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Virtual screening of phytochemical compounds from *Physalis peruviana* as perspective anti-schistosomiasis

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Abstract

Schistosomiasis is a neglected tropical disease (NTD) causing by a *Schistosoma japonicum* parasite via *Oncomelania hupensis* snails. Even if the the number of cases decreases significantly, there is still drawbacks of conventional medication. *Physalis peruviana* is promising plant that rich phytochemicals as prospective drug candidiate of schistosomiasis. This study aimed to virtually screen the inhibitory activity of anti-schistososmiasis agents derived from *P. peruviana* body portion. Compound data were mined from PubChem and assessed their drug properties and target prediction using SwissADME and PASSOnline. Selected phytochemical compounds were screen the pharmacokinetics and toxicity by admetSAR webserver. 1,2-benzenedicarboxylic acid and docosane was final filtered compounds as promising anti-schistosomiasis target. Daily dose arrangement should be confirmed through in vitro and in vivo because of the hepatoxicity characteristics of the compounds. Protein kinases of helminth projected to be next protein target of alternative therapeutics for vital roles in organism. To be concluded, 1,2-benzenedicarboxylic acid and docosane is functioned as anti-schistosomiasis candidates with further validation in different analyses.

Keywords: *Physalis peruviana*, Schistosomiasis, Protein kinase, Anti-helminth, Anti-parasite

Introduction

Schistosomiasis is an acute and chronic helminthiasis disease and part of the neglected tropical disease (NTD)[1,2]. It reported 251.4 million people required preventive care with more than 75.3 million

receiving it in 2021[3]. In Indonesia, schistosomiasis cases have been declining year after year and there were four high-risk settlements in Celebes Island. This disease solely was caused by *Schistosoma japonicum* and transmitted to humans by intermediary snail, *Oncomelania hupensis* lindoensis[4,5].

Praziquintel (PZQ) is frequently used to treat therapeutic to cure schistosomiasis and other flatworm parasites[6]. However, many records about PZQ medication revealed inefficiencies[7,8]. So, alterative therapeutic should be developed to alleviate the load of global case. Natural product metabolites can be promising candidates for its antioxidant and anti-parasitic properties such as *Allium sativum* and *Nigella sativa*[9,10].

Physalis peruviana (Solanaceae) is indigenous plant from Andean region, South America, which morphologically semi-upright herbaceous shrub or perennial, producing a group branch of stems. This plant is also classified as the extensively distributed species from *Phyasalis* genera[11]. *Physalis* consists numerous species for ethnomidicinally use to treat a variety of diseases such as cancer, hepatitis, bacterial infection, and malaria[12]. However, *P. peruviana* application in Indonesia is primarily limited in fruit consuming[13]. Besides that, no studies have been recorded for antihelminth properties. Thus, the aim of this study was to virtually screen the inhibitory activity of anti-schistososmiasis agents derived from *P. peruviana* body portion.

Materials and Methods

Study Area

This study conducted using *P. peruviana* phytochemical constituents from the body sections were mined from online database[11,14]. Canonical SMILES of the compounds were carried out to determine the the drug properties; target prediction; and pharmacokinetics in open webservers. Selected phytochemicals would be visualized with software for next therapeutic proposing.

Procedures

Ligand Preparation

The compounds contained in body parts of P. peruviana were retrieved from the PubChem (https://pubchem.ncbi.nlm.nih.gov/). The information was taken from this database consisted of CID, 3D structure, and canonical SMILES[14].

Drug Properties Assessment and Target Prediction

Selected phytochemicals obtained from the PubChem were evaluated using SwissADME webserver (www.swissadme.ch/) to derive the medicinal parameters according to the Lipinski rules of five (LRo5). Filtered compounds would be reviewed by fulfilling molecular weight (MW, ≤500 Da), high lipopolicity (mLogP, ≤4.15), hydrogen bond donor (nOH, ≤5), and hydrogen bond acceptor (nNHOH, ≤10)[15]. Following that, PASS Online webserver (https://www.way2drug.com/passonline/) was utilized to identify the target prediction for antihelminthic, anti-inflammatory, and antiparasitic inhibition. Threshold of the assessment was set more than 0.3 for the prediction activity (Pa >0.3)[16].

Pharmacokinetics Screening and Visualization

Pharmacokinetics method is part of in silico approach for identifying the absorption, distribution, metabolism, excretion, and toxicity (ADMET). This method employed canonical SMILE submission in admetSAR 2.0 (http://lmmd.ecust.edu.cn/admetsar2/)[17]. Parameters of this screening consists human intestinal absorption (HIA), blood brain barrier permeability (BBB), P-glycoprotein inhibitor (P-gp), CYP4501A2 inhibitor (1A2), CYP450C19 inhibitor (C19), CYP4502C9 inhibitor (2C9), CYP4502D6 inhibitor (2D6), CYP4503A4 inhibitor (3A4), Caco-2 permeability (Caco-2), carcinogenicity, Ames mutagenicity, hepatotoxicity, acute oral toxicity (AOT), and human oral availability (HOA). Filtered

phytochemical compounds would be visualized throughout BIOVIA Discovery Studio software with specific coloration[15].

Results

Phytochemical Compounds in Body Parts of P. peruviana *Based on Database*

Based on the literature article, there were 9 bioactive constituents isolated from body of P. peruviana. Those compounds were assessed in PubChem to get the CID, 3D structure, and canonical SMILE. However, only 6 compounds left on the PubChem11 (Table 1).

Table 1. Phytochemical Compounds from Body Parts of *P. peruviana*.

Phytochemical Compounds	CID	Canonical SMILE
(S)-4-Iodo-1,2-epoxybutane	-	-
1,1,1,5,7,7,7-Heptamethyl-3,3 bis(trimethylsiloxy) tetrasiloxane	6329081	C[Si](O[Si](C)(C)C)O[Si](O[Si](C)(C)C)(O[Si](C)(C)C)O[Si](C)(C)C
1,2,3-Tri(t-butyl) cyclopropenylium tribromide	-	-
1,2-Benzenedicarboxylic acid	1017	C1=CC=C(C(=C1)C(=O)O)C(=O)O
3,3-Dimethyl-hexane	11233	CCCC(C)(C)CC
3,3-Dimethyl-octane	138117	CCCCCC(C)(C)CC
Diethyl ester	6781	CCOC(=O)C1=CC=CC=C1C(=O)OCC
Docosane	12405	CCCCCCCCCCCCCCCCCCCCCC
Eicosamethyl cyclodecasiloxane	-	-

Drug Properties Assessment and Target Prediction

During this screening, all compounds matched with LRo5. Furthermore, only 2 phytoconstituents were excluded the target prediction for three prospective inhibitory activities including 1,2 – benzenedicarboxylic acid and docosane (Table 2).

Table 2. Drug Properties Assessment and Target Prediction.

Phytochemical Compounds	MW	nOH	nNHOH	mLogP	Anti-helminthic	Anti-inflammatory	Anti-parasitic
1,1,1,5,7,7,7-Heptamethyl-3,3 bis(trimethylsiloxy) tetrasiloxane	443.96	5	0	0.20	-	-	-
1,2-Benzenedicarboxylic acid	166.13	4	2	1.20	0.310	0.496	0.368
3,3-Dimethyl-hexane	114.23	0	0	4.20	0.233	0.430	0.226
3,3-Dimethyl-octane	142.28	0	0	4.82	0.239	0.449	0.235
Diethyl ester	222.24	4	0	2.39	0.297	0.475	0.388
Docosane	310.60	0	0	7.82	0.412	0.424	0.427

Pharmacokinetics Screening and Visualization

After filtering in previous steps, we identified 2 phytochemical compounds that fulfilled the target prediction and drug-likeness analyses. Those ligands would be tested virtually to determine the pharmacokinetics and toxicity (Table 3).

Table 3. Pharmacokinetics Screening of Selected Compounds

Parameters	1,2-Benzenedicarboxylic acid	Docosane
HIA	0.9041 (+)	0.9917 (+)
BBB	0.5750 (+)	1.0000 (+)
P-gp	0.9849 (-)	0.8690 (-)
1A2	0.9621 (-)	0.6175 (-)
C19	0.9753 (-)	0.9540 (-)
2C9	0.9808 (-)	0.9349 (-)
2D6	0.8854 (-)	0.7215 (-)
3A4	0.9066 (-)	0.7947 (-)
Caco-2	0.6084 (+)	0.8902 (+)
Carcinogenicty	0.5753 (-)	0.5900 (-)
Ames Mutagenicity	0.9900 (-)	1.0000 (-)
Hepatotoxicity	0.8000 (+)	0.8836 (+)
AOT	0.7284 (IV)	0.6143 (III)
HOA	0.9000 (+)	0.5286 (+)

Discussion

Virtual screening demonstrated 1,2-benzenedicarboxylic acid and docosane as anti-schistosomiasis drug candidate after many filters applied including for absorption (HIA, P-gp; Caco-2); distribution (BBB); metabolism (CYP4501A2, -C19, -2C9, and -3A4); and toxicity (carcinogenicity, Ames mutagenicity, hepatotoxicity, AOT, and HOA). 1,2-Benzenedicarboxylic acid also known as phtalic acid is one of the aromatic dicarboxylic acid[18]. This compound has been detected in the organic extracts of certain plant species and can be synthesized by all plant organs including *P. peruviana*[19]. The primary biological activity of this constituent refers to be allelopathic or phytotoxic agent by releasing into the environment[20,21]. On the other hand, antimicrobial and insecticidal activities have been noticed from many derivatives of phtalic acid[19,22–24]. However, no reports record about specific antihelminth activities specifically to combat *Schistosoma sp*.

According to several articles, docosane is a straight-chain alkane with 22 carbon atoms that serves as plant metabolite. In P. peruviana, docosane was discovered in all parts of plants and extracted by GC-MS analysis[19,25]. However, there is no specific role of docosane due to the various constituents under its terminology. Numerous activities such as antimicrobial, anticancer, and wound healing exist in most of plants with docosane for ethnotherapeutic usage in Ayurvedic traditional medicine[26].

Both 1,2-benzenedicarboxylic acid and docosane predicted positive in hepatotoxicity, therefore daily drug consumption should be monitored to prevent liver damage. 1,2- benzenedicarboxylic acid predicted to be in class IV (slightly toxic) yet docosane is be in class III (moderately toxic). Thus, LD50 should be implemented based on the toxicity class, ranging 500-5,000 and 50-500 mg/kg, respectively[27]. After predicting ADMET parameters, the validation should be continued with in vivo and in vitro analyses (Table 4, Figure 1).

Schistosoma has two distinctive reproductive cycles which is asexual in snails (*Oncomelania sp*. for *S. japonicum*) and sexual in mammals. Cercaria is the late stage of asexual reproduction in intermediate hosts after which they migrate to freshwater and infect mammals including the humans.

They mate, produce eggs, and release through feces or urine, and the cycle repeats[28]. Various therapeutics and vaccines have been repurposed to combat the burden of this disease. However, specific molecular engineering is still under investigation[28–30]. Target protein is current alternative proposing in some recent years. *S. japonicum* was projected to phosphate kinase (PK) that responsible in mostly in growth and development beside in homeostasis, signaling pathway, and survival for inhibitory actions[31]. Furthermore, those proteins could be assessed as a potential target of 1,2-benzenedicarboxylic acid and docosane.

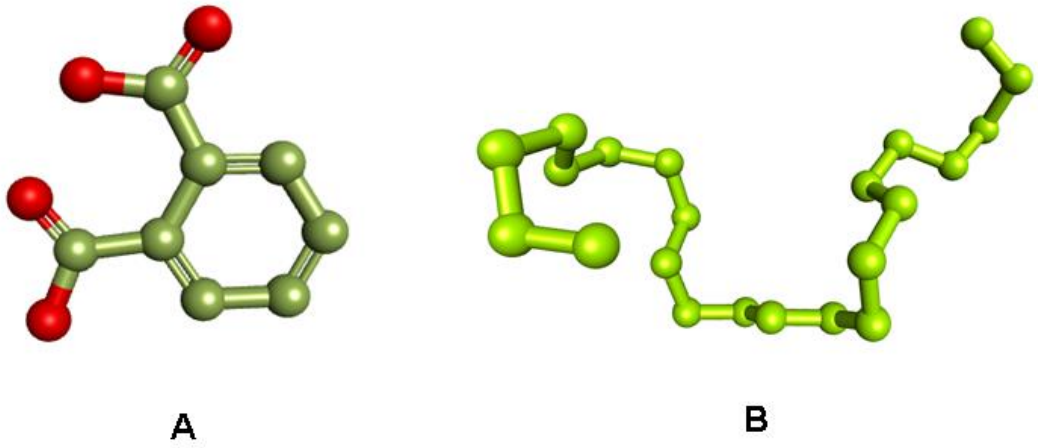

Figure 3. Selected promising anti-schistosomiasis compounds from P. peruviana body portions: A) 1,2-benzenedicarboxylic acid and B) docosane compounds.

Conclusions

1,2-benzenedicarboxylic acid and docosane from *P. peruviana* demonstrated promising potential as anti-schistomiasis agents due to their results by virtually screening. This outcome needs further experiments by *in vitro* and *in vivo* analyses to determine the daily dosage of consumption due to the hepatotoxicity effects.

Acknowledgments

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Conflicts of Interest

There are not potential conflicts of interest.

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