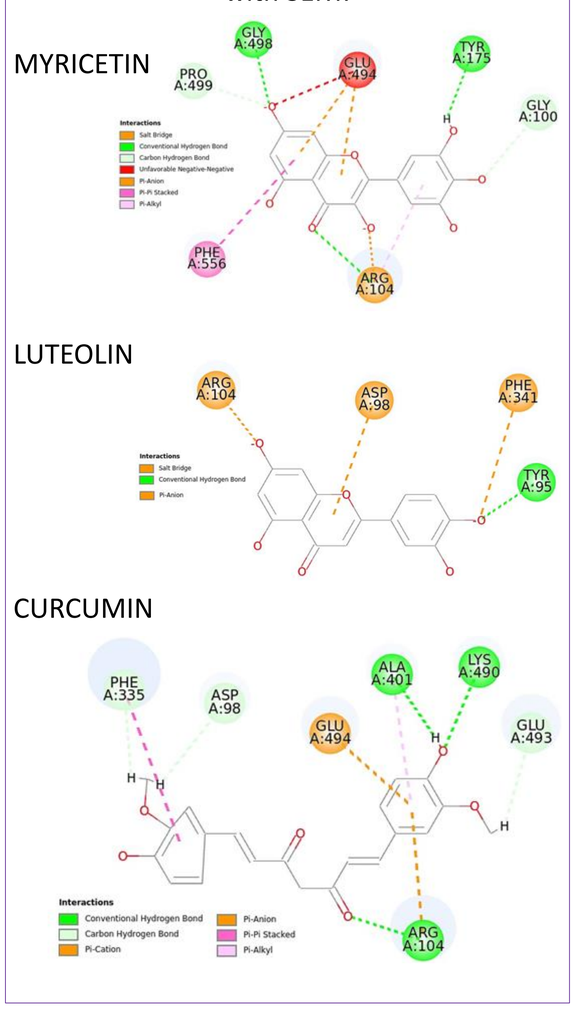
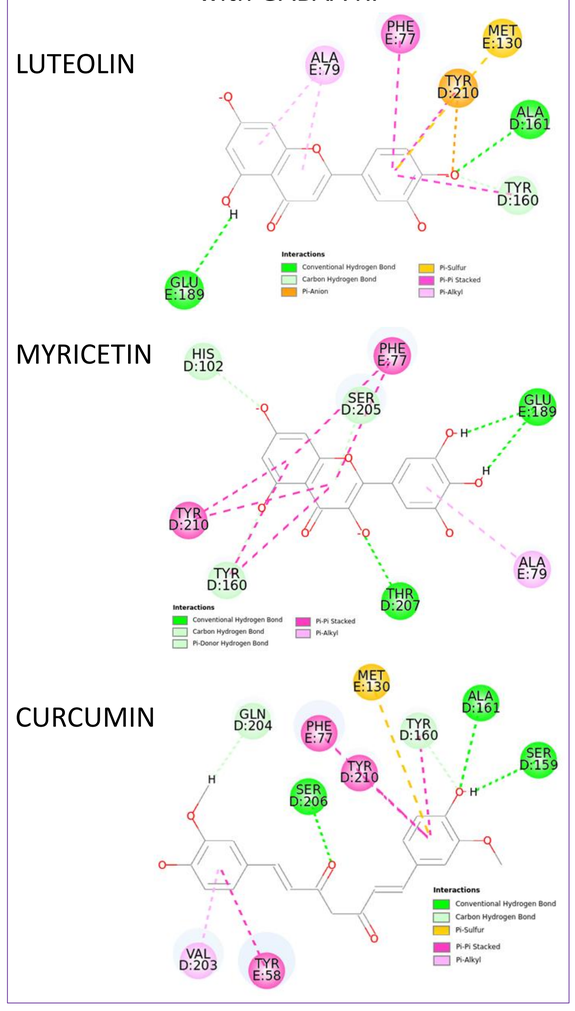


Figure 3. 2D interaction maps of compounds with GABAA R.



-Luteolin, myricetin, curcumin, as well as apigenin, fisetin, baicalein and chrysin comply with the drug-likeness rules of Lipinski and Ghose

-The compounds present favorable bioavailability scores

-Regarding their pharmacokinetic features, results show that:

-all compounds present a suitable gastrointestinal absorption,

-all compounds can be distributed to the central nervous system

-the compounds are not hepatotoxic or cardiotoxic and do not present AMES toxicity

Conclusion

Our results point toward luteolin, myricetin and curcumin as common ligands for SERT and GABAA R, suggesting their beneficial effect in both anxiety and depression. Molecular dynamics simulations are further required to validate the stability of complexes formed by these ligands with the proteins.

Acknowledgement: This work was supported by a grant of the Ministry of Research, Innovation and Digitization, CNCS/CCCDI—UEFISCDI, projects number PN-III-P1-1.1-TE-2021-1375, PN-III-P2-2.1-PED-2021-2866 and PN-III-P2-2.1-PED-2019-1471.

ECMC 2022
The 8th International Electronic Conference on Medicinal Chemistry
01–30 NOVEMBER 2022 | ONLINE