IN SILICO ANALYSIS OF SELECTED COMPOUNDS USING PASS, SWISSADME AND MOLINSPIRATION

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ABSTRACT: The last few decades have seen many pandemic outbreaks of diseases like COVID-19 that need to be fought by a heuristic approach involving modern trends in the drug designing process. The discovery of novel drugs will help us to combat this apart from prevention by vaccination and safety precautions. Building a database of potential candidate drugs will help to develop a drug on a fast track. In this study, five phytochemical compounds (Lycorine, Luteolin, Emodin, Herbacetin and Isobavachalcone) were selected based on the earlier literature available. These compounds were subjected to PASS prediction and the bioactivities of these compounds were screened based on their Pa & Pi values (stimulating activity and inhibitory activity). ADMET studies were done using SwissADME software and the results were discussed. All five compounds were found to be satisfying Lipinski's rule of five. The Molecular properties analysis such as m Log P, nOHNH, nON, number of violations, and TPSA showed good results as predicted by Molinspiration software. This study brings out the importance of natural products and the use of combinatorial methods in the drug development process. Their physical properties, ADMET analysis and bioactive prediction revealed the importance of the selected compounds to be used to fight against many diseases.

KEYWORDS: SwissADME, PASS, Molinspiration, nOHNH, nON.

INTRODUCTION:

Natural products have been found to be the sources of active compounds with promising activity against microbes and other diseases. These compounds may serve as a starting point for the development of newer molecular entities with greater efficacy and affinity, and with fewer side effects (Newman and Cragg, 2020). Nowadays, computational techniques are being extensively used to investigate the inhibitory potential of phytocompounds against several microbes. Various studies have demonstrated the antiviral activities of various flavonoids including their use to cure respiratory diseases. In this study five compounds (Luteolin, Luteolin, Emodin, Herbacetin and Isobavachalcone) have been selected to analyze their bioactivity score, molecular and pharmacokinetic properties which were calculated by online computer software programs viz. PASS, SwissADME and Molinspiration. Among these, Lycorine is a bioactive phenanthridine alkaloid isolated from bulbs of *Lycoris radiata* (Family Amaryllidaceae). Lycorine has also shown suppressive activity on in vitro viral replication of flaviviruses. Luteolin, 3′, 4′, 5, 7-tetrahydroxyflavone, is a common flavonoid that exists in many types of plants including fruits, vegetables, and medicinal herbs. Plants rich in luteolin have been used in Chinese traditional medicine for treating various diseases such as hypertension, inflammatory disorders, and cancer (Lin *et al*, 2008). Emodin is an anthraquinone plant metabolite found in Traditional Chinese Medicine. Emodin (1,3,8-trihydroxy-6-methyl anthraquinone), the naturally occurring anthraquinone present in the root and bark of numerous plants of the genera *Rheum* and *Polygonum*. Herbacetin diglucoside can be isolated from flaxseed hulls. Isobavachalcone (IBC) is a prenylated chalcone of the flavonoid subclass isolated from *Psoralea corylifolia*, an annual herb used in traditional Chinese medicine. However, these compounds are to be tested in clinical trials to enrich the repository of candidate drugs against viral infections as well as adjuvant therapy.

Computational tools and novel algorithms have been implemented over the last few decades to accelerate and optimize the drug discovery process (Wouters *et al*., 2020). Several methods have been shown to reduce drug development costs up to 50%, such as chemoinformatics, quantitative-structure activity relation (QSAR), docking, molecular similarity, network pharmacology and pharmacogenomics computational *de novo* design, to mention a few examples (Ou-yang *et al*., 2021). Nowadays chemical libraries databases are available which contain information about structure and the properties of publicly disclosed chemical compounds, e.g., PubChem (Li *et al*., 2010 & Wang *et al*., 2014) and ChEMBL (Bento *et al*., 2014). To analyze the probable biological activity of the molecules, online tools like PASS are available. PASS (Prediction of Activity Spectra for Substances) software was assimilated from the biological activities of more than 2, 70,000 compound-ligand pairs (Mervin *et al*., 2015). The PASS development started more than 25 years ago (Poroikov *et al*., 1993 & Filimonov *et al*., 1995), and during this time its performance has continuously and significantly improved. PASS in its 2017 version predicts over 7,000 kinds of biological activity with an average accuracy of 94% based on the analysis of structure-activity relationships for more than 1 million known biologically active compounds.

The SwissADME web tool used here is freely accessible at http://www.swissadmise.ch and is meant for user-friendly submission and easy analysis of the results. Compared to the state-of-the-art of free web-based tools, SwissADME stands as an easy and effective tool that is integrated in the Swiss Drug Design workspace. It is one of the most recent and far-reaching sites run by the Swiss Institute for Bioinformatics (SIB) which encourages bioinformatics services and resources for scientists worldwide (Ndombera *et al*., 2019). It promotes the assessment of ADME parameters of drug candidates and molecules and provides information to determine Lipinski's rule of five (Lipinski *et al*., 2001) for drug likeness of oral bioavailability. In Molinspiration,

work was carried out to determine the Lipophilicity, TPSA index, nROTB and HBA/HBD count. Using Molinspiration (https://www.molinspiration.com), all pharmacokinetic parameters were performed to predict the bioactivity of compounds. Molinspiration, web-based software was used to obtain parameters such as MiLogP, TPSA, drug likeness scores. MiLogP is calculated by the methodology developed by Molinspiration as a sum of fragment based contributions and correction factors.

MATERIALS AND METHODS:

Five phytochemicals (Lycorine, Luteolin, Emodin, Herbacetin and Isobavachalcone) were selected based on their reported medicinal properties. The structures and the Physical properties of the phytochemicals were collected from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). The physical properties of the compound are presented in Table 1.

PASS (Prediction of activity spectra for substances) is an online server (http://www.way2drug.com/) that was to predict probable pharmacological effects of the compound based on their structural information. This tool is based on the comparative study of more than 300 pharmacological activities and the mechanism of action of different compounds. It gives the probability of activity (Pa) and inactivity (Pi) values of a particular compound under study (Lagunin *et al*., 2000). The compounds selected were subjected to ADMET analysis and PASS prediction studies.

The first step is to access the PubChem server (https://pubchem.ncbi.nlm.nih.gov/) to get canonical SMILE information (Kim *et al*., 2016). The second stage is to estimate their ADME (absorption, distribution, metabolism, and excretion) through SwissADME tool (http://www.swissadme.ch/) (Riyadi *et al*., 2020 & Riyadi *et al*., 2020).

SwissADME software (www.swissadme.ch) of Swiss Institute of Bioinformatics (http://www.sib.swiss) was accessed in a web server that displays the Submission page of SwissADME in Google was used to estimate individual ADME behaviors of the compounds from the plant. The input zone itself contains a molecular sketcher based on Chem Axons Marvin JS (http://www.chemaxon.com) that allows the user to draw and edit 2D chemical structures. The structures are transferred as a list to the right hand side of the submission page, which is the actual input for computation. On the other hand, the list is made using SMILES (simplified molecular input line entry system) and the results are presented for each molecule in tables, graphs and also an excel spreadsheet. The SwissADME output file comprises one panel per molecule for clear output and export, the panel comprises of all the information of the molecules (Egan *et al*., 2000)

The bioactivity scores analyses were carried out by using Molinspiration. It is a computational tool that helps to predict the pharmacokinetic properties of drug candidates. Bioactivity scores of the compounds against various receptor ligands, inhibitors and enzyme inhibitory activity were estimated using Molinspiration online toolkit.

In this computational chemistry technique, large chemical databases were analyzed in order to identify possible new drug candidates. In the Molinspiration tool, the MiScreen engine first analyzes a training set of active structures (in extreme cases even a single active molecule is sufficient to build a usable model) and compares it with inactive molecules by using sophisticated Bayesian statistics. Only SMILES or SDF file structures of active molecules are sufficient for the training, no information about the active site or binding mode is necessary.

The calculation of molecular properties like MiLog P, Total polar surface area (TPSA), number of hydrogen bond donors, and acceptors, molecular weight, number of atoms, number of rotatable bonds, etc., and bioactivity scores like GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors were done by Molinspiration.

Table 1: Properties of phytochemical compounds

S. no	Name of the compound	Pub chem. ID	Mol. Wt	Mol. Formula
1	Lycorin	614726	$C_{16}H_{17}NO_4$	287.31g/mol
2	Luteolin	5280445	$C_{15}H_{10}O_6$	286.24g/mol
3	Emodin	3220	$C_{15}H_{10}O_5$	270.24g/mol
4	Herbacetin	5280544	$C_{15}H_{10}O_7$	302.23g/mol
5	Isobavachalcone	5281255	$C_{20}H_{20}O_4$	324.4g/mol

RESULTS AND DISCUSSION:

The results obtained through the PASS online software are based on the computational method, with the ability to predict the activity and inactivity probabilities of more than 4000 molecules with their biological activity based on the structure (Lagunin *et al*., 2011 & Mishra *et al*., 2009). The results predicted from PASS gives us the pharmacological potential of the selected compounds. To analyze the results, a score is used to mention the confidence level of the activity. Higher probability of occurrence is mentioned with the value of ($Pa>0.7$) If the probability level is medium, then the value will be ($0.5<Pa<0.7$) and the unlikely probability of occurrence is mentioned as ($Pa<0.5$).

For Lycorine, PASS activity was predicted and the Antidyskinetic activity was found to be more as indicated with the Pa value of 0.813. Antidyskinetic property is the ability of (pharmacology) any drug that counters dyskinesia. MAP kinase stimulant activity was also high with the Pa value of 0.755. MAP kinase stimulants are involved in directing cellular responses to a diverse array of stimuli, such as mitogens, osmotic stress, heat shock and pro-inflammatory cytokines. Neurotransmitter uptake inhibitory activity also was more for this compound (Pa is 0.735). Neurotransmitter uptake inhibitor drugs are the drugs that inhibit the

transport of neurotransmitters into axon terminals or into storage vesicles within terminals. For the compound Luteolin, PASS predicted it as the chlordecone reductase inhibitor with a high Pa value of 0.978. Membrane integrity agonistic activity was also predicted by PASS with a Pa value of 0.965. Membrane integrity agonist is defined as the ability to keep the quality or state of the complete membrane in perfect condition. HIF1A expression inhibitory activity was predicted with a high Pa value of 0.964. HIF1A expression inhibitors are functioning as Topoisomerase 1 inhibitors, which include irinotecan, topotecan and camptothecin all of which have been approved for the treatment of various types of cancer.

The PASS software predicted Emodin with the CYP2C12 substrate as the highest activity (Pa is 0.932). CYP2C12 substrate affects drug metabolism influencing the therapeutic efficacy and safety of drugs. Aldehyde oxidase inhibitory activity was high in this compound with the Pa value of 0.905. Aldehyde oxidase inhibitor is a metabolizing enzyme, located in the cytosolic compartment of tissues in many organisms. AO catalyzes the oxidation of aldehydes into a carboxylic acid, and in addition, catalyzes the hydroxylation of some heterocycles. Histidine kinase inhibitory activity was another property of this compound showing a high value of Pa 0.902 and Pi is 0.002. Histidine kinase in *Escherichia coli* plays an essential role in sensing external environmental changes.

The phytochemical compound herbacetin, showed the kinase inhibitory activity with the highest value of Pa is 0.957. Kinase inhibitors are a large group of unique and potent antineoplastic agents which specifically target protein kinases that are altered in cancer cells and that account for some of their abnormal growth. Peroxidase inhibitory activity also was also predicted by PASS software for this compound (Pa is 0.953). Peroxidase inhibitors block the endogenous peroxidase activity. Another important activity of this compound as predicted by PASS was CYP1A inducing activity with the Pa value of 0.928. CYP1A inducers are highly inducible by PAHS and halogenated aromatic hydrocarbons via aryl hydrocarbon receptor – mediated gene transcription.

The compound Isobavachalcone, when subjected to PASS prediction, showed many biological activities including apoptosis agonistic activity with the highest value (Pa is 0,858). Apoptosis agonistic activity involves the process of programmed cell death. It is used during the early stages of development to eliminate unwanted cells. Skin whitening activity also was predicted as the activity of this compound (Pa is 0.813). Skin whitener in skin lightening or skin bleaching is a cosmetic procedure that aims to lighten dark areas of skin or achieve a generally Paler skin tone. Anti-ulcerative was another activity predicted with a high value for this compound (Pa is 0.814). Anti-ulceratives are the agents that prevent the formation or promote the healing of ulcers. The use of anti-ulceratives lead to a reduced need for surgical treatment of peptic ulcers.

The results obtained from *in silico* studies using SwissADME clearly indicated that the compounds could be druggable substances. MW1, log P, HBA, HBD and TPSA can be predicted using SwissADME. It was interesting to note that the results from the Swiss ADME predictor values of Log P, molar refractivity and the total polar surface area in there molecules were in excellent agreement with the most important rules of drug likeness. The results showed the physicochemical properties, Lipophilicity, Water solubility, Pharmacokinetics, Drug likeliness and Medicinal chemistry of the selected compounds. All the five compounds have zero violations of Lipinski's rule of five.

Several pharmaceutical companies in different countries conduct their research related to ADMET more efficiently through the introduction of combinatorial chemical technology, which allows the synthesis and screening of numerous compounds at the same time. (Montanari & Bolzani, 2001)

With the use of ADMET analysis it is easier to predict the action and behaviour of numerous bioactive compounds from plant that has a better screening process of substance with advanced research experiments, affordable cost and time consumption during drug development (Hansch *et al*., 2004 & Czodrouski *et al*., 2009). Lipinski *et al.* (1997) inferred that molecules that exhibit a lower number of hydrogen bond donor atoms (HBD), a higher number of H bond acceptor atoms (HBA), O and N have the most favourable ADMET profile. Liposolubility (Log P) is a property of great significance and it is used as an indicator of oral bioavailability of drug candidate molecules, also constituting one of the main parameters of ADMET (Hadda *et al*., 2013).

Computational modeling is often used to select new molecules for therapeutic purposes, based on the most relevant biological properties for pharmacological interaction. Molinspiration software provides bioactivity scores for the five compounds selected with respect to different cell receptors such as ionic channels, GPCR enzymes, proteases, kinases and nuclear receptors. (Balakrishnan & Kandakalta, 2015 & Proudfoot, 2002).

Table 2a and 2b represent the results of the selected compounds showing that all of them obeyed Lipinski's rule of five and showed good drug likeliness scores. Mi log P values were less than 5 for all the compounds with the highest for Isobavachalcone (4.81) and the lowest for Lycorine (1.28) which indicated their good permeability across the cell membrane. TPSA was found to be much less than the threshold value of 140 A^0 with the maximum value for Herbacetin and the minimum for Lycorine with 131.35A^0 and 62.16A^0 respectively. Number of atoms ranges from 20-24 and they are high in Isobavachalcone with 24 and low in Emodin with 20. Number of ON bonds was high for Herbacetin and low for Isobavachalcone. Number of OHNH bonds was maximum in Herbacetin and minimum in Lycorine. No compound showed violations.

The bioactivity of the selected compounds as predicted by Molinspiration is shown Table 2a & 2b

Table 2a: Molecular property of phytochemical compounds

S. No	Phytochemical compounds	MiLogP	TPSA	natoms	nON	nOHNH	nviolations	nrotb
1	Lycorin	1.28	62.16	21	5	2	0	0
2	Luteolin	1.97	111.12	21	6	4	0	1
3	Emodin	3.01	94.83	20	5	3	0	0

4	Herbacetin	1.91	131.35	22	7	5	0	1
5	Isobavachalcone	4.81	77.75	24	4	3	0	5

Table 2b: Bioactivity score of phytochemical compounds

N o	Phytochemical compounds	GPCR ligand	Ion Channel Modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Lycorine	0.29	0.11	-0.20	-0.06	0.12	0.33
2	Luteolin	-0.02	-0.07	0.20	0.39	-0.22	0.28
3	Emodin	-0.14	-0.14	0.07	0.17	-0.21	0.21
4	Herbacetin	-0.08	-0.17	0.30	0.34	-0.24	0.32
5	Isobavachalcone	0.15	0.06	-0.17	0.04	0.02	0.38

The bioactivity scores of the above compounds for drug targets were also predicted by Molinspiration and are presented in Table 2b. A molecule having bioactivity score more than 0.00 is presumed to exhibit significant biological activities, while values between -0.50 to 0.00 are expected to be moderately active and if score is less than -0.50 it is considered to be inactive.

The results in this study clearly revealed that the biological actions of the compounds analyzed might involve multiple mechanisms and could be attributed to the interactions with GPCR ligands, nuclear receptor ligands, inhibitory activity over protease and other enzymes. The bioactivity score of compounds indicates that some compounds like show high interaction and others have moderate interaction as evident from the table. The most promising compounds as per the bioactivity scores were identified to be Lycorine and Isobavachalcone which were showing positive score for at least four activities. (Table 2b).

MiLogP (octanol / water partition coefficient) is a sum of contributions based on fragments and correction factors, this method, considered robust, can treat practically all organic molecules and most organometallic molecules. The TPSA molecular polar surface is calculated based on the methodology published as the sum of fragmentary contributions (Remko, 2009). In the pharmacokinetic study made by Abraham (2003), hydrophobicity of the molecule is assessed by evaluating logP value because hydrophobicity plays a vital role in the distribution of the drug in the body after absorption. TPSA (Topological Polar Surface Area) is a very useful physicochemical parameter of a molecule that gives the information about polarity of compounds. Polar surface area is the sum of all polar atoms mainly oxygen and nitrogen including attached hydrogen.

SUMMARY & CONCLUSION:

In our study, five compounds were selected based on the earlier literature available. The compounds selected were Lycorine, Luteolin, Emodin, Herbacetin and Isobavachalcone. These compounds were subjected to PASS prediction and the bioactivities of these compounds were predicted and their Pa & Pi values were analyzed. Next the ADMET studies were done by using SwissADME software and the results were discussed. Here most of the compounds had good absorption properties, metabolic nature with a low active toxicity value. All five compounds satisfy Lipinski's rule of five. The result of the ADMET properties indicates that these compounds could be used as the lead compounds in drug development. The Molecular properties analysis such as Milog P, HBA, HBD, number of violations, nOHNH, n-ON and TPSA showed good results as predicted by Molinspiration. The bioactivity scores such as GPCR ligand, Ion channel modulation, kinase inhibitor, nuclear receptor ligand, protein inhibitor and Enzyme inhibitor value were predicted and tabulated. This study brings out the importance of natural products in the drug development process and their physical property, ADMET analysis and bioactive prediction revealed the importance of the selected compounds to be used to druggable compounds. Further docking studies need to be conducted in the future in order to reaffirm our findings.

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