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Research Article

"CLINCAL ANLYSIS OF POLY HERBAL COMPOUNDS IN THE MANAGEMENT OF TAMAKA ŚWĀSA (BRONCHIAL ASTHMA) – AN IN SILICO APPROACH OF VASAKA (*Adhatoda vasica Nees*)"

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ABSTRACT

Tamaka Śwāsa (Bronchial Asthma) is a syndrome characterized by airflow obstruction with reduced airflow, symptomatic wheezing and dyspnoea. Among all the treatment modalities, polyherbal combinations are well-accepted, safe and effective in asthma. An open clinical trial was conducted on 60 patients of either sex in between 10-70 years age to assure the clinical response of an herbal compound in bronchial asthma at Department of Kayachikitsa, Govt. Ayurvedic College & Hospital, and Guwahati-14. Along with this study, an attempt has also been made to identify the potential drug target of Asthma followed by a molecular interaction of Vasak compounds with the target protein of Asthma. The clinical trial results show clinical and symptomatological improvement. Also, improvement in Peak Expiratory Flow Rate was seen suggesting broncho-dilator effect, significant reduction of AEC and ESR was observed showing the anti-allergic effect of the drug. During the course of treatment no any adverse effects were noticed. Thus, the herbal compound is found out to be an ideal and safe preparation in the management of Tamaka Śwāsa. In molecular docking studies all the Screened 8 ligands out of 12 phytochemicals of *Adhotada vasica* with target protein of Asthma i.e IL3, IL4, IL5, IL13, TNF-α and EOTAXIN shows Vasicinolone to be most potent ligand that binds with IL-5 at the most minimum binding affinity of -7.7 kcal/mol.

INTRODUCTION

"Asthma is a heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation."[GINA 2015][1]

Tamaka Śwāsa signs and symptoms in Ayurveda has a close resemblance to Bronchial Asthma[2], it has been mentioned as a disease entity and an independent disease having its own etiology, pathogenesis and management. Bronchial Asthma is one of the most distressing disease and is quiet common in all the socio- economic strata in all age group and distributed all over the world. The recent revised global estimate of asthma suggests that as many as 334 million people have asthma. 14% of the world's children experience asthma symptoms, 8.6% of young adults (aged 18-45) experience asthma symptoms and it is the 14th most important disorder in the World in terms of the extent and duration of disability[3]. Ayurveda is the World's most ancient and being a complete health care science was formulated on the scientific parameters in those times with natural remedies and time tested therapies for various diseases. A personalized, multi-factorial approach to healthcare and cure has been the basic strategy. Among all the treatment modalities, polyherbal combinations are said to be well-accepted, non-toxic, safe, affordable and well effective in treatment of asthma. A considerable research is going on in this regard, but still none of the available treatments are found to be effective to provide a complete cure of this disease.

In this study, we propose to observe the efficacy of poly-herbal compound consisting of five(5) herbal drugs – Bark of Shirish(*Albizia lebbeck* Benth), Whole plant of Kantakari(*Solanum xanthocarpum Sachrod* Wendl), Root of Yastimadhu (*Glycyrrhize glabra* Linn), Leaf of Vasaka (*Adhatoda vasica* Ness), Leaf of Tulsi (*Ocimum Sanctum* Linn) on their authentic background of the reliable classical references and also considering their action on the respiratory

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tract especially on Bronchial Asthma with Clinical Study. Along with study the Vasaka in silico approach- Virtual Screening and Molecular Docking studies for discovery of potent drug candidates among compounds of *Adhatoda vasica* against Bronchial Asthma where also done. For the clinical study trial drug permission has been taken from Institutional Ethical Committee, Govt. Ayurvedic College & Hospital, Jalukbari and Guwahati-14. Ref. No.; IEC/15, 20-63 dated 28-04-2015.

MATERIALS AND METHODS

Materials

Material for Clinical Studies

Patients

The study design was open clinical trial done on total numbers of 60 cases of bronchial asthma registered for the study undertaken during 2014–2015 were collected from O.P.D and I.P.D. section at the P. G. Department of Kāyachikitsā, Govt. Ayurvedic College & Hospital, Jalukbari, and Guwahati-781014.

Inclusion Criteria

Total 60 patients of either sex suffering from bronchial asthma, Patients in between the age group of 10-70 years of either sex, Chronicity less than 10 years, Uncomplicated case of Bronchial asthma.

Criteria for Selection of Patient

Based on the diagnostic clinical features as given in the classics (Ca. Chi/17) i.e. Tama anupashaya (Paroxysmal nocturnal dyspnoea), Pratiloma pranvayu (Breathlessness/Dyspnoea), Kasa (Cough), Ghurghur Dhwani (Wheezing with ronchii on auscultation), Parswa avagraha (Tightness of chest), Kasten sleshma nisravanam(Difficulty in expectoration), Peenasa (Rhinitis), Kshavathu (Sneezing), Anidra (Insomnia), Usna abhinandati (Relief by hot regimen)

Exclusion Criteria

Patients less than age of 10 years and more than age of 70 years, Patients suffering from dysponeic problem of cardiac origin, Pulmonary Tuberculosis, Massive pulmonary embolism, Acute exacerbation of COPD, Psychogenic Dyspnoea, Metabolic acidosis, Renal Pathology, Left ventricular failure, Acute severe asthma (Status asthmaticus), Pneumonia, Malignancy, Surgical intervention, Pregnant Women and those who were not willing for the particular herbal treatment were excluded. The written consent was made from each patient and institutional ethical committee approving clinical studies.

Allocation

60 patients were treated by herbal compound drug. All the cases were advised to take the drug during the scheduled period of time and to visit the hospital in 30 days interval for clinical and investigative follow up before and after completion of treatment for at least 3 consecutive sequences i.e. 3 months.

Investigation: Blood Routine examination, Stool Routine examination, Urine Routine examination, Sputum Test, Chest X-ray, Pulmonary Function Test, ECG and IgE levels.

Therapeutic Study

Selection of trial Drug: The selection of the drug was done on the authentic background of the reliable classical references and also considering the action on the respiratory tract especially on Bronchial asthma.

Composition and Preparation of a Trial Drug

Sanskrit Name	Botanical Name	Part Used	Dose
Shirish	*Albizia lebbeck Benth*	Bark	2gm
Kantakari	*Solanum xanthocarpum Achrod wendl*	Whole plant	2gm
Yastimadhu	*Glycyrrhize glabra Linn*	Root	2gm
Vasaka	*Adhatoda vasica Ness*	Leaf	2gm
Tulsi	*Ocimum Sanctum Linn*	Leaf	2gm
	Total		10gm

The mixture coarse powdered drugs are advised to prepare in kwāth (decoction) form. The kwāth (decoction) was prepared by boiling 2 teaspoon full (10gms) of powdered drugs in 160 ml of water till 40 ml remains.

The compound drugs were dried in coarse powder form. The drug was tested at Drug Testing Laboratory (AYUSH), Govt. Ayurvedic College, Guwahati -14 and DTL Ref. No: DTL (AY)/PGR/68/2015 dated 01-04-2015.

Dose & Duration: 40ml kwāth (decoction) twice daily a day for 3 months.

Trial Methodology: Open Trial

Criteria for Assessment of Treatment

Subjective Assessment: Keeping in view on the Ayurvedic clinical and symptomatological improvement of the patients observing in 3 different follow ups at 1st month, 2nd month & 3rd month respectively.

To assess the severity of the disease all the signs and symptoms were graded by the following Grade rating scale-

Rating scale	Grade
Absent	0
Mild	1
Moderate	2
Severe	3

Objective assessment

Objective assessment of response of the trial drugs was carried out following pathological and radiological investigation, PEFR, ESR and AEC recorded before and after treatment and PEFR is recorded at 1st, 2nd and 3rd month of interval respectively**.**

Statistical analysis: The data obtained was summarized & analyzed using frequency distribution method. The arithmetic mean, percentage, standard deviation and z-test of significant, we calculate using appropriate statistical tools.

Materials for in silico Studies

The databases used for the study includes KEGG[4] for pathway analysis and identifying drug targets, KNApSAcK Family Database[5] for use to search for metabolites based on an accurate mass, molecular formula, metabolite name or mass spectra in several ionisation modes, RCSB[6] -Research Collaboratory of Structural Bioinformatics RCSB for retrieving

pdb format of identified drug targets. The software used for the study include MarvinSketch[7] to visualized the 3D structure of the compound, converted .mol formats to .smiles, .sdf and .pdb format to visualize the compounds in OSIRIS property explorer, OSIRIS[8] for Toxicity Risk Assessment, cLogP Prediction, Solubility Prediction, Molecular Weight, Drug-Likeness Prediction, Overall Drug-Score, QikProp[9] Schrödinger Software for assessing , Binding to Human Serum Albumin, Human Oral Absorption, Predicted Brain/Blood Partition Coefficient, Predicted Central Nervous System Activity, Cell Permeability . Finally docking studies were made by Auto Dock Vina[10].

METHODOLOGY

Methods for Clinical Studies

Based on the inclusion and exclusion criteria and investigation report of blood, stool, urine, sputum etc. 60 subject was finalized which had under gone a clinical trial. "Broncho-T Plus" an herbal compound, formulated and prepared by five herbs and was selected based on authentic background of the reliable classical references and also considering the action on the respiratory tract especially on Bronchial Asthma. The coarse powder was asked to prepared in kwath (decoction) form by boiling 2 teaspoon (10 gms) of prepared powdered drug in 160 ml of water, it is advice to boil the drug till 40 ml remains and is given twice daily preferably after food. The trial drug was given for a period of 3months to each patient with follow up at 1st month, 2nd month & 3rd month respectively.

The assessment of result of the patient is done based on subjective and objective criteria in due course of the treatment**.** The data obtained from the treatment were then organized and summarized using the method of frequency distribution. The data were then analyzed using appropriate statistical techniques such as arithmetic mean, percentage, standard deviation and z-test of significance.

Methods for In silico Studies

Pathway analysis: To understand the molecular basis of occurrence of asthma, we have performed pathway study from KEGG to identify potent drug targets. The pathway was analyzed thoroughly and essential genes were identified responsible for the late phage of Asthma.

Protein and Ligand Preparation: Target Protein of Asthma IL3[11], IL4[12], IL5[13], IL13[14], EOTAXIN[15] and TNF-α (Tumor Necrosis factor α)[16] were identified and cross validated using PDTD(Potential Drug Target Database), and the 3D Structure files of identified target protein was retrieved from RCSB Server in the form of *.pdb File (text)* format. Compounds of Adhatoda vasica i.e Vasicinolone[17], Adhatodine, Vasicoline, Vasicolinone[18] , Vasicol[19], Anisotine, Deoxyvasicinone, Peganine, Vasicinol, Vasicinone[20], 4,2'-Dihydroxychalconoe 4-glucoside[21], Paganidine[22] and have been retrieved from Knapsack Family Data Base in the form of .mol format, they are converted into .smiles and .pdb format using Marvin Sketch. Toxicity assessment of compounds was done using OSIRIS Property Explorer and Biological Activity assessed using Schrodinger Quick Prop utility.

Optimization of Protein and Ligand*:* Finally proteins were optimized for protein ligand interation studies by deleting all hetero atoms, ligands and water molecules and optimized by minimization of energy by using AutoDock Vina. The grid parameter was set and the obtained structure was saved as .pdbqt. Ligands obtained from Knapsack Family Data Base in the form of .mol format converted into .pdb format using *Marvin Sketch* was optimized by using AutoDock Vina. Later, all the optimized ligands were saved in .pdbqt format.

Study of Molecular Descriptors: The molecular descriptors of screened eight components of *Adhatoda vasica* were predicted by loading them into online server, OSIRIS property explorer. This prediction process depends on comparison between precomputed set of structural moieties whose properties are already known and the structural moieties of loaded molecules. Molecular descriptors like clogP, solubility, drug score and side effects such as mutagenicity, tumorocity, irritant and reproductive effective were determined. To calculate the overall drug score, OSIRIS combined c logP, solubility, molecular weight, drug-likeness, drug score and toxicity risks into a single number to predict the molecule's over all drug potential. Eight out of twelve compounds are selected for molecular docking depending upon their drug score and toxicity risks.

Docking Studies*:* Eight compounds were selected based on experimental and insilico studies i.e. Vasicolinone, Vasicoline, Vasicol, Vasicinolone, Vasicinone, Vasicinol, Peganine, Deoxyvasicinone were docked with target proteins using a genetic algorithm and simulated annealing approach to explore wide range of ligand conformational flexibility and rotational flexibility of Auto Dock . The based protein ligand complex was analysed based on minimum binding affinity. Finally molecular docking was performed between *Identified Target Protein and the Screened ligands* using Autodock Vina. The docked complexes were visualized in AutoDock Vina.

RESULTS

Results of Clinical Studies

Table 1 Response of the treatment on subjective assessment:

Sl. No.	Sign & Symptoms	Number of Patients		Percentage of Relief
		BT	AT	
1	Paroxysmal dyspnoea	60	10	83.33%
2	Cough	60	14	76.66 %
3	Rhonchi Wheezing	56	08	85.71 %
4	Prolonged Expiration	60	12	80 %
5	Tightness of Chest	46	12	73.91 %
6	Crepitations	18	02	88.88 %
7	Coryza	40	08	80 %
8	Insomnia	26	04	84.61%
9	Headache	24	02	91.66 %

Table 2 Effect of treatment on objective assessment

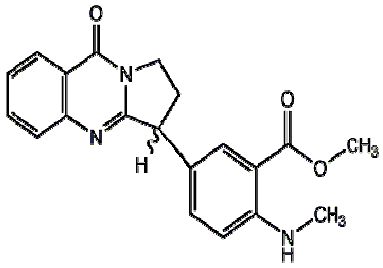
Sign & Symptoms & Effect of treatment	Mean value ± S.D.			SE	z- value	p-value
	BT	AT	BT – AT			
Paroxysmal dyspnoea	2.6 ± 0.47	0.16± 2.88	± 2.44	0.37	6.59	< 0.01
Cough	2.4± 1.66	0.30± 0.21	± 2.1	0.21	10	<0.001
Rhonchi/wheezing	1.57±0.73	0.35±0.82	±1.22	0. 14	0.14	<0.001
PEFR	142± 44	212± 48.74	70±4.74	8.47	8.2	<0.01
AEC	580.4± 268	416± 83.91	164±184.09	36.25	4.5	<0.01
ESR	23.2± 6.57	19± 2	4.2±4.57	0.88	4.77	<0.01

Results of In Silico Studies

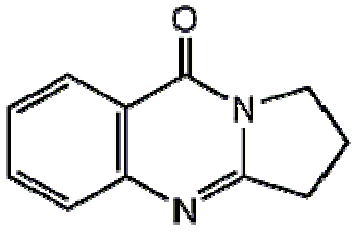
In the Silico Study we performed virtual screening of 12 ligands of *Adhatoda vasica* - Anisotine, Deoxyvasicinone,

Peganine, Vasicinol, Vasicinone, Adhatodine, Vasicinolone, Vasicoline, Vasicol, and Vasicolinone, 4,2'-dihydroxychalcone 4-glucoside, Peganidine (Table 3) for their molecular properties, biomolecular activity properties, drug score, drug likeliness as well as for their possible side effect like tumerogenecity, mutagenicity, irritation and reproductive effect. Then we extended our study by going through an *in silico*[23] study on possible molecular level interaction of the best druglike compounds and proteins responsible for asthma i.e. IL-3, IL-4, IL-5, IL-13, EOTAXIN and TNFα were selected for molecular interaction of the ligand with the genes.

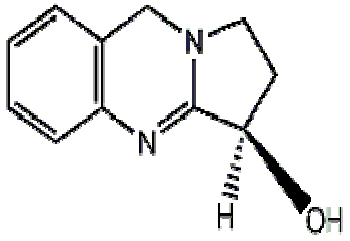
Table 3 Phytochemicals of *Adhatoda vasica* (Note:CN= Compound Name, CID=Compound Identification Number, MF=Molecular Formula, MW=Molecular Weight)



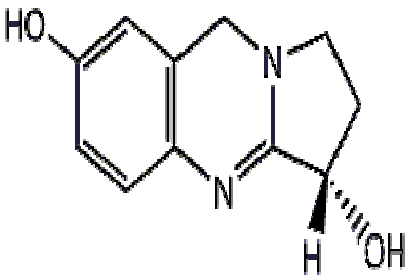
CN : Anisoine
CID : C00002134
MF : C20H19N303
MW : 349.14



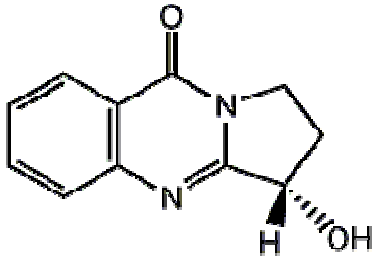
CN : Deoxyvasicinone
CID :C00002150
MF : C11H10N20
MW : 86.08



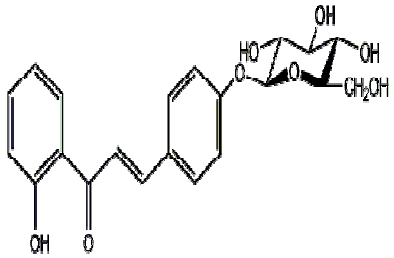
CN : Peganine
CID :C00002191
MF : C11H12N20
MW : 188.09



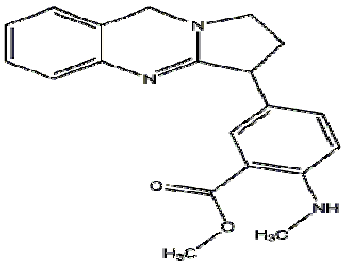
CN : Vasicinol
CID : C00002201
MF : C11H12N202
MW :204.09



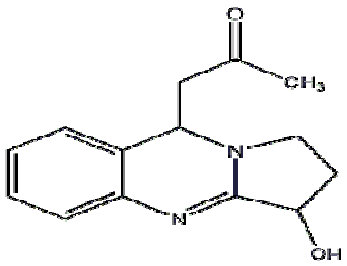
CN : Vasicinone
CID : C00002202
MF : C11H10N202
MW : 202.07



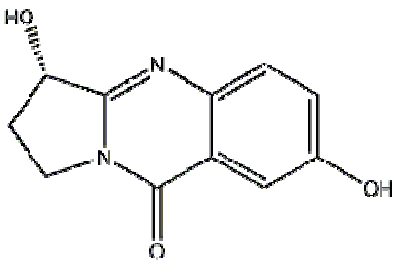
CN:4,2'-Dihydroxychalconoe4-glucoside
CID : C00007183
MF : C21H2208
MW : 402.13



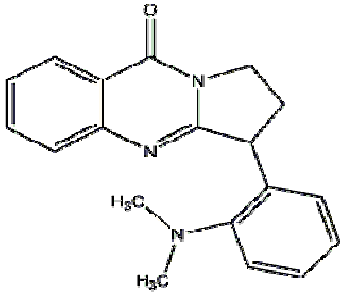
CN : Adhatodine
CID : C00026236
MF : C20H21N302
MW : 335.16



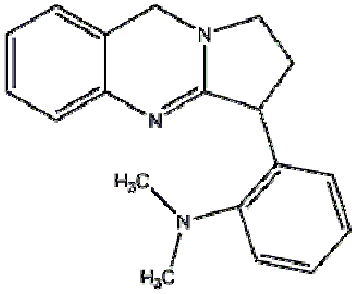
CN : Peganidine
CID : C00026249
MF :C14H16N202
MW : 244.12



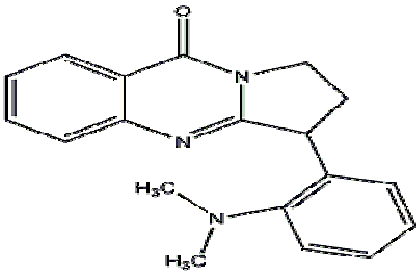
CN : Vasicinolone
CID : C00002623
MF : C11H10N203
MW : 218.07



CN : Vasicol
CID : C000026254
MF : C11H14N202
MW : 206.10



CN : Vaicoline
CID : C000026255
MF : C19H21N3
MW : 291.17

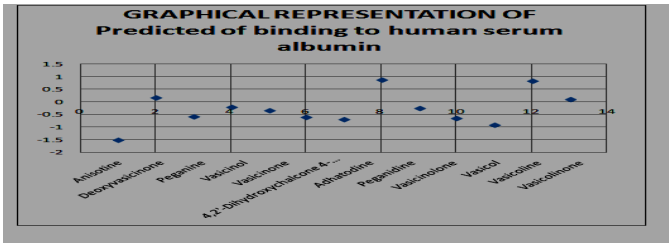


CN : Vasicolinone
CID : C000026256
MF : C19H19N30
MW : 305.15

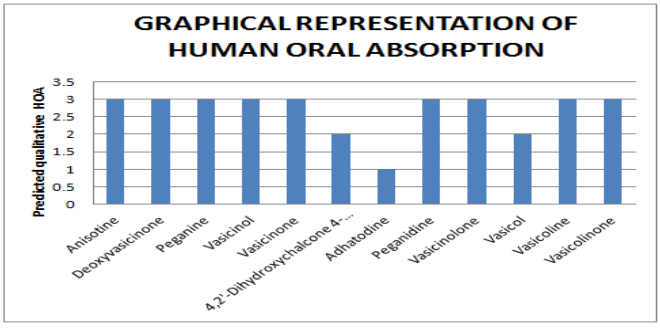
The protein downloaded from RCSB PDB server is prepared by removing water and other hetero molecules and it was geometrically optimized by AutoDock Vina. All the Ligands were optimized to its least possible energy conformation. All the compounds were screened for its toxicity properties, based on the findings 4 compounds where excluded for further study i.e Adhatodine, Anisotine were screened out for its tumerogenic effect; Paganidine was screened out for its irritant effect and 4, 2'-Dihydroxychalconoe 4-glucoside was screened out for its partial drug likeness and drug score. Another assessment of Ligands has also done to check its drug like nature using Schrodinger,QuickProp utility [Graph 1,2,3,4,5]. All the compounds shows good binding to human serum albuminis (QPlogKhsa) in the range of –1.5 to + 1.5; good binding to human oral absorption at the range of + 3 High, +2 Medium , +1 Low respectively; good in regard to CNS activity Predicted its activity at a range of –2 (inactive) to +2 (active) scale; good blood brain partition coefficient and crosses the blood-brain barrier Range: <25 poor, >500 great; all compounds except Adhatodine are more likely to be orally available and follows Jorgensen's rule of three which are: QPlogS > -5.7, QP PCaco > 22 nm/s, Number of Primary Metabolites < 7, Compounds with fewer (and preferably no) violations of these rules are more likely to be orally available.

All the proteins Docked individually with selected 8 ligands in the molecular docking software - AutoDock Vina give the good binding affinity as shown in (Table 4) among all vasicinolone is showing the minimum binding affinity with IL-5 (Fig. 6) with the binding energy of -7.7 kcal/mol.(Fig. 7). No literature references described about the drug candidature of these compound. It is assumed that vasicinolone is having much external hydrogen bonding energy that leads to better binding than any other Ligands.

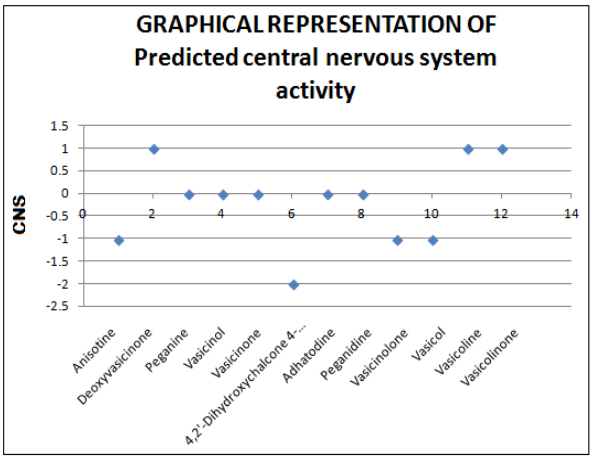
QUICK PROP Analysis results



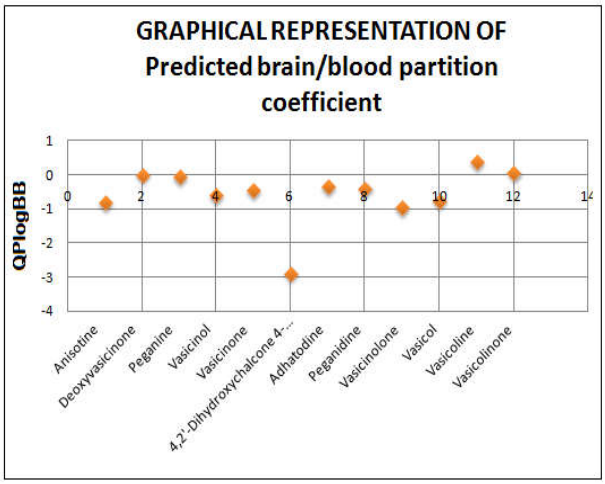
Graph 1 Binding to HSA Analysis: All compounds shows good binding to human serum albumin as QPlogKhsa is in the range of –1.5 to + 1.5



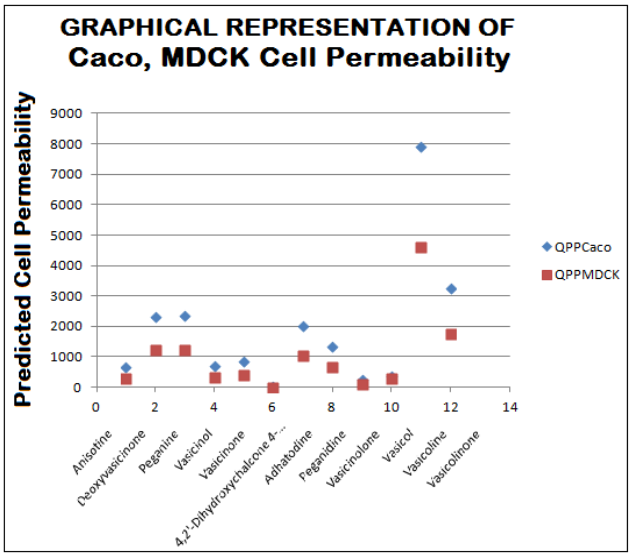
Graph 2 HOA. Analysis: All compounds shows good human oral absorption (+ 3 High, +2 Medium , +1 Low)



Graph 3 CNS Activity. **Analysis:** Predicted central nervous system activity on a –2 (inactive) to +2 (active) scales.



Graph 4 BB partition coefficient **Analysis:** QPlogBB Predicted brain/blood partition coefficient. (Range –3.0 to + 1.2) All compounds shows good blood brain partition coefficient and crosses the blood-brain barrier



Graph 5 Cell Permeability. **Analysis:** All compounds except compound 6 showing High Permeability (Caco-2 cell permeability- gut-blood barrier,MDCK cell permeability - mimic for the blood brain barrier) Range : <25 poor, >500 great

Summarized table of binding affinity in the docked complex of target protein and ligands

Table 4 Binding Affinity in the Docked Complex of Target Protein and Ligands

SL NO.	LIGANDS	TARGET PROTEINS					
		IL-3	IL-4	IL-5	IL-13	EOTAXIN	TNF-α
1	DEOXYVASICINONE	-5.0	-4.7	-6.3	-5.1	-4.9	NILL
2	PEGANINE	-5.0	-6.0	-5.6	-5.6	-4.8	-7.1
3	VASICINOL	-5.3	-6.1	-5.8	-5.9	-4.9	-5.6
4	VASICINONE	-5.4	-5.6	-7.4	-6.1	-5.2	-5.5
5	VASICINOLONE	-6.0	-6.0	**-7.7**	-5.4	-5.1	-6.4
6	VASICOL	-5.0	-5.5	-5.3	-5.4	-4.7	-6.5
7	VASICOLINE	NILL	NILL	-6.2	NILL	NILL	NILL
8	VASICOLINONE	-6.7	-6.3	-6.9	-6.5	-5.6	-6.4

Visualization of target protein ligand interaction in the docked complex

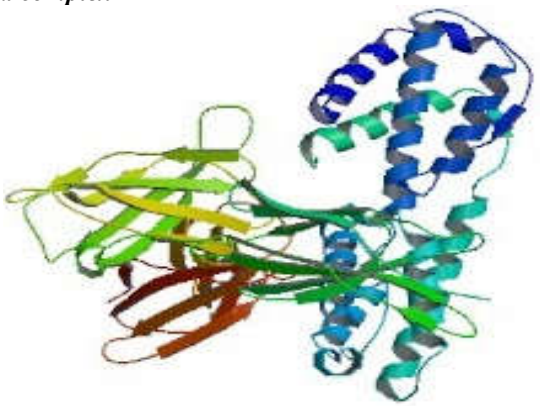


Fig 6 The IL-5 Protein Structure

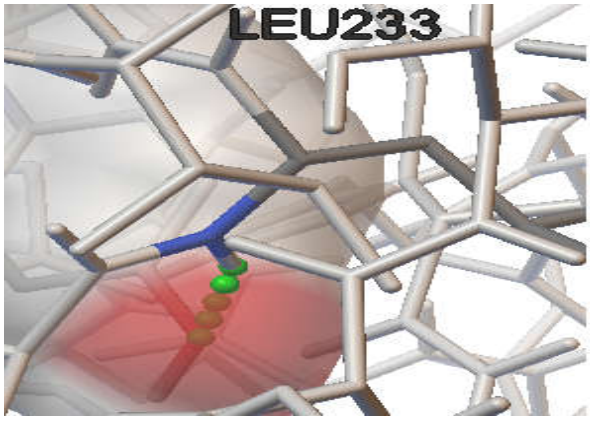


Fig 7 Interaction between LEU233 residue of IL- 5 with Vasicinolone

DISCUSSION AND CONCLUSION

The effect of therapy "Broncho-T Plus" was found to be very encouraging in the treatment of Tamaka Śwāsa. In signs and symptoms remarkable relief was observed in Tama anupashaya 83.33%, Kasa 76.66%, Ghurghur Dhwani 85.71% and Pratiloma Vayu 80%. Also significant improvement is observed in allied symptoms such as Parswa avagraha was relieved in 73.91%, Crepitations in 88.88%, Kshavathu was relieved in 80% of cases, Ānidra in 84.61% and Sankha Bheda in 91.66 %. Effect of the drug on PEFR was also found to significant. The trial drug also shows significant reduction in ESR and AEC. During the course of treatment no any side effects or adverse reactions were noticed. Hence it may be inferred that this herbal compound is an ideal and safe preparation in the management of Tamaka Śwāsa.

In this present work we have considered only Vasak for *in-silico* study since the studies on poly-herbal formulation is time consuming and requires huge amount of computational power, and advanced software tools to virtually synthesize new chemical compounds by a series of virtual reaction performed on the permutation of chemical compounds found in the constituents of the poly-herbal formulation. Ayurveda has mentioned the use of Vasak in Asthma. However, how the compounds of Vasak functions at the molecular level is yet unknown. So, an attempt has been made on virtual Screening and molecular docking studies for discovery of potent drug candidates among compounds of *Adhatoda vasica* against the potential drug target of Bronchial Asthma. Target Protein of Asthma was identified by a study on Asthma Pathway derived from KEGG Pathway Database and cross validated using PDTD , and the 3D Structure files of identified target protein was retrieved from RCSB Server. Compounds have been retrieved from Knapsack Family Data Base and toxicity assessment of compounds was done using OSIRIS Property Explorer. Schrodinger, Quick Prop utility was also used to check its drug like nature. Finally docking was performed using Autodock Vina. The identification of target protein was made by using PDTD, 12 Phytochemicals of Adhotada Vasica was retrieval from Knapsack Family Database, the 3D structure files of identified Target Protein was retrieval from RCSB Server, Toxicity assessment and Virtual Screening of ligands was done by using OSIRIS Property Explorer and Molecular Docking studies of identified Target Protein with the Screened ligands by using AutoDock. 8 compounds i.e Vasicolinone, Vasicoline, Vasicol, Vasicinolone, Vasicinone, Vasicinol, Peganine, Deoxyvasicinone were selected for further study and the 4 compounds were excluded i.e Adhatodine, Anisotine, Paganidine and 4,2'-Dihydroxychalconoe 4-glucoside. Molecular docking studies of 8 ligands with target protein of Asthma (IL3, IL4, IL5, IL13, TNF-α and EOTAXIN) were performed. Based on binding energy and hydrogen bond formation, docking results were analyzed by using AutoDock tools and visualized through Autodocked. Summarizing the entire study vasicinolone showed the most minimum binding ENERGY with IL5, ΔG = -7.7 kcal/mol. Thus the *in-Silico* methods adopted in the present study helped to identify that vasicinolone can be used as a potent drug candidate for Asthma.

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