ECB 2021

sciforum

Proceedings

The study of natural compounds as antidepressants by bioinformatics methods †

Speranta Avram [1], Miruna Silvia Stan [1,2], Ana Maria Udrea [3], Catalin Buiu [4,*] and Maria Mernea [1]

[1] University of Bucharest, Faculty of Biology, Department of Anatomy, Animal Physiology and Biophysics, SplaiulIndependentei, No 91-95, 050095, Bucharest, Romania; speranta.avram@gmail.com (S.A.), maria.mernea@bio.unibuc.ro (M.M.)

[2] University of Bucharest, Research Institute of the University of Bucharest–ICUB, 91–95, Splaiul Independentei, 050095, Bucharest, Romania; miruna.stan@bio.unibuc.ro (M.S.S.)

[3] Laser Department, National Institute for Laser, Plasma and Radiation Physics, 077125 Magurele, Ilfov, Romania; ana.udrea@inflpr.ro (A.M.U.)

[4] Department of Automatic Control and Systems Engineering, Politehnica University of Bucharest, 313 Splaiul Independenței, 060042 Bucharest, Romania; catalin.buiu@upb.ro (C.B.)

* Correspondence: catalin.buiu@upb.ro; Tel.: +40214029167 (C.B.); maria.mernea@bio.unibuc.ro; Tel.: +40213181573 (M.M.)

† Presented at the 1st International Electronic Conference on Biomedicine, 01–26 June 2021; Available online: https://ecb2021.sciforum.net/.

Published: 31 May 2021

Abstract: According to the World Health Organization, the neuropsychiatric disorders pose an increasingly greater burden on health, society and economy of countries. Currently there are strategies to prevent some of these disorders and there are treatments or means to alleviate their symptoms. In the case of depression, the medication consists of antidepressant drugs. Such drugs can also be used in other conditions like anxiety, pain or insomnia. A shortcoming of the currently used antidepressants is the occurrence of side effects that sometimes are unbearable for the patient. In this respect, a promising direction is the usage of medicinal plants. Plant parts are rich in phytochemicals that could be beneficial in mental disorders by acting on various targets. Here we investigated the antidepressant effect of ten natural compounds from sage, mint and citrus. The biological activity of these compounds was investigated by calculating pKi values and affinities for dopamine receptor D2, serotonin transporter (SERT) and 5-hydroxytryptamine receptor 1A (5-HT$_{1A}$) using Almond-Pentacle software. Our results showed that linalyl acetate, 1,8 cineole and neryl acetate could be efficient antidepressants and neuroleptics.

Keywords: antidepressant; natural compounds; QSAR

1. Introduction

According to the World Health Organization (WHO), depression is a prevalent mental disorder that seriously affects the function of patients inside their family, at their work place or at school. Patients with mild to severe depression are offered treatment as antidepressant drugs and psychotherapy [1]. The drugs prescribed in depression fall in three categories: monoamine oxidase inhibitors, tricyclic antidepressants and second-generation antidepressants like norepinephrine, serotonin or serotonin–norepinephrine reuptake inhibitors [2]. These present a series of adverse side effects like anxiety, tachycardia, tremor, sedation, blurred vision, etc [2,3]. The intensity of these adverse effects is sometimes unbearable for patients that become intolerant to the treatment [4]. In this context, natural products might represent an alternative to conventional drugs for the treatment of depression.

Up to date, the beneficial effect of plant compounds in depression was extensively reviewed. From these we can mention Chinese herbal medicines [5], Ayurvedic single or

holistic approaches [6] and many other phytochemicals or medicinal herbs [7,8]. The usage of natural compounds for therapy imposes some challenges concerning their pharmacokinetic and pharmacodynamic properties [9], meaning that a thorough characterization of these compounds is required. Cheminformatics methods can be of great assistance, allowing the description of the compounds and prediction of their biological effect.

Using the experience from our previous studies in predicting the anti-Alzheimer effect of natural compounds from *Mentha spicata* essential oil [9] or in predicting the antidepressant effect and the targets of candidate compounds [10,11], here we used cheminformatics methods to investigate the antidepressant potential of ten natural compounds from diverse sources: 1,8-cineole (eucalyptus, sage), limonene (peppermint, spearmint), sabinene (lemon, mint), resveratrol (skin of grapes), chamazulene (german chamomile, roman chamomile), germacrene D (peppermint), linalyl acetate (sage), nerol (common grapes), neryl acetate (lemon balm, peppermint), and quercetin (grape). These compounds were mentioned in the literature as having antidepressant or neuroprotective effects [12]. We calculated the pharmacokinetic profiles of compounds. The prediction of their antidepressant effect was performed by building three quantitative structure-activity relationship (QSAR) models that took into account three proteins important in depression, namely the serotonin transporter (SERT), dopamine receptor 2 (D2) and 5-hydroxytryptamine receptor 1A (5-HT_{1A}).

2. Materials and methods

2.1. Ligand selection and assessment of their drug and lead-likeness features

We selected ten natural compounds from various vegetable sources, namely 1, 8 cineole, limonene, sabinene, resveratrol, chamazulene, germacrene D, linalyl acetate, nerol, neryl acetate and quercetin based on previous studies mentioning their possible beneficial effects in neuropsychiatric treatments. The Simplified Molecular Input Line Entry (SMILES) files of selected compounds were obtained from the PubChem database [13] and were used for further bioinformatics and cheminformatics analysis. Spatial structures of compounds were obtained in the Molecular Operating Environment (MOE) software (https://www.chemcomp.com/Products.htm), using the MMFF94x force field with a 0.005 gradient and Gasteiger-type charges. To evaluate the drug-likeness features of selected compounds we used Lipinski [14], Veber [15], Ghose [16] and Egan [17] filters implemented in SwissADME web tool [18].

2.2. Computational pharmacokinetics profiles of natural compounds

The absorption, distribution, metabolism, excretion (ADME) and toxicity profiles of compounds were determined using pkCSM database [19]. From all the properties calculated, we focused on the intestinal absorption (human,%), blood-brain barrier (BBB) permeability (log BBB), central nervous system permeability (CNS), fraction unbound (human) and feature of renal organic cation transporter 2 (OCT2), AMES toxicity, hepatotoxicity, LD50 (median lethal dose) and maximum tolerated dose (human).

2.3. Predicted pharmachodynamic profiles of natural compounds on SERT, 5-HT_{1A} and D2 active sites by 3D-ALMOND-QSAR

The biological activities expressed as pKi (log 1/Ki, Ki represents the inhibition constant) of natural compounds at SERT, 5-HT_{1A} and D2 receptors were evaluated by a non-aligned 3D-QSAR method and by 3D-QSAR-ALMOND [10], using Pentacle software (http://www.moldiscovery.com/software/pentacle/). We built three QSAR models as QSAR-SERT, QSAR-5-HT_{1A}, QSAR-D2 with good statistical parameters r^2 fitted correlation coefficient (greater than 0.8) and q^2 cross-validated correlation coefficient (greater than 0.6). In building the models we considered synthetic antidepressant and neuroleptic molecules in the training and validation sets. The experimental biological activities of molecules from training and validation sets were derived from PDSP Ki Database — Psychoactive Drug Screening Program [20]. In the case of all three QSAR models, the test set was represented by the selected natural compounds, namely 1, 8 cineole, limonene, sabinene,

resveratrol, chamazulene, germacrene D, linalyl acetate, nerol, neryl acetate and quercetin.

3. Results and discussions

3.1. The drug-likeness features and pharmacokinetics profiles of compounds

The results of filtering by Lipinski, Ghose, Veber, and Egan rules showed that all considered natural compounds present drug-like features, which is correlated with possible drug actions and good bioavailability.

Predicted absorption, distribution, elimination and toxicity features of compounds show that: (i) all compounds present a good intestinal absorption, (ii) all compounds except for quercetin present a good BBB permeability, (iii) the compounds except sabiene and chamazulene present a good CNS permeability, (iv) all compounds recorded a low human fraction unbound, (v) none of the compounds are substrates of renal OCT2 and (vi) none of the compounds present hepatotoxicity, cardiotoxicity or AMES toxicity.

3.2. Predicted pharmachodynamic profiles of natural compounds on SERT, 5-HT$_{1A}$ and D2 active sites

Three 3D-QSAR-ALMOND models (QSAR-SERT, QSAR-5HT-1A, QSAR-D2) with good statistical parameters were built by considering the simultaneous contribution of several descriptors in various combinations like hydrophobicity, electrostatic, hydrogen bond donor/acceptor. The QSAR models were used to predict the biological activities of 1, 8 cineole, limonene, sabinene, resveratrol, chamazulene, germacrene D, linalyl acetate, nerol, neryl acetate and quercetin at SERT, 5-HT$_{1A}$ and D2.

Initially we applied QSAR-SERT model to predict the biological activity of compounds at SERT. We observed that limonene, sabiene, chamazulene, germacrene D, linalyl acetate, nerol and neryl acetate have a strong antidepressant character. In this case the reference was paroxetine, the most active antidepressant from the training set used to build the model.

When predicting the biological activity of natural compounds at 5-HT$_{1A}$ using QSAR-5-HT$_{1A}$ model, we observe that the natural compounds have a medium antidepressant activity. Potentially the most active compounds are 1,8 cineole and linalyl acetate, as determined by comparison with ziprasidone, the most active compound in QSAR-5-HT$_{1A}$ training set.

In order to determine the neuroleptic activity of compounds we applied QSAR-D2 model. Relative to spiperone, the most active compound in QSAR-D2 training set, the most active natural compounds appear to be quercetin, neryl acetate, linalyl acetate and 1,8 cineole.

4. Conclusions

Here we investigated the potential of ten natural compounds (1, 8 cineole, limonene, sabinene, resveratrol, chamazulene, germacrene D, linalyl acetate, nerol, neryl acetate and quercetin) to exhibit antidepressant effects by acting on SERT and 5-HT$_{1A}$ receptors or neuroleptic activity acting on D2 receptors. This was performed using three QSAR models developed for predicting the activity of compounds at each target.

Prior to building the models, the compounds were filtered by drug and lead-likeness rules showing that all compounds comply with the rules, presenting drug-likeness and good bioavailability features. Also, the compounds were filtered based on their predicted ADME and toxicity profiles and all compounds resulted to have good BBB and CNS permeability while being non-toxic on the liver or heart and not mutagenic.

By applying the QSAR models that we built we noticed that seven out of ten compounds should have a good biological activity on SERT, two compounds should modulate 5-HT$_{1A}$ receptors and four compounds should modulate D2 receptors. From these, linalyl acetate appears the only compound modulating all three protein targets, 1,8 cineole should modulate 5-HT$_{1A}$ and D2 receptors and neryl acetate should modulate SERT and D2 receptors.

Author Contributions: conceptualization, S.A.; methodology, S.A.; software, S.A. and C.B.; investigation, S.A. and A.M.U.; formal analysis, C.B.; writing—original draft preparation, A.M.U. and S.A.; writing—review and editing, M.M. and M.S.S.

Funding: The study was supported by UEFISCDI through the projects PN-III-P2-2.1-PED2019-1471 "New biocompatible shagaol and curcuminoid-like products used as adjuvantes in cancer radiotherapy" and PN-III-P1-1.2-PCCDI-2017-0728 "Integrated project for the development of technologies dedicated to advanced medical treatments".

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

References

1. World Health Organization (WHO) Depression. Available online: https://www.who.int/news-room/fact-sheets/detail/depression (accessed on 24 April 2021).
2. Lee, G.,Bae, H. Therapeutic Effects of Phytochemicals and Medicinal Herbs on Depression. BioMed Res Int 2017; 2017, 6596241.
3. Predictable, S., Laurencic, G.,Malone, D. Side effects of antidepressants: An overview. Cleve Clin J Med 2006; 73, 351.
4. Trivedi, M.H., Fava, M., Wisniewski, S.R., Thase, M.E., Quitkin, F., Warden, D., Ritz, L., Nierenberg, A.A., Lebowitz, B.D.,Biggs, M.M. Medication augmentation after the failure of SSRIs for depression. N Engl J Med 2006; 354, 1243-1252.
5. Wang, Y., Li, M., Liang, Y., Yang, Y., Liu, Z., Yao, K., Chen, Z.,Zhai, S. Chinese Herbal Medicine for the Treatment of Depression: Applications, Efficacies and Mechanisms. Curr Pharm Des 2017; 23, 5180-5190.
6. Sharma, R., Kabra, A., Rao, M.M.,Prajapati, P.K. Herbal and Holistic Solutions for Neurodegenerative and Depressive Disorders: Leads from Ayurveda. Curr Pharm Des 2018; 24, 2597-2608.
7. Sarris, J., Panossian, A., Schweitzer, I., Stough, C.,Scholey, A. Herbal medicine for depression, anxiety and insomnia: A review of psychopharmacology and clinical evidence. Eur Neuropsychopharmacol 2011; 21, 841-860.
8. Lee, G.,Bae, H. Therapeutic Effects of Phytochemicals and Medicinal Herbs on Depression. Biomed Res Int 2017; 2017, 6596241.
9. Avram, S., Mernea, M., Bagci, E., Hritcu, L., Borcan, L.C.,Mihailescu, D.F. Advanced Structure-activity Relationships Applied to Mentha spicata L. Subsp. spicata Essential Oil Compounds as AChE and NMDA Ligands, in Comparison with Donepezil, Galantamine and Memantine - New Approach in Brain Disorders Pharmacology. CNS Neurol Disord Drug Targets 2017; 16, 800-811.
10. Avram, S., Duda-Seiman, D., Borcan, F.,Wolschann, P. QSAR-CoMSIA applied to antipsychotic drugs with their dopamine D2 and serotonine 5HT2A membrane receptors. J Serb Chem Soc 2011; 76, 263-281.
11. Avram, S., Buiu, C., Duda-Seiman, D.M., Duda-Seiman, C.,Mihailescu, D. 3D-QSAR design of new escitalopram derivatives for the treatment of major depressive disorders. Sci pharm 2010; 78, 233-248.
12. Zhang, Y., Long, Y., Yu, S., Li, D., Yang, M., Guan, Y., Zhang, D., Wan, J., Liu, S.,Shi, A. Natural volatile oils derived from herbal medicines: A promising therapy way for treating depressive disorder. Pharmacol. Res 2020, 105376.
13. Kim, S., Chen, J., Cheng, T., Gindulyte, A., He, J., He, S., Li, Q., Shoemaker, B.A., Thiessen, P.A., Yu, B., Zaslavsky, L., Zhang, J.,Bolton, E.E. PubChem in 2021: New data content and improved web interfaces. Nucleic Acids Res 2020; 49, D1388-D1395.
14. Lipinski, C.A., Lombardo, F., Dominy, B.W.,Feeney, P.J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 1997; 23, 3-25.
15. Veber, D.F., Johnson, S.R., Cheng, H.Y., Smith, B.R., Ward, K.W.,Kopple, K.D. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem 2002; 45, 2615-2623.
16. Ghose, A.K., Viswanadhan, V.N.,Wendoloski, J.J. A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases. J Comb Chem 1999; 1, 55-68.
17. Egan, W.J., Merz, K.M.,Baldwin, J.J. Prediction of Drug Absorption Using Multivariate Statistics. J Med Chem 2000; 43, 3867-3877.
18. Daina, A., Michielin, O.,Zoete, V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Sci Rep 2017; 7, 42717-42717.
19. Pires, D.E., Blundell, T.L.,Ascher, D.B. pkCSM: Predicting Small-Molecule Pharmacokinetic and Toxicity Properties Using Graph-Based Signatures. J Med Chem 2015; 58, 4066-4072.
20. PDSP (Psychoactive Drug Screening Program) Ki Database https://pdsp.unc.edu/databases/kidb.php.