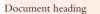Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Biomedicine

journal homepage:www.elsevier.com/locate/apjtb

Lead finding from *Phyllanthus debelis* with hepatoprotective potentials

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ARTICLE INFO

ABSTRACT

Objective: Present communication deals with the study of antihepatotoxic activity and molecular prediction of compounds isolated from *Phyllanthus debelis* in order to search lead compound. **Methods:** Five compounds from the whole plant of *P. debelis* were subjected to molecular properties prediction and drug–likeness by Lipinski rule of five & Molinspiration software. **Results:** All the compounds were found in compliance with Lipinski 'Rule of Five' except the Milog P valve of compound No. I–IV were found above five means these compounds have less permeability across the cell membrane. The Milog P valve of Compound No V & standard compound silibinin VI were found below five, suggest that the molecules have good permeability across the cell membrane. In respect of TPSA, all the compounds were within the limit i.e. 160 Å. The bioactivity score was also calculated for GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand. All the compound showed activity through enzyme inhibition. **Conclusions:** Our study shows that compound V debelolactone has good drug likeness score with no violations & good bioactivity score as compared to silibinin which is potent hepatoprotective drug. So compound V debelolactone can be a lead compound with hepatoprotective activity from *Phyllanthus debelis*.

1. Introduction

Phyllanthus debelis (Euphorbiacae) is distributed in India, Sri Lanka, Burma, Indonesia, Pacific Islands and the West Indies. It commonly grows as a weed in rice fields, moist lands and muddy flats amidst grasses and restricted to the coastal regions. It has been reported to possess immunomodulatory Activity [1] analgesic, anti–inflammatory Activities [2], antioxidant activity [3] and antihepatotoxic activity [4].

The literature survey has revealed that neither chemical investigation has been done nor any chemical compound has been isolated. We have isolated five compounds from whole plant of P. debelis, these compounds are isolated first time from this plant. Compound no V is a furanocoumarin which is a new compound. We have published a paper of the antihepatotoxic activity of compound V named debelolactone [5].

Our previous study showed that *Phyllanthus debelis* extract & compound V has significant antihepatotoxic activity against CCl4 induced toxicity on wistar rats [4, 5].

In continuation of our research all the compounds were further subjected to molecular properties prediction and drug–likeness by Molinspiration software.

2. Materials and Methods

2.1. *Lipinski's rule*

The rule was formulated by Christopher A Lipinski in 1997. The rule describe molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism and excretion (ADME). The rule is important for drug development where a pharmacologically active lead structure is optimized step–wise for increased activity and selectivity, as well as drug–like properties. The modification of the molecular structure often leads to drugs with higher molecular weight, more rings, more rotatable bond and a higher lipophilicity.

Physicochemical parameters play a vital role in generation and escalation of bioactivity of chemical entity. Molinspiration, web based software [6] was used to obtain parameter such as MiLogP, TPSA, drug likeness. MiLogP

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(octanol/water partition coefficient) is calculated by the methodology developed by Molinspiration as a sum of fragment based contributions and correction factors and used to predict the permeability of molecule across the cell membrane. The method is very robust and is able to process practically all organic and most organometallic molecules. Molecular Polar Surface Area TPSA is calculated based on the methodology published by Ertl et al. as a sum of fragment based contributions in which O– and N– centered polar fragments are to be considered and calculated by surface areas that are occupied by oxygen and nitrogen atoms and by hydrogen atoms attached to them [7]. TPSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco–2 permeability and blood brain barrier penetration. Thus, the TPSA is closely related to the hydrogen bonding potential of a compound. Method for calculation of molecular volume developed at Molinspiration is based on group contributions.

Number of Rotatable Bonds – nrotb is a simple topological parameter that measures molecular flexibility. It has been shown to be a very good descriptor of oral bioavailability of drugs [8]. Rotatable bond is defined as any single non–ring bond, bounded to nonterminal heavy (i.e., non–hydrogen) atom. Amide C–N bonds are not considered because of their high rotational energy barrier.

Druglikeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and presence of various pharmacophoric features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others.

Lipinski's rule of five states that, in general, an orally active drug has not more than 5 hydrogen bond donors (OH and NH groups), not more than 10 hydrogen bond acceptors (notably N and O), molecular weight under 500 g/mol, partition coefficient log P less than 5, number of violation less than 4 [9].

2.2. Bioactivity score

The drugs are also checked for the bioactivity by calculating the activity score for GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand. All the parameters were checked with the help of software Molinspiration drug–likeness score online (www.molinspiration.com). Calculated druglikeness score of each compounds and compared with the specific activity of each compound, and the results were compared with standard drug.

3. Result

Physico–chemical properties of compounds I–V are shown in Table 1. The druglikeness score was calculated by considering partition coefficient (log P), molar refractivity, molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation.

The druglikeness score and the calculated value of various parameters of the isolated compounds summarized in the Table 2.

The bioactivity scores were also compared with standard drug score and the bioactivity score for GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand for the isolated compounds tabulated in Table 3.

Table 1

Drug likeness score for compounds (I–VI)

S.N.	Compd.No.	miLogP	TPSA	NAtoms	MW	nON	nOHNH	n violation	Nrotb	volume
1	I	8.125	17.071	31.0	222.697	1	0	1	1	449.555
2	II	7.686	20.228	18	256.474	1	1	1	15	306.042
3	III	9.812	37.299	30.0	424.754	2	1	1	26	493.044
4	IV	7.152	99.38	41.0	576.859	6	4	2	9	588.638
5	V	1.152	102.412	23.0	314.249	7	1	0	1	244.452
6	VI (Std. Compound)	1.465	155.147	35.0	482.441	10	5	0	4	400.862

Table 2

Bioactivity score of the compounds (I–VI)

S.No.	Compound	GPCRligand	Ion channel ligand	Kinase inihibitor	Nuclear receptor ligand	Protease inihibitor	Enzyme inhibitor
1	I	0.20	0.02	−0.59	0.85	0.09	0.53
2	II	−0.10	0.03	−0.19	−0.06	−0.16	0.09
3	III	0.13	0.04	−0.08	0.19	0.15	0.13
4	IV	0.15	−0.21	−0.47	0.33	0.11	0.41
5	V	−0.30	−0.24	−0.49	0.04	−0.13	0.15
6	VI (Std. compound)	0.07	−0.05	0.01	0.16	0.02	0.23

Table 3

Physico–chemical Properties of Compounds I–VI

Compd. Code	Compound Name	m.p. (oC)	Mol. Formula/ Mol. Wt.	Solubility	IUPAC Name
I	Glochidon	160–161	C30H46O422	Chloroform	Lup–1(2), 20(29)–diene–3–one
II	Heptadecyl alcohol	56–58	C17H36O256	Chloroform	n–Heptadecanol
III	Montanic acid	75–77	C28H56O2424	Chloroform	n–Octacosanoic acid
IV	β–Sitosterol glucoside	250–252	C35H60O6576	Methanol	Stigmast–5(6)–ene–3–O–β–D–glucopyranoside
V	Debelolactone	260–263	C16H10O7314	Methanol	5–hydroxy–7–methoxy–furano coumarin–9(14)– cyclohex–12(13)–oxirano–11–one
VI	Standard compound (Silibinin)	247	C25H22O10482	Methanol	2,3–Dihydro–3–(4–hydroxy–3–methoxyphenyl)– 2–(hydroxymethyl)–6–(3′,5′,7′–trihydroxy–4′– oxobenzopyran–2′–yl)benzodioxin

4. Discussion

On close inspection of all the compounds were found in compliance with Lipinski 'Rule of Five' except the Milog P valve of compound No. I–IV were found above five means these compounds have less permeability across the cell membrane. The Milog P valve of Compound No V & standard compound silibinin VI were found below five, suggest that the molecules have good permeability across the cell membrane which in turn is needed for generation of bioactivity. Number of violations for compounds IV & standard compound silibinin VI were zero it means both compounds will easily bind to the receptor.

In respect of TPSA, all the compounds were within the limit i.e. 160 Å which implies that molecules are fulfilling the optimal requirement for drug absorption.

The bioactivity score was also calculated for GPCR ligand, ion channel modulator, kinase inhibitor, nuclear receptor ligand. For average organic molecules the probability is if the bioactivity score is more than 0.00 then it is active, if − 0.50 to 0.00 then moderately active, if less than − 0.50 then inactive.

On comparing the relative bioactivity scores of Silibinin VI with I–V compounds utilizing the above discussed four classes, all the compounds were showed expected similar bioactivity especially in case of enzyme inhibition.

Standard compound VI showed highest bioactivity score 0.23 through enzyme inhibition it means all the compound showed hepatoprotective activity through enzyme inhibition. In enzyme inhibition bioactivity score of compounds in decreasing order :

I> IV> V> III> II= 0.53> 0.41> 0.15> 0.13> 0.09

But as in Table 1 showed compound V showed good drug likeness score as compared to others.

5. Conclusion

On comparision of compounds 1–V with silibinin VI by molinspiration software, the V has fullfill Lipinski rule of five and showed good bioactivity score of 0.15 as silibinin showed 0.23 score. Our study shows that compound V debelolactone a has good bioactivity score as compared to silibinin which is potent hepatoprotective drug. So compound V debelolactone can be a lead compound with hepatoprotective activity from *Phyllanthus debelis*.

Conflict of Interest statement

We declare that we have no conflict of interest.

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