WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 6.805
Volume 5, Issue 7, 1751-1760. Research Article ISSN 2277– 7105

IN SILICO PASS PREDICTION, MOLECULAR DOCKING AND ADME/T PROPERTY ANALYSIS OF ISOLATED COMPOUNDS FROM *TINOSPORA CORDIFOLIA* FOR NEW THROMBOLYTIC DRUG DISCOVERY.

Joy Chakraborty[1], Mohammad Shah Hafez Kabir[2], Hilton Banik[1], Sabuj Majumder[1], Mohammed Abu Sayem[1], Tazrin Karim[1], Nazma Akhter[3], Tanvir Ahmad Chowdhury[2,4], Abul Hasanat[2,4] and Kazi Ashfak Ahmed Chowdhury[2]*

[1]Department of Pharmacy, BGC Trust University Bangladesh, Chittagong-4000, Bangladesh.

[2]Department of Pharmacy, International Islamic University Chittagong, Chittagong-4203, Bangladesh.

[3]Department of Pharmacy, Southeast University, Dhaka, Bangladesh.

[4]Department of Pharmacy, State University of Bangladesh (SUB), Dhaka- 1205, Bangladesh.

Article Received on
18 May 2016,
Revised on 08 June 2016,
Accepted on 28 June 2016
DOI: 10.20959/wjpr20167-6632

***Corresponding Author**
Dr. Kazi Ashfak Ahmed Chowdhury
Department of Pharmacy, International Islamic University Chittagong, Chittagong-4203, Bangladesh.

ABSTRACT

The aim of the study to find the mechanism of action of the isolated compounds from *Tinospora cordifolia* was explored the thrombolytic activity by molecular docking analysis used for five phytoconstituents to be specific syringin, tinocordiside, n-methyl-2-pyrrolidine, tinoporaside, heptacosanol, octacosanol isolated from *T. cordifolia*. To distinguish whether these phytoconstituents connect with the capable protein (tissue-type plasminogen activator). Furthermore ADME/T properties of the phytoconstituents were dissected utilizing Qikprop 3.2 module. In the PASS expectation for their thrombolytic mobility of the disengaged phytoconstituents, we discovered extensive variety of action. An extensive variety of docking score found amid sub-molecular docking by CPI server. syringin, tinocordiside, n-methyl-2-pyrrolidine, tinoporaside, heptacosanol, octacosanol demonstrated the docking score - 6.5, - 8, - 4.1, - 7.9, - 5.2, - 5.5. Both *in silico* models showed different value for the two compounds. Because syringin and tinocordiside displayed the high value in both in silico model. All the data support thatsyringin and tinocordisideis the best compounds for thrombosis management, as syringin possessed higher value in PASS prediction and

tinocordiside possessed higher value in Molecular docking. It cleared that most of the studied compounds might safe for human. Further *in vivo* investigation need to identify whether syringin and tinocordiside and other compounds have thrombolytic effects or not.

KEYWORDS: *Tinospora cordifolia*, PASS prediction, Molecular docking, ADME/T properties, syringing, tinocordiside.

INTRODUCTION

In the field of medicine, biotechnology and pharmacology drug discovery is the process by which new medication are discover. In the ancient, drugs are discovered through the traditional remedies. This drugs medicine were derived from plant and supplemented by animal material and minerals. Such drugs were most of this wrong experimentation and observation of human and animal body reaction. In middle age, drug are discovered and modified by chemical molecules, plant extract and natural product.[1]

Tinospora cordifolia is an evergreen tree which has a place with the family Menispermaceae generally known, as "Amrita" or "Guduchi" is an imperative medication and utilized as a part of meds since times immemorial. The medication is utilized as a part of fevers, diabetes, dyspepsia, jaundice, urinary issues, skin infections and endless looseness of the bowels and dysentery1. It has been likewise shown valuable in the treatment of heart ailments, uncleanliness, helmenthiasis and rheumatoid arthritis.[2][3][4][5] The starch got from the stem known as "Guduchi-satva" is exceedingly nutritive and digestive and utilized as a part of numerous ailments. Amid most recent two decades, the medication has been subjected to broad phytochemical, pharmacological and clinical examinations and numerous fascinating discoveries in the regions of immunomodulation, anticancer movement, liver issue and hypoglycaemic are accounted for.

Thromboembolic diseases are serious and life threatening. Regardless of the accessibility of antithrombotic medications for the avoidance and treatment of blood vessel and venous thrombosis, thrombotic maladies keep on being a noteworthy reason for death and handicap around the world. Therefore, there remains a need for more effective therapies to combat these disorders.[6]

In the recent years, there has been a developing enthusiasm for utilizing therapeutic characteristic items as a part of the counteractive action and treatment of numerous

sicknesses, including cardiovascular disorders. Day-by-day the connection, idea and techniques for the employments of normal items in treatment of human have experienced exceptional changes. Such changes happened because of the way that characteristic pharmaceutical or conventional medication made a progressive return with reestablished quality and life to assume a more huge part in the administration of human wellbeing. Critical endeavors have been concentrating towards the revelation and improvement of regular items from different plant and creature sources which have antiplatelet[7], anticoagulant, antithrombotic[8] and thrombolytic activity. Epidemiologic studies have provided evidence that foods with experimentally proved antithrombotic effect could reduce risk of thrombosis. Some plants or plant parts showing thrombolytic activity have also been reported.[9]

The aim of the study to find the mechanism of action of the isolated compounds from *T. Cordifolia* was explored the thrombolytic impact, which was finished by utilizing two as a part of *in silico* instruments PASS prediction and Molecular docking. Furthermore ADME/T properties of the phytoconstituents were examined utilizing Qikprop 3.2 module.

MATERIALS AND METHODS

In silico Prediction of activity spectra for substances (PASS)

Prediction of phytoconstituents namely syringing, tinocordiside, n-methyl-2-pyrrolidine, tinoporaside, heptacosanol, octacosanol isolated form *Tinospora cordifolia*[10,11] for thrombolytic activity was done with the help of computer program, PASS (Prediction of activity spectra for substances). Software estimates predicted activity spectrum of a compound as probable activity (P_a) and probable inactivity (P_i). The prediction of activity is based on structure-activity relationship analysis of the training set containing more than 205,000 compounds exhibiting more than 3750 kinds of biological activities. The values of P_a and P_i vary between 0.000 and 1.000. Only activities with $P_a > P_i$ are considered as possible for a particular compound. If $P_a > 0.7$, the probability of experimental pharmacological action is high and if $0.5 < P_a < 0.7$, probability of experimental pharmacological action is less. If the value of $P_a < 0.5$, the chance of finding the activity experimentally is less, but it may indicate a chance of finding a new compound.[12-15]

In silico Molecular docking

All the structures of phytoconstituents need to upload in mol2 format with charges and hydrogens added. When a molecule submitted, The CPI server checks the format suitability and calculates the interaction profile of this drug towards all the targets in the database using

DOCK6.[16, 17] Users can view the real-time progress online, and the page showing the current docking status of the uploaded drug will also be provided for bookmarking. It takes between 6 and 20 h to finish a one-molecule task and an email will be sent on completion. The outputs comprise the two following major elements:

(i) Library drugs which share similar (or opposite) interaction profile with the user's molecule, ranked by the similarity (or disparity) with known indications and ADR information, suggesting the underlying new indication and ADR of the user's molecule.

(ii) The candidate off-targets that tend to interact with the user's molecule. The server will visualize the drug-protein interactions, with amino acid residues around $6A^{o}$ of the molecule highlighted.

ADME/T property analysis

Ligand based ADME/Toxicity prediction

The QikProp module of Schrodinger (Maestro, version 10.1) is a quick, accurate, easy-to-use absorption, distribution, metabolism and excretion (ADME) prediction program design to produce certain descriptors related to ADME. It predicts both physicochemical significant descriptors and pharmacokinetically relevant properties. ADME properties determine drug-like activity of ligand molecules based on Lipinski's rule of five. ADME/T properties of the compound (DIM) was analyzed using Qikprop 3.2 module.[18]

RESULTS

***In silico* PASS prediction**

Six constituents namely syringin, tinocordiside, n-methyl-2-pyrrolidine, tinoporaside, heptacosanol, octacosanol were analyzed by the PASS for their thrombolytic activity and results were used in a flexible manner. All the compounds showed greater Pa than Pi (Table-1). Syrigenin showed highest Pa for thrombolytic activity (Pa=0.681). All the result showed in Table 1.

Table 1: PASS prediction of Syrigenin, Tinocordiside, N-methyl-2-pyrrolidine, Tinoporaside, 1- Heptacosanol, 1- octacosanol for Thrombolytic activity

Phytocompounds	PASS prediction for thrombolytic activity	
	Pa	Pi
Syrigenin	0.681	0.009
Tinocordiside	0.620	0.009
N-methyl-2-pyrrolidine	0.350	0.074
Tinoporaside	0.190	0.087
1- Heptacosanol	0.238	0.033
1- octacosanol	0.238	0.033

***In silico* Molecular docking**

In the present study, molecular docking performed to identify the docking score of Syrigenin, Tinocordiside, N-methyl-2-pyrrolidine, Tinoporaside, 1- Heptacosanol, 1- octacosanol towards tissue-type plasminogen activator (PDB code 1A5H), which is a protein involved in the breakdown of blood clots. A wide range of docking score found during molecular docking by CPI server. Syrigenin, Tinocordiside, N-methyl-2-pyrrolidine, Tinoporaside, 1-Heptacosanol, 1- octacosanol showed the docking score -6.5, -8, -4.1, -7.9, -5.2, -5.5 respectively. All the results presented in Table 2 and Figure 1.

Table-2: Docking results with Syringin, Tinocordiside, N-methyl-2-pyrrolidine, Tinosporaside, 1- Heptacosanol, 1- octacosanolin the tissue-type plasminogen activator

Drug name	Docking score
Syrigenin	-6.5
Tinocordiside	-8.0
N-methyl-2-pyrrolidine	-4.1
Tinoporaside	-7.9
1- Heptacosanol	-5.2
1- octacosanol	-5.5

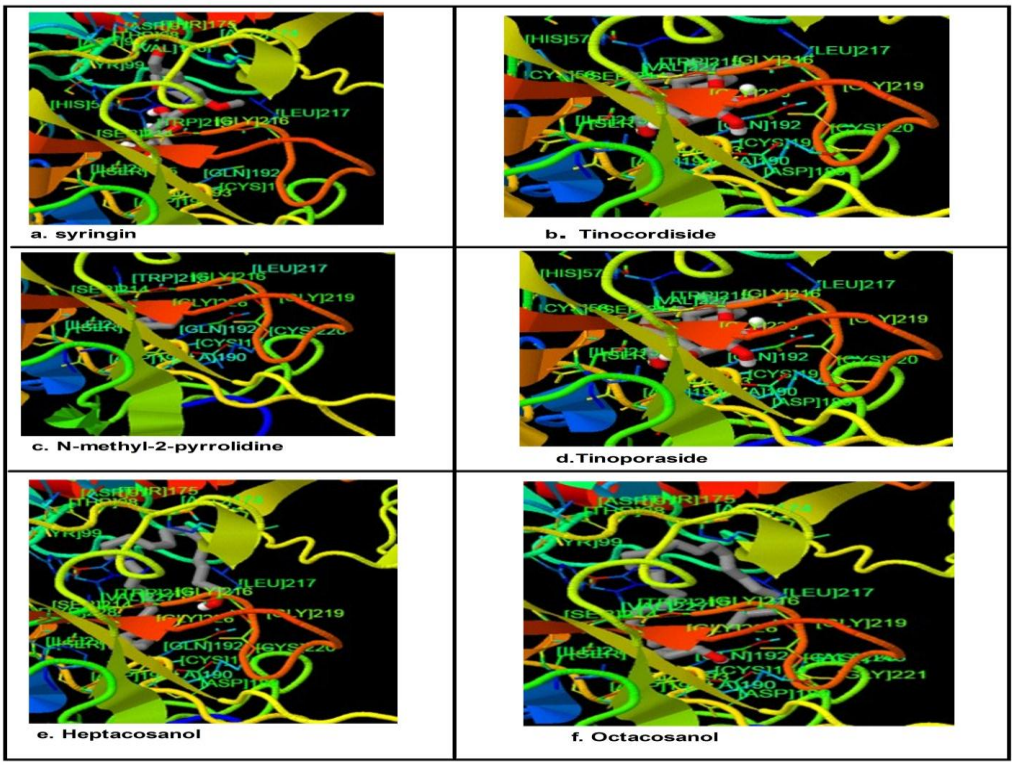


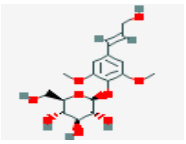
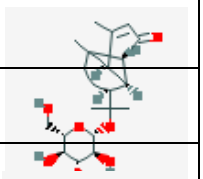
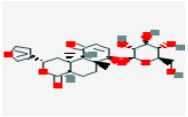
Figure 1: Molecular docking analysis of Syringin, Tinocordiside, N-methyl-2-pyrrolidine, Tinosporaside, 1- Heptacosanol, 1- octacosanolin the tissue-type plasminogen activator complex obtained from docking.

ADME and Toxicity analysis

Ligand based ADME/Toxicity prediction

The drug-like activity of the ligand molecule was categorized using ADME properties by Qik Prop module of Schrodinger. The ADME properties of the Syrigenin, Tinocordiside, N-methyl-2-pyrrolidine, Tinoporaside, 1- Heptacosanol, 1- octacosanol were evaluated with QikProp module of Schrodinger, shown in Table 3. The selected properties are known to influence metabolism, cell permeation, and bioavailability. All the predicted properties of the isolated compounds were in the range for satisfying the Lipinski's rule of five to be considered as drug like potential, except Tinosporaside for molecular weight and 1-Heptacosanol & 1- octacosanol for LogP, where they showed unsatisfactory value.

Table 3: ADME/T Properties of Syrigenin, Tinocordiside, N-methyl-2-pyrrolidine, Tinoporaside, 1-Heptacosanol, 1-Octacosanol by Lipinski rules of five.

Name of molecules	MW[α]	HB donor[β]	HB accepter[ϵ]	Log P[¥]	MOLAR REFRACTIVITY[µ]	Pubchem ID	Structure
Syringin	394	2	9	4.83	111.02	5316860	
Tinocordiside	440	4	7	1.24	100.34	102504931	
N-methyl-2-pyrrolidine	97	0	1	0.04	29.69	13387	
Tinosporaside	522	1	10	0.41	119.63	14194109	
1- Heptacosanol	370	1	1	5.75	102.46	74822	
1- octacosanol	384	1	1	6.08	107.82	68406	

[α]Molecular weight (acceptable range: <500).

[β]Hydrogen bond donor (acceptable range: ≤5).

[€]Hydrogen bond acceptor (acceptable range: ≤10).

[¥]High lipophilicity (expressed as LogP, acceptable range: <5).

[μ]Molar refractivity should be between 40-130.

DISCUSSIONS

In order to accelerate the research for potent natural products, computer-aided drug discovery program PASS was used to predict the biological activity. PASS prediction tools were constructed using 20000 principal compounds[19] and about 4000kinds of biological activity on the basis of structural formula with mean accuracy about 90%.[20] The result of anticipation is presented as the account of activities with adapted Pa and Pi ratio. Eight phytoconstituents namely of syrigenin, Tinocordiside, N-methyl-2-pyrrolidine, Tinoporaside, 1-Heptacosanol, 1-Octacosanol were analyzed by the PASS prediction for their thrombolytic action and begin advanced ambit of activity. Syringin, Tinocordiside was the best compound for thrombolytic effect from all the compounds. Though syringin has had bigger Pa value (0.681). According to Pa value, the compounds showed thrombolytic effect as following, syringin > tinocordiside > N-methyl-2-pyrrolidine > 1-heptacosanol and 1-octacosanol >Tinoporaside. In molecular docking study, syringin, tinocordiside, N-methyl-2-pyrrolidine, Tinoporaside, 1-heptacosanol, 1-octacosanol showed the docking score- 6.5, - 8.0, - 4.1, - 7.9, - 5.2, - 5.5, respectively, towards tissue-type plasminogen activator. From all these phytocompounds tinocordiside exhibited best docking score (-8.0). In our study, we also tried to explore out the ADME and toxicity profiles all of six compounds, syringin, tinocordiside, N-methyl-2-pyrrolidine, Tinoporaside, 1-heptacosanol, 1-octacosanol. As described in Table 3, the ADME profile of all the compounds had wide range, but all were within the acceptable range, except tinosporaside which for molecular weight and 1-heptacosanol, 1-octacosanol for LogP, where they showed unsatisfying value. From the ADME profiles of syringin and tinocordiside it cleared that they might be safe for human.

CONCLUSION

From the study it was found that, *T. cordifolia* could be abundant antecedent of latest thrombolytic drugs. Both *in silico* models showed different value for the two compounds, because syringin, tinocordiside showed high value in both *in silico* models. All the data support that syringin and tinocordiside are best compound for thrombolytic drugs. As syringin possessed high value in PASS prediction and tinoporaside possessed high value in

docking score. So, syringin and tinocordiside may be competitive candidate for promising thrombolytic agent. From the ADME profiles of syringin and tinocordiside, it cleared that they might be safe for human. Further *in vivo* investigation need to identify whether syringin and tinocordiside and other compounds have thrombolytic effect or not.

Conflict of interest statement

The authors declare that they have no conflict of interest.

ACKNOWLEDGEMENTS

The authors thank GUSTO (A research group) for providing the software and the financial support. The authors are thankful to all members of GUSTO (A research group) for their kind help in the experiments.

REFERENCE

1. Hill RG: Drug Discovery and Development: Technology in Transition: Elsevier Health Sciences, 2012.
2. Misra B, Bhava Prakash Nighantu, Vol. 1, (Hindi commentary by K C Chunekar), (Chowkhamba Vidya Bhavan, Varanasi), 1969; 269.
3. Kirtikar K R & Basu B D, Indian Medicinal Plants, Vol. 2, (Lalit Mohan Basu, Leader Road, Allahabad), 1933; 77.
4. Sharma P V, Dravya Guna Vigyan, Vol. 2, (Chowkhambha Vidya Bhavan, Varanasi), 1969; 680.
5. Shah Bapalalji, Nighantu Adarsh Vol. 1, (Hindi translation), (Chowkhambha Vidya Bhavan, Varanasi), 1969; 35
6. Gross PL, Weitz JI: New anticoagulants for treatment of venous thromboembolism. *Arterioscler Thromb Vasc Biol.*, 2008; 28(3): 380-386.
7. Demrow HS, Slane PR, Folts JD: Administration of wine and grape juice inhibits in vivo platelet activity and thrombosis in stenosed canine coronary arteries. *Circulation,* 1995; 91(4): 1182-1188.
8. Rajapakse N, Jung WK, Mendis E, Moon SH, Kim SK: A novel anticoagulant purified from fish protein hydrolysate inhibits factor XIIa and platelet aggregation. *Life Sci.,* 2005; 76(22): 2607-2619.
9. Rahman MA, Sultana R, Bin Emran T, Islam MS, Chakma JS, Rashid HU, Hasan CM: Effects of organic extracts of six Bangladeshi plants on in vitro thrombolysis and cytotoxicity. *BMC Complement Altern Med.,* 2013; 13(25): 1472-6882.

10. Sharma U, Bala M, Kumar N, Singh B, Munshi RK, Bhalerao S: Immunomodulatory active compounds from Tinospora cordifolia. *Journal of ethnopharmacology*, 2012; 141(3): 918-926.
11. Bala M, Pratap K, Verma PK, Singh B, Padwad Y: Validation of ethnomedicinal potential of Tinospora cordifolia for anticancer and immunomodulatory activities and quantification of bioactive molecules by HPTLC. *Journal of ethnopharmacology*, 2015; 175: 131-137.
12. Goel RK, Singh D, Lagunin A, Poroikov V: PASS-assisted exploration of new therapeutic potential of natural products. *Medicinal Chemistry Research*, 2011; 20(9): 1509-1514.
13. Khurana N, Ishar MPS, Gajbhiye A, Goel RK: PASS assisted prediction and pharmacological evaluation of novel nicotinic analogs for nootropic activity in mice. *European Journal of Pharmacology*, 2011; 662(1): 22-30.
14. Tiwari P, Kumar B, Kaur M, Kaur G, Kaur H: Phytochemical screening and extraction: a review. *Internationale pharmaceutica sciencia*, 2011; 1(1): 98-106.
15. Abul Hasanat MSHK, Mohammed Munawar Hossain, Mahmudul Hasan, Md. Abdullah Al Masum, Tanvir Ahmad Chowdhury, Didarul Islam Bhuiyan, Arafatul Mamur, Abu Sayeed Md. Golam Kibria: Antibacterial activity of methanol extract of Macaranga denticulata leaves and in silico PASS prediction for its six secondary metabolites. *World Journal of Pharmaceutical Sciences*, 2015; 3(6): 1258-1266.
16. Ewing TJ, Makino S, Skillman AG, Kuntz ID: DOCK 4.0: search strategies for automated molecular docking of flexible molecule databases. *Journal of computer-aided molecular design*, 2001; 15(5): 411-428.
17. Luo H, Chen J, Shi L, Mikailov M, Zhu H, Wang K, He L, Yang L: DRAR-CPI: a server for identifying drug repositioning potential and adverse drug reactions via the chemical–protein interactome. *Nucleic acids research*, 2011; gkr299.
18. Natarajan A, Sugumar S, Bitragunta S, Balasubramanyan N: Molecular docking studies of (4Z, 12Z)-cyclopentadeca-4, 12-dienone from Grewia hirsuta with some targets related to type 2 diabetes. *BMC complementary and alternative medicine*, 2015; 15(1): 73.
19. Lagunin AA, Gomazkov OA, Filimonov DA, Gureeva TA, Dilakyan EA, Kugaevskaya EV, Elisseeva YE, Solovyeva NI, Poroikov VV: Computer-aided selection of potential antihypertensive compounds with dual mechanism of action. *Journal of medicinal chemistry*, 2003; 46(15): 3326-3332.

20. A.V. P. Computer-Assisted Mechanism of Action Analysis of Large Databases, Including 250,000 Open NCI Database Compounds. Plant Resources, 1998; 34(1): 61–64.