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Application of computational tools for ADME and target modeling of bioactive compounds from hydroalcoholic extracts of *Erodium glaucophyllum* flowers

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ABSTRACT

Computational approaches based on predictive software used for computer-aided drug design to improve the quality control of drugs become a key tool in the selection and prioritization of drug targets. Seventeen identified compounds isolated from hydroalcoholic extracts of *Erodium glaucophyllum* flowers were subjected to *in silico* ADME and target prediction to evaluate their pharmacokinetics, drug-likeness and coupled target classes using Swiss ADME and Swiss Target Prediction programs. Results revealed that most of the tested compounds displayed good oral bioavailability and skin permeation suggesting that they are easily absorbed. They are also able to penetrate the blood-brain barrier and therefore to affect the central nervous system (CNS). Target

predictions indicate that all tested bioactive molecules (results shown only for gallic acid and luteolin) may be effectively coupled with a various number of essential enzymes and proteins reinforcing their behavior to be served for feature docking studies.

Keywords: Computational programs, Phyto-constituants, ADME, Drug-likeness, Pharmacokinetics, Target prediction.

1. INTRODUCTION

Recently, a great attention has been devoted regarding the application of Machine learning and computational approaches such as artificial intelligence or computational intelligence in drug discovery and design to reduce costs and ethical concerns on using both humans and animals trials (Aliper *et al.*, 2016; Ghannay *et al.*, 2020; Lavecchia, 2015; Othman *et al.*, 2020). It has been estimated that developing and introducing a new drug to the market would take about 15 years and cost about $4 billion. Therefore, application of *in silico* methods have the advantage to be less expensive and time-consuming, reducing significantly animal experiments and giving idea about the safety of the drug (Ghannay *et al.*, 2020; Othman *et al.*, 2020). Drug development was considered as the perfect ground for artificial intelligence due to the large amount of data that being collected and standardized (Sharma & Sharma, 2018; Wallach *et al.*, 2015). They offer efficient access and provide a set of tools in improving compound quality and success rate by investigating, exploring and predicting the drug's pharmacokinetic properties including absorption, distribution, metabolism, excretion, and toxicity (ADMET) (Kadri & Aouadi, 2020; Maltarollo *et al.*, 2017). Machine learning was considered as one of the most common forms of artificial intelligence which can be employed as a valid alternative to experimental procedures for prediction of druglikeness. It can also build predictive models illustrating the bioactivity level of potential targets from which structural patterns could be prospected and the structure-activity relationship could be correlated. Machine learning allows also finding out such similarity between the physicochemical properties and the biological behavior of drug therapies which can alter pharmacokinetic properties of the drugs (Khan & Sylte, 2007; Zhang *et al.*, 2012). The delivery of the drug may be influenced by several parameters such as hydrophobicity solubility, changes in gastrointestinal absorption and metabolism in the liver. Cytochrome P450 (CYPs) isoenzymes were implicated in the metabolism of a large number of drugs as inducers, inhibitors or substrates. Drug transporters such as P-glycoprotein are important. Some inhibitors of P-gp such as erythromycin, ketoconazole and verapamil can induce elevation of plasma digoxin concentrations to the toxic state. Successful drug used molecular computational databases to find out the best molecules that bind to the desired target *via* elucidation of the dynamics, energetics, as well as interactions with enzymes, ion channels, nuclear receptors, G protein-coupled receptors, etc (Chen *et al.*, 2018; Ghannay *et al.*, 2020; Masoudi-Nejad *et al.*, 2013; Othman *et al.*, 2020).

Finding new secondary metabolites from medicinal plants to be used as active compounds in drugs is of great task for the development of novel pharmaceuticals. They can target proteins to modulate their activities. In this contest, *E. glaucophyllum* (L.) belonging to Geraniaceae family is a common herb in Sahara, where it is known by Arabic names as Ragma, Dahma, Murrar and Tamir. In this study, we used computational software's to predict the ADME profiles and target endpoints of the hydroalcoholic extracts of *E. glaucophyllum* flowers, for further drug discovery and development.

2. METHODS

Samples

The compounds of hydroalcoholic extracts of *E. glaucophyllum* flowers have been identified previously (Bakari *et al.*, 2018). The ligand smiles were recovered from drug bank and pubchem compound for the identification of target classes using Swiss ADME and Target Prediction.

In silico ADME profiles

The pharmacokinetics properties of the identified compounds were evaluated through Swiss ADME freely online server (http://www.swissadme.ch/) by entering chemical structure followed by SMILES. The SMILES for each compound were generated automatically through the structure file generator, available at Swiss ADME program. Different parameters have been screened such as Consensus Log Po/w, blood brain barrier (BBB), GI absorption, bioavailability score and Lipinski's rule of five. The radar and the Boiled-Egg graphs have been assessed (Kadri & Aouadi, 2020).

Target prediction

Molecular target predictions are important to find the phenotypical side effects or potential cross reactivity caused by the action of small biomolecules. Swiss Target Prediction website (https://www.swisstargetprediction.ch) is a web tool, on-line since 2014, that

aims to predict the most probable protein targets of small molecules based on the two and three dimensional measures matching with known ligands (Gfeller *et al.*, 2014; Keiser *et al.*, 2007). The analysis was conducted from May 2020 to July 2020.

3. RESULTS

In silico ADME prediction

Druglikeness studies were carried out and the results illustrated the potential of small/bioactive molecules to be selected as candidates for further evaluations using *in silico* computational tools. As shown (Table 1), about 77 % of the identified compounds from the hydroalcoholic extracts of *E. glaucophyllum* flowers satisfy Lipinski's rule of five, suggesting a good oral bioavailability given by the value 0.55-0.56. Regarding the predicted consensus Log $P_{o/w}$, all compounds were found to be highly lipophilic. Blood-brain barrier (BBB) is a membrane that governs the passage of substances from the blood into the central nervous system (CNS). Twelve out of the seventeen compounds showed high BBB permeability indicating good distribution across the blood-brain barrier. Among them, 88% of were predicted to be not absorbed from the gastrointestinal tract and therefore may be excreted. The majority of phytoconstituants displayed good skin penetration given by the skin penetration coefficients (log Kp) as indicator of the transport of compounds through mammalian epidermis.

The druglikeness can be estimated via bioavailability radar (Figure 1) follows the pink area that indicates the optimal range for each property (lipophilicity, size, polarity, solubility, saturation and flexibility). Figure 1 displayed the some compounds (not all) of the extract that fall at least with 5 parameters the pink area and to be considered drug-like. The Boiled egg model (Figure 2) of the respective compounds has been established in order to evaluate the passive gastrointestinal absorption (HIA) and brain penetration (BBB) as a function of the position of the molecules in the WLOGP-versus-TPSA referential. We can underline that some of them like 2, 3, 4, 12, 14 and 15 appear in the white ellipse demonstrating their ability to be passively absorbed by the gastrointestinal tract. Compound 12 with blue point indicate that it can be substrate of the P-gp, while the others with red point were found to be non-substrate of the P-gp.

Table 1 ADME properties of identified compounds predicted by SwissADME

Entry	Name	Consensus Log $P_{o/w}$	BBB	GI absorption	Log K_p (cm/s)	Bioavailability Score	Lipinski's rule of five
1	Quinic acid	-1.66	Low	No	-9.15	0.56	Yes
2	Gallic acid	0.21	High	No	-6.84	0.56	Yes
3	Protocatchuic acid	0.65	High	No	-6.42	0.56	Yes
4	Caffeic acid	0.93	High	No	-6.58	0.56	Yes
5	p-coumaric acid	1.26	High	Yes	-6.26	0.56	Yes
6	Trans frulic acid	1.36	High	Yes	-6.41	0.56	Yes
7	Rutin	-1.51	Low	No	-10.26	0.17	No
8	Hyperoside	-0.38	Low	No	-8.88	0.17	No
9	Naringin	-4.13	Low	No	-13.14	0.11	No
10	Quercetin	1.23	High	No	-7.05	0.55	Yes
11	Apegenin-7-o-glucoside	0.52	Low	No	-7.65	0.55	Yes
12	Naringenin	1.84	High	No	-6.17	0.55	Yes
13	4,5-di-O-caffeoyquinic	0.63	Low	No	-8.37	0.11	No
14	Luteolin	1.73	High	No	-6.25	0.55	Yes
15	Apegenin	2.11	High	No	-5.80	0.55	Yes
16	Cirsitineol	2.53	High	No	-5.99	0.55	Yes
17	Acacetin	2.52	High	No	-5.66	0.55	Yes

In silico target prediction

The top 15 results of the closely associated receptors based on Target, Common Name, The top 15 results of the closely associated receptors based on Target, Common Name, Uniprot ID, ChEMBL-ID, Target Class, Probability and Known actives in 2D/3D were given as a pie-chart (Figure 2). As shown, Gallic acid (2) predicts 20% of family AG protein coupled receptor and ligand-gated ion channel, 13.3% of transferase and unclassified protein, and 6.7% of enzymes, lyase, protease, family C G protein-coupled receptor

and oxidoreductase. The ligand Luteolin (14) predicts 33.3% of enzymes, 13.3% primary active transporter and protease and 6.7% of family AG protein coupled receptor, kinase, nuclear receptor, isomerase, oxidoreductase and hydrolase.

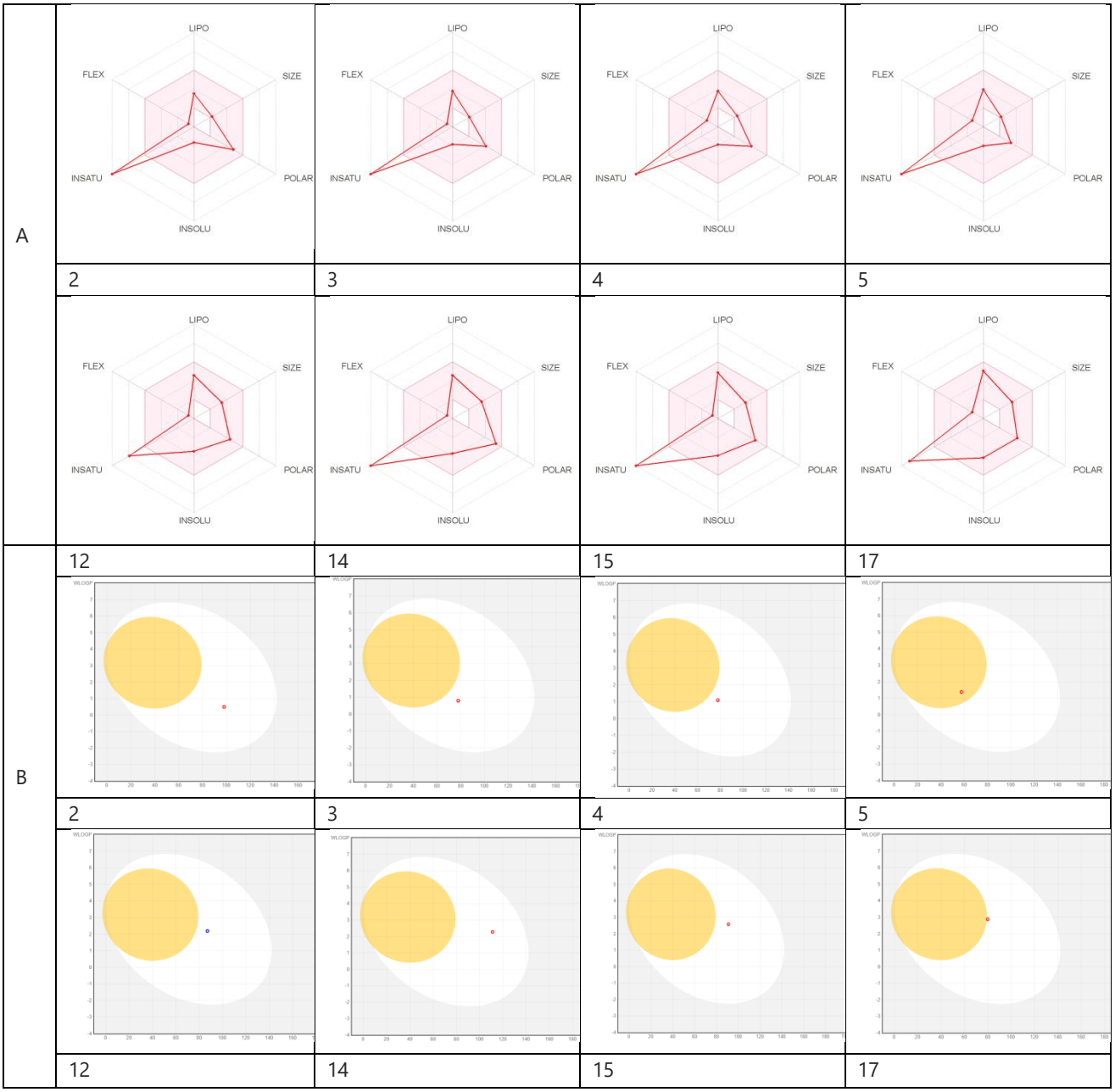
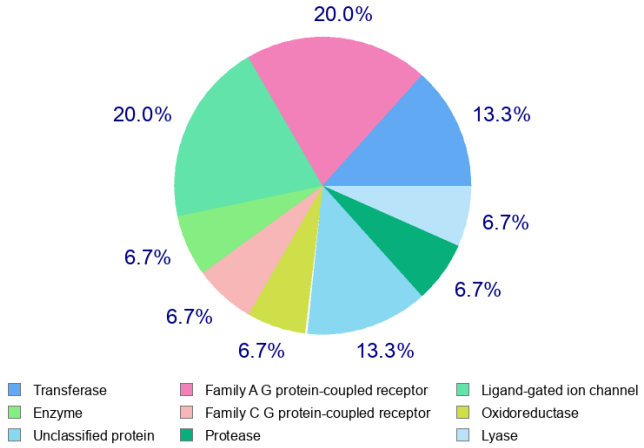


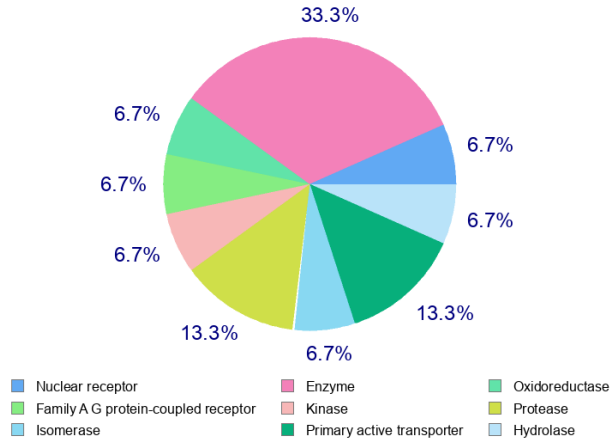
Figure 1 Bioavailability radar (A) and BOILED-Egg (B) model of compounds (1-5) using Swiss ADME predictor.

4. DISCUSSION

In this virtual screening study based on computational investigation *via* ADME and target prediction of identified compounds from the hydroalcoholic extracts of *E. glaucophyllum* flowers have been assessed. compounds found in the extract displayed seems to possess a number of hydrogen bond acceptors (O and N atoms) and number of hydrogen bond donors (NH and OH) less than 10 and 5, respectively which allowed them to be in compliance with the Lipinski's rule of five giving them the property to be orally active (Ghannay *et al.*, 2020). Most parameters such blood-brain barrier (BBB) permeation (to pass the BBB, the target may be related to nervous system), substrate or non-substrate of the permeability glycoprotein (P-gp), interaction of molecules with five major isoforms of the human cytochromes P450, passive human gastrointestinal absorption (GI) and skin penetration coefficient (for a drug that cannot be taken orally to be taken transdermally) can lead to pharmacokinetics-related drug-xenobiotics interactions.



Gallic acid



Luteolin

Figure 2 Top-15 of target predicted for Gallic acid and Luteolin from hydroalcoholic extracts of *Erodium glaucophyllum* flowers

The boiled egg graph based on information generated from Wlog P and Total Polar Surface Area (TPSA) suggesting well-absorbed molecules in space was given as an accurate predictive model to evaluate by computing data of both lipophilicity and polarity to characterize the absorbable effect in the gastrointestinal tract of extract and to get insights about absorption profile of novel molecules (Kwong, 2017).

5. CONCLUSION

This study aimed to use friendly *in silico* studies for freely ADME and target prediction of bioactive small molecules identified from the hydroalcoholic extracts of *E. glaucophyllum* flowers. Our results reflect that about 80% of the tested compounds exhibited suitable pharmacokinetic, drug-likeness and were strongly coupled with several enzymes and proteins. The obtained computational results may be completed with *in vivo* tests to improve the suitable bioactive molecules from this plant as the best drug with safety assessment.

Author Contributions

Dr. Fares Alshammari is the sole researcher contributing to this work.

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This study has not received any external funding.

Conflict of Interest

The authors declare that there are no conflicts of interests.

Data and materials Availability

All data associated with this study are present in the paper.

Peer-review

External peer-review was done through double-blind method.

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