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Virtual Screening of Molecular Properties and Bioactivity Score of compounds present in tephrosia purpurea plant

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ABSTRACT

Virtual Screening of Molecular Properties and Bioactivity Score of compounds isolated from tephrosia purpurea plant were carried out using molinspiration software. Fourteen compounds reported from tephrosia purpurea plant were taken for the prediction of molecular properties, drug likeness score on the basis of Lipinski's rule and bioactivity. The compounds Tephrosin, Rotenone, Diguelin, Purpurin, Pongaglabol, Pongamol, Semiglabrin, 5-methoxy isolonchocarpin and Quercetin fulfill Lipinski's rule and showed good drug likeness score. MiLog P values of these compounds were found to be below 5 that means these compounds showed good permeability across cell membrane. TPSA in the range of 20.228-131.351 (well below 160 Å2)and n violations =1 or <0 ,molecular mass <500 ,n rotb < 5 [10], No of hydrogen bond donors ≤ 5 (The sum of OHs and NHs),No of hydrogen bond acceptor ≤ 10 (The sum of Os and Ns) were observed for these compounds.This indicate that these compounds can easily bind to receptor and were taken further for the calculation of bioactivity score by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor and enzyme inhibitor.Compounds Tephrosin, and 5-methoxy isolonchocarpin showed good bioactivity score , on comparison with other compounds. On comparing the bioactivity score of the standard antioxidant compound BHT(butylated hydroxyl toluene), Tephrosin, Pongaglabol, Pongamol, Semiglabrin, 5-methoxy isolonchocarpin were found to be higher and hence these compounds may play a vital role as an antioxidant.

Keywords: Tephrosia Purpurea, Lipinski,s rule, MiLog P and BHT

INTRODUCTION

Tephrosia purpurea belong to the family Fabaceae[1] and it was found to possess various biological activity such as antioxidant, antiulcer, antimicrobial, antibacterial, antiviral, antiasthmatic ,hepatoprotective, antihyperglycemic, antihyperlipidemia, immunomodulatory, wound healing property, [2] and antiallergic activities. An infusion of the seeds can be given as a cooling medicine [3] .Tephrosia purpurea as anti-Helicobacter pylori agent in term of bacteriostatic and bactericidal activities efficacy at stomach acidic pH [4-6], likelihood of developing resistant

mutants and synergistic capacity with common antibiotic [7].They were found to be effective in treating various disorders like alcoholic liver cirrhosis, Viral hepatitis, Pre-cirrhotic conditions, Protein energy malnutrition, Radiation and chemotherapy induced liver spleen and kidneys damages, as an adjuvant with hepatotoxic drugs like antitubercular drugs ,Urinary tract anti-infective, antibacterial in acne vulgaris and acts as a blood purifier[8]. The roots were useful in, skin diseases, scrofula, elephantiasiss, dyspepsia, stomachalgia, flatulene, haemorrhoids, asthma, bronchitis, anaemia, hepatossplenomegaly, verminosis, strangury, dysmenorrhoea, chronic fever, boils, pimples, odontalegia & gingivitis antipyretic , anti-inflamatory[9], CNS depressant and analgesic activities[10] of different Extracts of Tephrosia Purpurea root were already reported by us [9,10].The roots were bitter and the decoction was used as a nematicide
for treatment against Toxocora canis larvae which cause a lung disease in Sri Lanka and also used for treating colic, chronic diarrhoea and as an antihelminthic[11]. In continuation of our work on DFT calculations and insilico drug activity Predictions for the bioactive constituent present in Tephrosia purpurea roots [12], Virtual Screening of Molecular Properties and Bioactivity Score of compounds present in tephrosia purpurea plant were carried out.

MATERIALS AND METHODS

Structures of all the fourteen compounds given as **fig.1-14** reported from tephrosia purpurea plant were taken from the literature[2] and their structures were drawn using online molinspiration software (www.molinspiration.com) for calculation of molecular properties (Log P, Total polar surface area, number of hydrogen bond donors and acceptors, molecular weight, number of atoms, number of rotatable bonds etc.) and prediction of bioactivity score for drug targets (GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors). The bioactivity score and drug likeness properties of the all the fourteen compounds were compared.

Fig1. Tephrosin

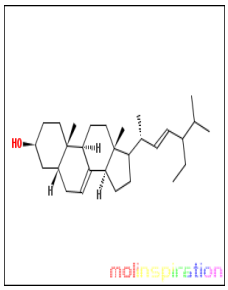


Fig2. Rotenone

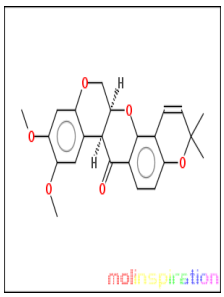


Fig3. Diguelin

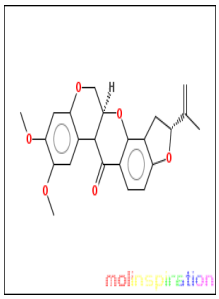


Fig4. Spinosterol

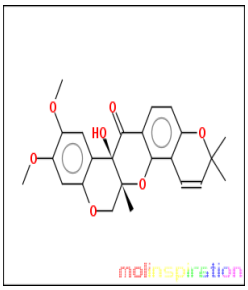


Fig5. Purpurin

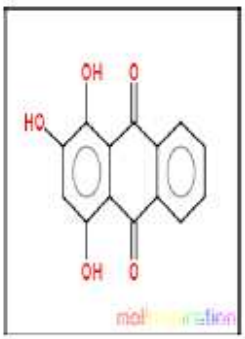


Fig6. Pongaglabol

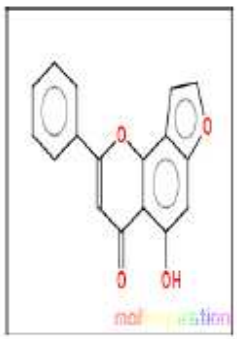


Fig7. Pongamol

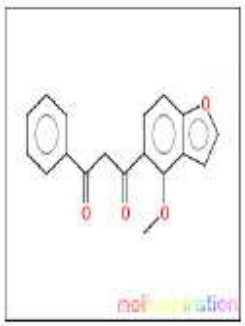


Fig8. β-sitosterol

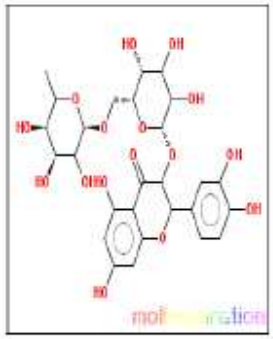


Fig9. Rutin

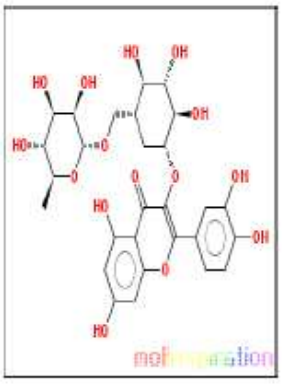


Fig10 Semiglabrin

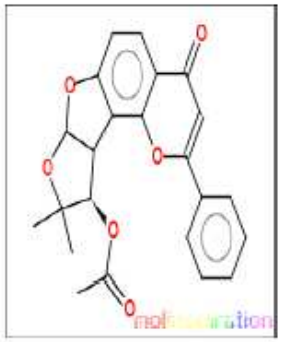


Fig11. 5-methoxy isolonchocarpin

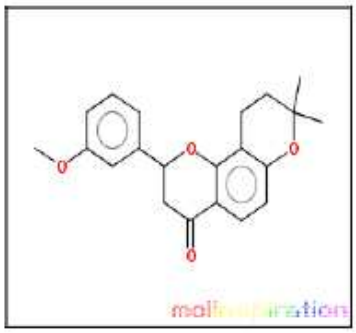


Fig12. . Quercetin

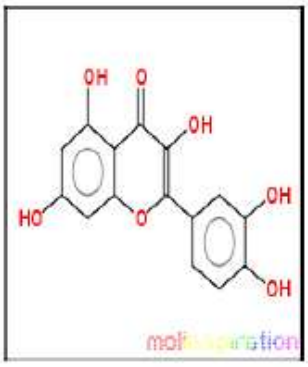


Fig13. Ursolic acid

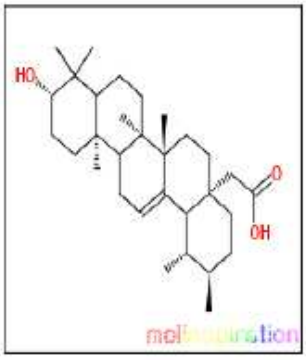
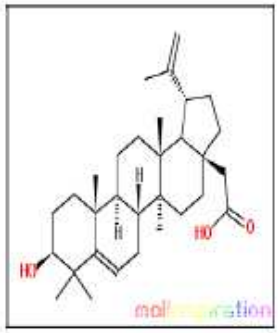


Fig14. Butelinic acid



Lipinski,s Rule [13,14]

Lipinski's rule of five also known as the Pfizer's rule of five or simply the Rule of five (RO5) is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997.

The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME")

Components of the Lipinski's rule:

Lipinski's rule states:

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular mass less than 500 daltons
- An octanal-water partition coefficient log P not greater than 5
- No more than one number of violation.

Molinspiration software

Molinspiration, web based software was used to obtain parameter such as MiLogP, TPSA, drug likeness. MiLogP, is calculated by the methodology developed by Molinspiration as a sum of fragment based contributions and correction factors [15,16].

MiLog P parameter is used to check good permeability across the cell membrane. Partition coefficient or Log P is an important parameter used in rational drug design to measure molecular hydrophobicity. Hydrophilic/lipophilic nature of drug molecule affects drug absorption, bioavailability, drug-receptor interactions, metabolism of molecules, as well as their toxicity.

Molecular Polar Surface Area TPSA is calculated based as a sum of fragment contributions of O- and N- centered polar fragments. Total polar surface area (TPSA) is closely related to the hydrogen bonding potential of a molecule [17]. and is a very good predictor of drug transport properties such as intestinal absorption, bioavailability, blood brain barrier penetration etc

Calculation of volume developed at Molinspiration is based on group contributors. Number of rotatable bonds measures molecular flexibility. It is a very good descriptor of absorption and bioavailbility of drugs. Through drug likeness datas of molecule, it can be checked molecular properties and structure feature in respect to known drugs.

Bioactivity score [15,16,18]

Bioactivity of the drug can be checked by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, enzyme inhibitor. All the parameters were checked with the help of software .Calculated drug likeness score of each compounds were compared with the specific activity of other compounds and the results were compared with standard drug.

For organic molecules the probability is if the bioactivity score is (>0) , then it is active, if (-5.0-0.0) then moderately active, if (< -5.0) then inactive. The drug likeness scores were calculated by considering MiLog P(partition coefficient), molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation, number of rotatable bonds and volume. The calculated value for the drug likeness score and the various parameters of the fourteen compounds reported from tephrosia purpurea plant were given in **Table 1**.

Bioactivity score of the compounds

The bioactivity scores of the the fourteen compounds reported from tephrosia purpurea plant like GPCR ligand, ion channel modulator, nuclear receptor legend , kinase inhibitor, protease inhibitor, enzyme inhibitor were given in **Table 2.**

Table1- Drug likeness score for compounds

S.N0	Compound	miLogP	TPSA	nAtoms	nON	nOHNH	nviolation	nrotb.	volume	MW
1	Tephrosin	3.455	83.469	31.0	7	1	0	2	371.386	424.449
2	Rotenone	3.585	63.241	29.0	6	0	0	3	348.335	394.423
3	Diguelin	3.583	63.241	29.0	6	0	0	2	347.455	394.423
4	Spinosterol	7.869	20.228	30.0	1	1	1	5	450.33	412.702

5	Purpurin	2.614	94.826	19.0	5	3	0	0	206.631	256.213
6	Pongaglabol	3.723	63.579	21.0	4	1	0	1	233.573	278.263
7	Pongamol	3.164	56.516	22.0	4	0	0	5	261.326	294.306
8	β-sitosterol	8.107	20.228	31.0	1	1	1	5	466.567	426.729
9	Rutin	-0.381	260.193	43.0	15	10	3	6	503.885	608.549
10	Semiglabrin	4.218	74.984	29.0	6	0	0	3	340.919	392.407
11	5-methoxy isolonchocarpin	4.544	44.773	25.0	4	0	0	2	313.126	338.403
12	Quercetin	1.683	131.351	22.0	7	5	0	1	240.084	302.238
13	Ursolic acid	7.059	57.527	34.0	3	2	1	2	488.291	470.738
14	Butelinic acid	7.129	57.527	34.0	3	2	1	3	482.634	468.722
15	BHT(butylated hydroxyl toluene) (Standard)	5.435	20.228	16	1	1	0	2	240.996	220.356

Table2-. Bioactivity score of the compounds.

S.No.	Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Tephrosin	0.13	-0.20	-0.13	0.36	0.04	0.34
2	Rotenone	-0.07	-0.37	-0.53	0.21	-0.41	0.28
3	Diguelin	-0.01	-0.30	-0.23	0.30	-0.12	0.31
4	Spinosterol	0.18	0.05	-0.30	0.68	0.06	0.53

5	Purpurin	-0.18	-0.13	0.10	0.06	-0.28	0.28
6	Pongaglabol	0.01	-0.03	0.28	0.26	-0.30	0.24
7	Pongamol	0.01	0.01	-0.30	-0.22	-0.29	-0.01
8	β-sitosterol	0.18	-0.18	-0.48	0.77	0.04	0.55
9	Rutin	0.02	-0.48	-0.08	-0.09	0.15	0.19
10	Semiglabrin	0.10	-0.19	0.00	0.22	-0.04	0.46
11	5-methoxy isolonchocarpin	0.24	-0.15	-0.38	0.55	0.17	0.23
12	Quercetin	-0.06	-0.19	0.28	0.36	-0.25	0.28
13	Ursolic acid	0.29	-0.01	-0.47	0.70	0.15	0.61
14	Butelinic acid	0.32	0.05	-0.40	0.70	0.07	0.55
15	BHT(butylated hydroxyl toluene) (Standard)	-0.34	0.00	-0.48	-0.08	-0.57	-0.07

>0- active, -5.0-0.0- moderately active , < -5.0- inactive.

RESULTS AND DISCUSSION

I .Drug likeness calculation on the basis of Lipinski rule of five

The drug likeness score was calculated by considering MiLog P(partition coefficient), molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation, number of rotatable bonds, volume. These properties were calculated and discussed on the basis of Lipinski's rule and its component.

a) MiLog P

The compounds Tephrosin, Rotenone, Diguelin, Purpurin, Pongaglabol, Pongamol, Semiglabrin, 5-methoxy isolonchocarpin and Quercetin among the 14 compounds obeyed the Lipinski's rule and showed good drug likeness score (Table1) . MiLog P values of these compounds were found below 5 that means these compounds showed good permeability across cell membrane.

b) TPSA.

Except the compound Rutin , all other compound were found to have TPSA in the range of 20.228-131.351 and was well below 160 Å2.

c) Molecular weight

Low molecular weight drug molecules (<500) are easily transported, diffuse and absorbed as compared to heavy molecules. Except the compound Rutin , molecular weight of all other compounds were found to be less than 500.

d) Hydrogen bond donors and acceptors

Hydrogen bond donors ≤ 5 (The sum of OHs and NHs), No. of hydrogen bond acceptor ≤ 10 (The sum of Os and Ns). All the compounds except the compound Rutin were found to have number of hydrogen bond donors≤ 5. Except the compound Rutin ,all other compound were found to have number of hydrogen bond acceptors <10 which were found to be within Lipinski's limit i.e. less than 10 and 5 respectively.

e) Rotatable bonds and n violations

Number of rotatable bonds is a simple topological parameter that measures molecular flexibility and is considered to be a good descriptor of oral bioavailability of drugs. Among all the screened compounds except the compounds Rutin and Pongamol were flexible (3 rotatable bonds) .

n violations =1 or <0 it means compound easily bind to receptor. All the compounds except Rutin were found to have n violations ≤1.

II. Bioactivity score of the compounds

The bioactivity scores of the fourteen compounds selected for the virtual screening on the basis of GPCR ligand, ion channel modulator, nuclear receptor legend , kinase inhibitor, protease inhibitor, enzyme inhibitor were given in Table -2 showed the following observations as per the rule. "For organic molecules the probability is if the bioactivity score is (>0) , then it is active, if (-5.0-0.0) then moderately active, if (< -5.0) then inactive".

a)GPCR ligand-

Calculation of druglikeness score towards GPCR ligands showed that Tephrosin, Pongaglabol, Pongamol, Semiglabrin, 5-methoxy isolonchocarpin were found to be highly bioactive (>0)and Rotenone, Diguelin, Purpurin and Quercetin were found to have moderate bioactivity(<0).

b)Ion channel modulator

Except Pongamol(.01), all other compound were found to be moderately bioactive(<0).

c)Kinase inhibitor

Purpurin, Pongaglabol, Semiglabrin and Quercetin were found to be active towards Kinase inhibitor(>0) than other compounds. Pongaglabol and Quercetin were found to have the highest value of 0.28 compared to others.

d)Nuclear receptor ligand

Tephrosin, Rotenone , Diguelin, Purpurin, Pongaglabol, Semiglabrin, 5-methoxy isolonchocarpin and Quercetin can act as a active Nuclear receptor ligand (the values range from 0.06-0.77) than other compounds.

e)Protease inhibitor

Tephrosin and 5-methoxy isolonchocarpin were found to be active Protease inhibitor (>0) ,whereas other compounds were found to be moderately active (<0) towards Protease.

f) Enzyme inhibitor

Except Pongamol(0.01), all other compound were found to be a active Enzyme inhibitor(0.06-0.61).

CONCLUSION

Among the 14 compounds selected from tephrosia purpurea plant for the prediction of the drug likeness score (MiLogP), showed that compounds Tephrosin, Rotenone, Diguelin, Purpurin, Pongaglabol, Pongamol, Semiglabrin, 5-methoxy isolonchocarpin and Quercetin were found to obeys the Lipinski's rule and showed good drug likeness score. (MiLog P below 5). Compared to the Standard BHT(butylated hydroxyl toluene), the above compounds were found to have good drug likeness score in the range1.683-4.544 which were lower than the Standard BHT(5.435).

The bioactivity scores of the above compounds indicated the following observations:

- Tephrosin, Pongaglabol, Pongamol, Semiglabrin, 5-methoxy isolonchocarpin were highly active (>0) than BHT(-0.34) towards GPCR ligands .
- Pongamol (0.01) was found to have similar Ion channel modulator as BHT(0.00).
- Kinase inhibitor activity of both Pongaglabol and Quercetin(0.28) were higher than BHT(-0.48).
- Tephrosin, Rotenone, Diguelin, Purpurin, Pongaglabol, Semiglabrin, 5-methoxy isolonchocarpin(0.55) and Quercetin were observed to be active Nuclear receptor ligands than BHT(-0.08)
- Protease inhibitor activity of Tephrosin(0.04) and 5-methoxy isolonchocarpin(0.17) were found to be higher than BHT(-0.57)
- Compared to BHT (-0.07),Tephrosin(0.34), Rotenone, Diguelin, Purpurin, Pongaglabol, Semiglabrin, 5-methoxy isolonchocarpin and Quercetin were found to be good Enzyme inhibitor .

On comparing the bioactivity score of the standard antioxidant compound BHT(butylated hydroxyl toluene), Tephrosin, Pongaglabol, Pongamol, Semiglabrin, 5-methoxy isolonchocarpin were found to be higher and hence these compounds may play a vital role as an antioxidant.

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