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# EXPLORING THE POSSIBLE MECHANISM OF *ALBIZZIA LEBBECK* COMPONENTS BINDING WITH DRUG TARGETS OF BRONCHIAL ASTHMA –AN INSILICO AND CLINICAL ANALYSIS

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**Keywords:**

*Tamaka Swasa, Bronchial Asthma, Shirish, Albizia lebbeck Benth, Lebbecacidin*

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**ABSTRACT:** Asthma is a multi factorial disease characterized by airflow obstruction, wheezing and dysonea and for this many genes are responsible. In this study, an attempt has been made to identify genes along with the proteins encoded by them which are responsible for Asthma along with clinical trials. In the practice of Ayurveda, it's well established that shirish (*Albizzia lebbeck*) can be used as a treatment of Asthma. However, how the compounds of shirish bark functions at the molecular level is yet unknown. The present study shows an insilico molecular interaction studies and clinical trials as well for the compounds of shirish bark. The results show how the compounds of shirish bark affect the target proteins of asthma which actually will aid in the design of putative inhibitor. Among the screened 9 (nine) compounds of shirish, all the compounds are giving good binding affinity to the selected proteins and among them lebbecacidin interacts potentially and is also showing lowest binding energy with IL-5, one of the target proteins. Lebbecacidin has satisfied all the criteria for a potential lead with drug likeliness 1.26, drug score 0.83, high solubility and high cell membrane permeability and it has also been calculated to be non toxic which was also validated by clinical studies.

**INTRODUCTION:** Asthma a clinical syndrome is prevalent in human beings both adults as well as children. The symptoms of this syndrome are variable from air flow obstruction till bronchial hyper responsiveness.

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Asthma occurs when inhaled antigens encounter antigen presenting cells (APC) that lines the airway inflammation. When IgE activates APC, the naïve T cells get differentiated into TH2 cells which further binds to IgE receptors (present on mast cells). The later interactions result in release of biologically active mediators either histamine or leukotrienes, which mediates the symptoms of allergy. IL-5 is essential for recruitment of eosinophils which has a major role in pathogenesis of asthma [1]. The recruitment of eosinophil leads to

release of toxic granules further leading of damage of tissue and chronic inflammation.

Ayurveda, the great indigenous system of medicine of India is a complete healthcare system with a holistic approach to health and personalize medicine. Ayurveda consider body, mind and spirit along with their relationship with the bio-culture environment. Man has been using herbs and plants products for combating diseases since time immemorial [2]. Tamaka Swasa is the name given to bronchial asthma in Ayurveda [3].

Asthma is one of the most common chronic diseases globally [4] and currently affects 300 million people worldwide with 250,000 annual deaths attributed to the disease [5] and is the third-ranking cause of hospitalization among children under 15 [6]. The overall burden of asthma in India is estimated at more than 15 million patients and is recognized to be a major cause of morbidity and mortality in people of all age groups.

*Albizia lebbeck* (Benth.), a flora of the family Mimosaceae is traditionally used for treating asthma and other allergic diseases [7]. The plant has anti-asthmatic and anti-anaphylactic [8], anti-inflammatory, anti-allergy, anti-histaminic, anti-oxidant, anti-convulsant, anti-spermatogenic, anti-microbial, anti-fungal, anti-microbial, cardio tonic, and also acts as hypo cholesterolemia etc. [9]. The medicinal properties of plants are determined by the chemical compounds present in the various parts of the plant. In this study, we propose to observe the efficacy of compounds of bark of *Albizia lebbeck* on bronchial asthma using *in silico* and clinical study.

## MATERIALS AND METHODS:

### Materials for Clinical Studies

**Patients:**

The study was made on a total of 60 patients of either sex suffering from bronchial asthma between the age group of 10 to 70 years. The study was carried out at Government Ayurvedic College & Hospital, Jalukbari, Guwahati, Assam, India, based on inclusion & exclusion criteria described as follows:

**Inclusion Criteria:**

Patients between the age group of 10 to 70 of either sex were "inclusion", having chronicity less than 10 years. The cases considered were uncomplicated.

**Exclusion Criteria:**

Patients less than the age of 10 years and more than age of 70 years besides having bronchial asthma, were also accompanying 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 and along with that 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 undergo methodical investigations before and after completion of treatment; the cases will be advised to visit the hospital in 30 days interval for clinical and investigative follow up for at least 3 consecutive sequences i.e. 3 months.

### 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 [7].

### Preparation of the Trial Drugs

The coarse powder from the bark of Shirish (*Albizia lebbeck* Benth) was prepared in laboratory. The bark was dried and finally processed in coarse powder form. The drug was tested at Drug Testing Laboratory (AYUSH). Govt. Ayurvedic College, Guwahati-14. DTL Ref. No: DTL (AY)/PGR/11/2013. Dated 21-08-2013.

The coarse powder from the bark of Shirish was obtained from Banaras, India. The coarse powder of *Albizia lebbeck* was prepared in kwath (decoction) form by boiling 2 teaspoon (10 gms) of prepared powder in 200 ml of water and

concentrated by evaporation to till 50 ml. The suspension was given twice daily preferably after food for three months.

**Assessment of Treatment**

All the patients were evaluated once a month for their different follow ups to assess the sign & symptoms of the severity of the disease. Based on the severity the grade rating scale was made for absent 0, Mild 1, moderate 2, and severity 3. 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 at Govt. Ayurvedic College & Hospital. "Broncho-T" an herbal compound, formulated and prepared by single 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 [7].

The assessment of result of the patient is done based on subjective (clinical and symptomatological improvement) and objective (pathological and radiological investigation) criteria in due course of the treatment**.**

**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 in silico studies were further made to validate experimental studies. The databases and software's used for the study includes KEGG for pathway analysis and identifying drug targets [10]. Moreover, 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.

Molinspiration tool was used for large-scale calculation of molecular properties and database searches [11]. The molecular descriptors of screened nine components of *Albizia lebbeck* were predicted by loading them into online server, OSIRIS property explorer [12]. This prediction process depends on comparison between pre-computed 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. 4 (four) out of 9 (nine) compounds are selected for molecular docking depending upon their drug score and toxicity risks [13, 14].

Chemspider web server tool [15] was used for providing fast access to over 26 million structures, properties and associated information [16]. RCSB for retrieving pdb format of identified drug targets [17]. The 3D structure of components of *Albezia lebbeck* and its physiochemical properties were retrieved from Chemspider tool [15] and were virtually screened for active drug molecule based on CMC's rule and Lipinski rule of five.

Based on above studies the key genes found responsible in bronchial asthma were IL-3, IL-4, IL-5, IL-9, IL-10, IL-13 and TNF (Tumor Necrosis factor α). Out of the proteins encoded by these genes, IL4, IL5, IL10, IL13 and TNF α were downloaded from RCSB Protein Data Bank (PDB) and IL3 and IL9 structures were predicted by homology modeling with Swiss Modeler [18]. The active sites were predicted by Molegro Virtual Docker [19].

**Molecular docking analysis**

Finally docking studies were made by Auto Dock suite [20]. The compounds D-catachin, melacacidin, friedelin, β-sitosterol, leucoantho-cynadin, lebbecacidin, leucocynadin, leucocynidin and betulinic acid were retrieved from Chemspider database and saved as .pdb files. Genes (Interleukin) i.e. IL-3, IL-4, IL-5, IL-9, IL-10, IL-13 and TNFα were identified as drug targets based on review further proteins encoded by them were retrieved from RCSB and saved as.pdb files. Proteins (IL-3, IL-4, IL-5, IL-9, IL-10, IL-13 and TNFα) were optimized for protein ligand interation studies by deleting all hetero atoms, ligands and water molecules and optimized by minimization of

energy by using Auto Dock Vina. The grid parameter was set and the obtained structure was saved as .pdbqt. Ligands obtained from Chemspider as mol was optimized by using AutoDock Vina.

Later, all the optimized ligands were saved in .pdbqt format. Four compounds were selected based on experimental and insilico studies i.e. D-Catachin, Melacacidin, Lebbecacidin and Leucocynadin were docked with proteins IL- 3, IL-4, interleukin 5 (colony-stimulating factor, eosinophil), interleukin 9, interleukin 10, interleukin 13 and TNF- α 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 analyzed based on minimum binding affinity. The docked complexes were visualized in Pymol [21, 22] showing how the ligands interact with the IL-3, IL-4, IL-5, IL-9, IL-10, IL-13 and TNFα.

## RESULTS:

### Results of clinical studies

The observation and result was done under two different heading. The first part consists of demographic study and secondly consists of therapeutic response of the trial drug in the patient of bronchial asthma meeting both the subjective and objective parameters of assessment.

Observations made on 60 patients of bronchial asthma showed that maximum number of patients i.e. 33.33% were in the Age group of 21 – 40 years. It was observed that male was dominant having 50.00% of cases while Hindu were dominant among the sufferer having 80.00%.

Women were 35.00% and students were 15.00% sufferer respectively. Middle class having 50.00% and Rural Population having 60.00% were found to be affected more in the study. Majority of the patient in the study were Non-vegetarian i.e. 91.67%. Addiction to Beetle Nut and Smoking was observed in total 41.67%. Family history of the disease was found to be Positive in 33.33% while Personal History of other Allergic disorders was positive in 60.00%. Majority of patients i.e. 33.33% were found to be suffering from Illness with duration of less than 1 year.

The effect of therapy was found to be encouraging. In sign and symptoms about 85.00% relief was observed in Paroxysmal Dyspnoea, Prolonged Expiration and Rhonchi followed by 83.33% relief in Cough. Also significant improvement is observed in allied symptoms like Tightness of Chest, Frequent Coryza, Exertional Dysponea, Crepitation, Weakness, Headache, Insomnia and Fever.

Effect of the drug on Dysponea, Cough and Wheezing was found to be highly significant. Respiratory rate, Peak Expiratory Flow Rate and Breath Holding Time were also found to be highly significant. Absolute Eosinophil Count and Erythrocyte Sedimentation Rate were also highly significant. The result showed highly significant with p-value <0.001. Thus the overall outcome of the study was significant indicating that the 'Bronchio-T' has an effective role in the management of Bronchial Asthma. Further no adverse or side effect was observed in any of the patients in the entire clinical study and overall therapeutic response was highly encouraging.

## IN SILICO STUDIES

We performed a virtual screening of 9 compounds viz. D- Catachin, Melacacidin, Friedelin, β-Sitosterol, Leucoantho-cynadin, Lebbecacidin, Leucocynadin [23, 24], Betulinic acid [25] and Echinocystic acid [26] found in the bark of *Albizia lebbeck* for their molecular properties, bioactivity 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* [27] study on possible molecular level interaction of the best drug like co66mpounds and proteins responsible for asthma i.e. IL-3 [28], IL-4, IL-5, IL-9, IL-10, IL-13 and TNFα were selected for molecular interaction of the ligand with the genes.

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 of *A. lebbeck* bark were screened for its toxicity properties **(Table 1)**. Among them the best compounds showing maximum drug likeness are

listed in **Table 1** and a graphical comparison of their molecular properties have been shown in **Graph 1 to 4**.

**TABLE 1. PHYSIO-CHEMICAL ANALYSIS OF ALBIZIA LEBBECK BARK.**

| Trial Drug | Organolaptic analysis | | Physico-chemical analysis | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Colour | Odor | Foreign matter | Moisture | Ash | Acid | Water | Alcohol |
| **Albizia lebbeck** | Light yellow to gray | Very astringent | Nill | 14.65% | 7.96% | 0.97% | 6.95% | 15% |

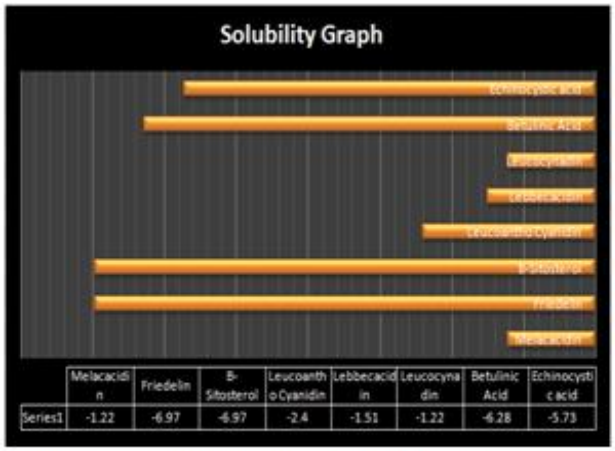



Figure 1: Lipophilicity Graph Pattern of C Log

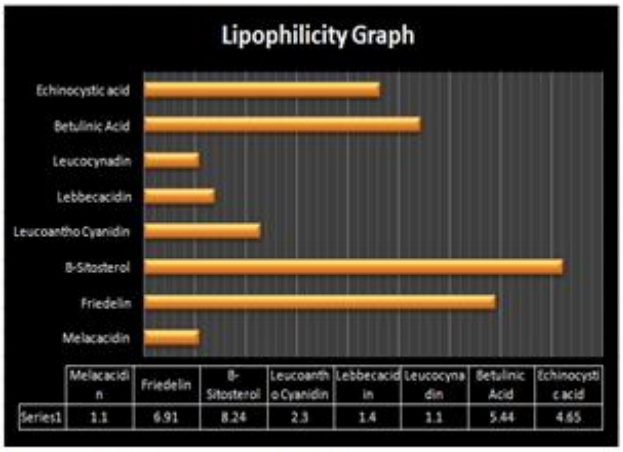



Figure 2: Solubility Graph

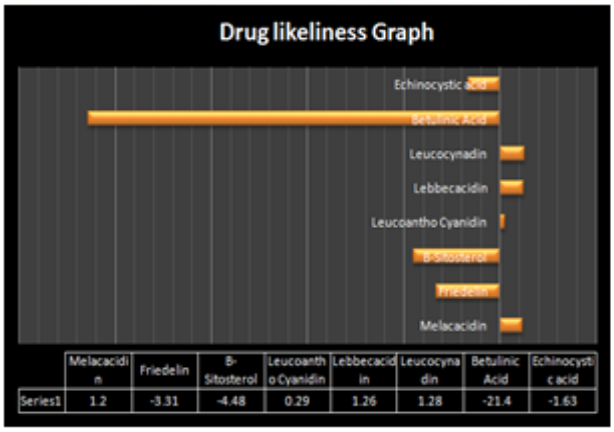



Figure 3 Drug Likeliness Graph

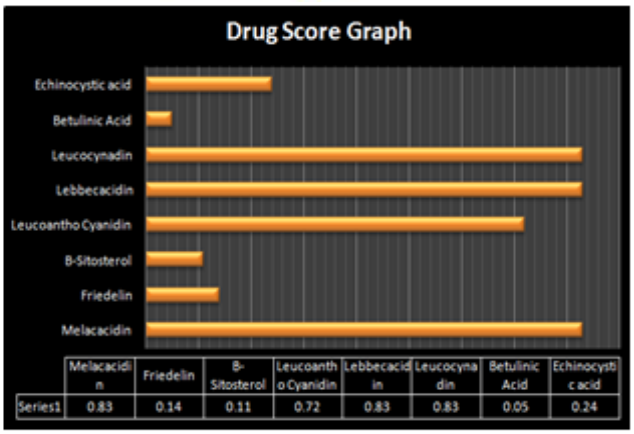



Figure 4- Drug Score

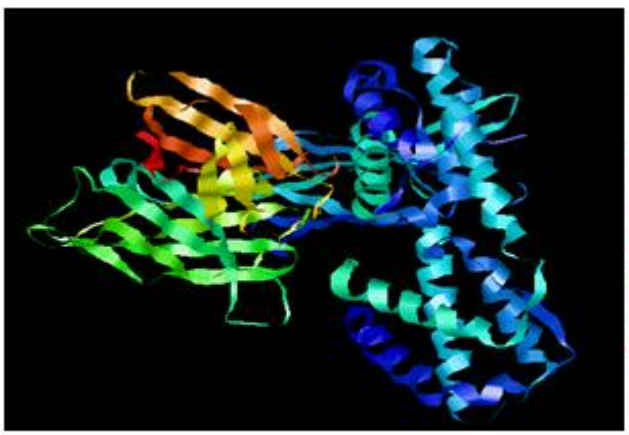


Figure 5: The IL-5 Protein Structure

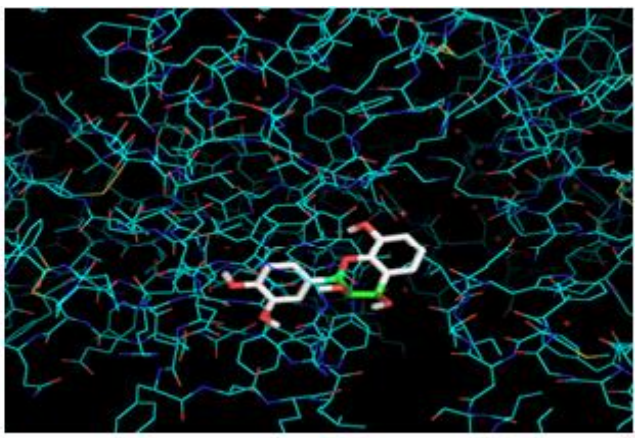


Figure 6 : The Ligand Inside the cavity of Protein

We found that D- Catachin, Melacidin, Lebbecacidin and Leucocynadin are the most important components of *Albizia lebbeck* bark on the ground that they are non mutagenic, non tumerogenic, non irritant in nature with no reproductive effect. Whereas the other components of bark such as Friedelin, β- Sitosterol, Leucoantho cyanidin, Betulinic acid and Echinocystic acid as given in **Table 4**. were found to be bad drug candidates. All the docking results of the selected four Ligands with the selected seven proteins give the good binding affinity as shown in **Table 5**., among all the binding of ligand and protein Lebbecacidin **(Fig 1)** is showing the minimum binding affinity with IL-5 **(Fig 2)** with the binding energy of -8.3kcal/mol **(Fig 3)**.

**TABLE 2. EFFECT OF THERAPY INCLUDING SYMPTOMS ALONG WITH PERCENTAGE OF RELIEF**

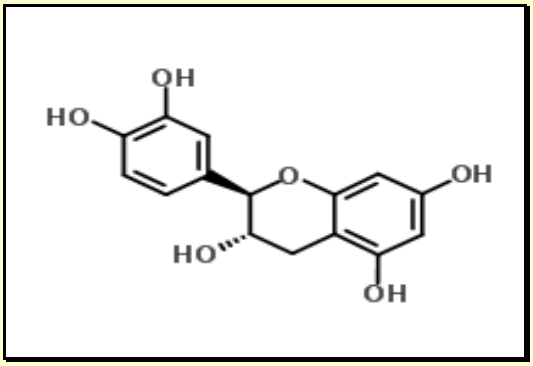
| Sl. No. | Sign & Symptoms | Number of Patients | | Percentage of Relief |
|---|---|---|---|---|
| | | Before Treatment | After Treatment | |
| **1** | Paroxysmal dyspnea | 60 | 09 | 85.00% |
| **2** | Cough | 60 | 10 | 83.33% |
| **3** | Prolonged Expiration | 60 | 09 | 85.00% |
| **4** | Rhonchi / Wheezing | 60 | 09 | 85.00% |
| **5** | Tightness of Chest | 52 | 12 | 76.92% |
| **6** | Frequent Coryza | 40 | 12 | 70.00% |
| **7** | Exertional Dyspnoea | 25 | 10 | 60.00% |
| **8** | Crepitations | 13 | 04 | 69.23% |
| **9** | Weakness | 36 | 06 | 83.33% |
| **10** | Headache | 20 | 02 | 90.00% |
| **11** | Insomnia | 15 | 02 | 86.67% |
| **12** | Fever | 05 | 00 | 100% |

**TABLE 3. EFFECTS OF THE TRIAL DRUG**

| Sl No | Effect of Drug | Mean Value | | | S.D | | | z-value | p-value |
|---|---|---|---|---|---|---|---|---|---|
| | | BT | AT | BT-AT | BT | AT | BT-AT | | |
| **1** | Dysponea | 2.53 | 0.28 | 2.25 | ±2.42 | ±0.76 | ±1.66 | 6.82 | <0.01 |
| **2** | Cough | 2.47 | 0.28 | 1.13 | ±60 | ±70 | ±10 | 8.42 | <0.01 |
| **3** | Wheezing | 2.32 | 0.31 | 2.01 | ±0.59 | ±0.79 | ±0.20 | 2.54 | <0.01 |
| **4** | BHT | 12.33 | 19 | 7.33 | ±12.02 | ±2.52 | ±9.52 | 4.9 | <0.01 |
| **5** | PEFR | 151.5 | 242.5 | 91 | ±60.05 | ±44.31 | ±15.74 | 9.45 | <0.01 |
| **6** | Respiratory Rate | 24.81 | 20.78 | 4.03 | ±2.43 | ±1.84 | ±1.16 | 10.33 | <0.01 |
| **7** | Ab. EC | 503.2 | 328.9 | 174.3 | ±571.73 | ±150.42 | ±421.31 | 2.28 | <0.01 |
| **8** | ESR | 32.02 | 19.52 | 12.5 | ±25.86 | ±34.16 | ±8.3 | 2.26 | <0.01 |

**TABLE 4. CHEMICAL STRUCTURE, BIOACTIVITY AND TOXICITY OF ALBIZIA LEBBECK CHEMICAL COMPOUND**

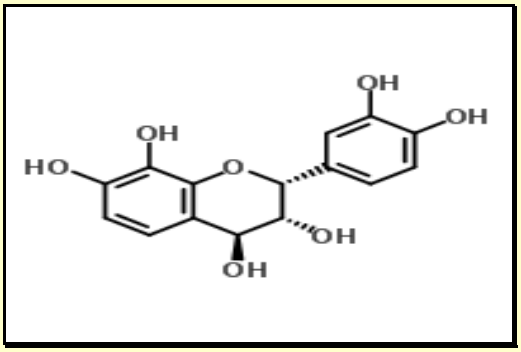
**Chemical Structure of D-Catechin**




**Bioactivity and Toxicity of D-Catechin**

| | |
|---|---|
| Mutagenicity | No |
| Tumorogenicity | No |
| Irritant | No |
| Reproductive Effective | No |
| C Log P | 1.88 |
| Solubility | -1.76 |
| Molecular Weight | 290 |
| Drug Likeliness | 1.92 |
| Drug Score | 0.87 |

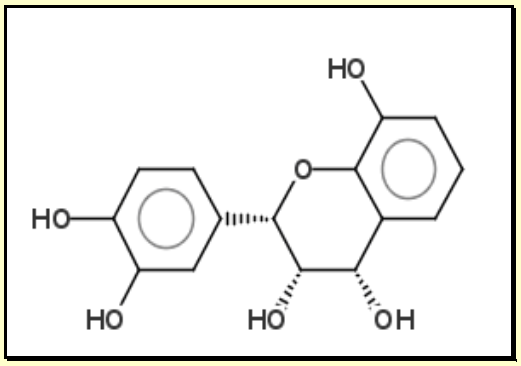
**Chemical Structure of Melacacid**




**Bioactivity and Toxicity of Melacacid**

| | |
|---|---|
| Mutagenicity | No |
| Tumorogenicity | No |
| Irritant | No |
| Reproductive Effective | No |
| C Log P | 1.1 |
| Solubility | -1.22 |
| Molecular Weight | 306 |
| Drug Likeliness | 1.2 |
| Drug Score | 0.83 |

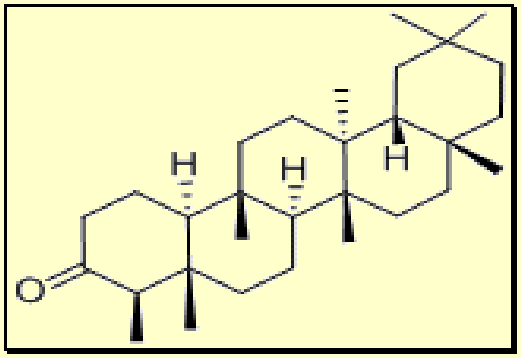
**Chemical Structure of Lebbecacidin**




**Bioactivity and Toxicity of Lebbecacidin**

| | |
|---|---|
| Mutagenicity | No |
| Tumorogenicity | No |
| Irritant | No |
| Reproductive Effective | No |
| C Log P | 1.4 |
| Solubility | -1.51 |
| Molecular Weight | 290 |
| Drug Likeliness | 1.26 |
| Drug Score | 0.83 |

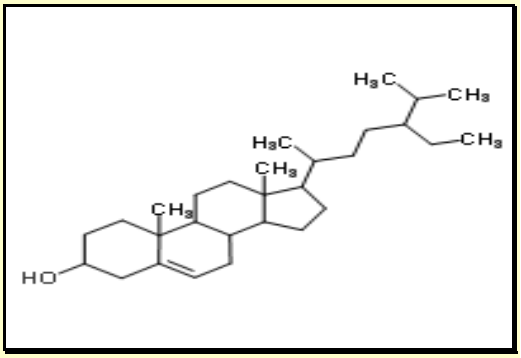
**Chemical Structure of Friedelin**




**Bioactivity and Toxicity of Friedelin**

| | |
|---|---|
| Mutagenicity | No |
| Tumorogenicity | No |
| Irritant | No |
| Reproductive Effective | No |
| C Log P | 6.91 |
| Solubility | -6.97 |
| Molecular Weight | 426 |
| Drug Likeliness | -3.31 |
| Drug Score | 0.14 |

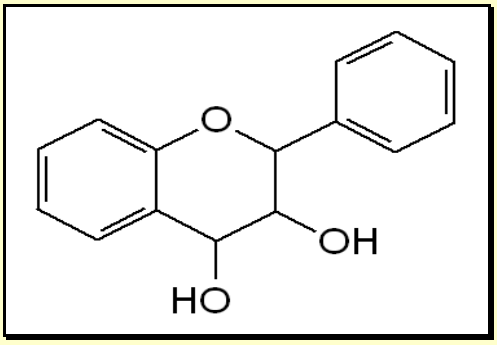
**Chemical Structure of B-Sitosterol**




**Bioactivity and Toxicity of B-Sitosterol**

| | |
|---|---|
| Mutagenicity | No |
| Tumorogenicity | No |
| Irritant | No |
| Reproductive Effective | Yes |
| C Log P | 8.24 |
| Solubility | -6.97 |
| Molecular Weight | 414 |
| Drug Likeliness | -4.48 |
| Drug Score | 0.11 |

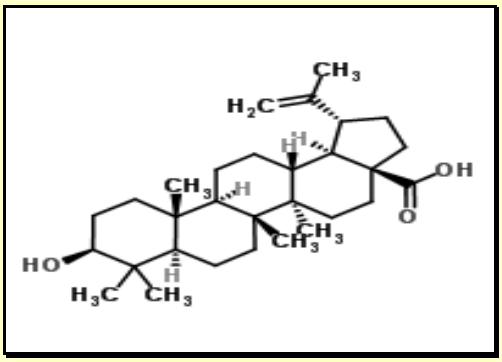
**Chemical Structure of Leucoanthocynadine**




**Bioactivity and Toxicity of Leucoanthocynadine**

| | |
|---|---|
| Mutagenicity | No |
| Tumorogenicity | No |
| Irritant | No |
| Reproductive Effective | No |
| C Log P | 2.3 |
| Solubility | -2.4 |
| Molecular Weight | 242 |
| Drug Likeliness | 0.29 |
| Drug Score | 0.72 |

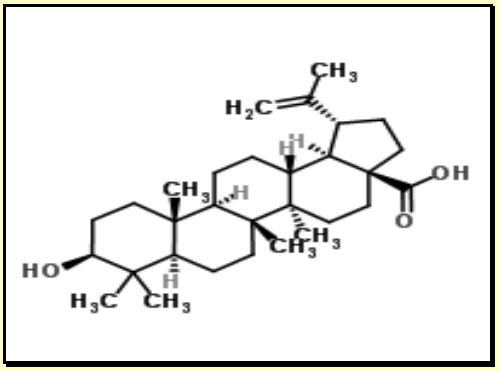
**Chemical Structure of Leucocyanidin**




**Bioactivity and Toxicity of Leucocyanidin**

| | |
|---|---|
| Mutagenicity | No |
| Tumorogenicity | No |
| Irritant | No |
| Reproductive Effective | No |
| C Log P | 1.1 |
| Solubility | -1.22 |
| Molecular Weight | 306 |
| Drug Likeliness | 1.2 |
| Drug Score | 0.83 |

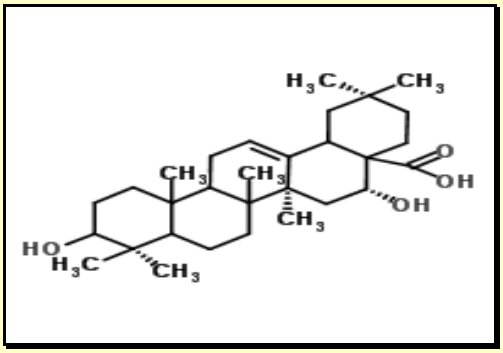
**Chemical Structure of Betulinic Acid**




**Bioactivity and Toxicity of Betulinic Acid**

| | |
|---|---|
| Mutagenicity | No |
| Tumorogenicity | No |
| Irritant | Yes |
| Reproductive Effective | No |
| C Log P | 5.44 |
| Solubility | -6.28 |
| Molecular Weight | 456 |
| Drug Likeliness | -21.4 |
| Drug Score | 0.05 |

**Chemical Structure of Echinocystic Acid**




**Bioactivity and Toxicity of Echinocystic Acid**

| | |
|---|---|
| Mutagenicity | No |
| Tumorogenicity | No |
| Irritant | No |
| Reproductive Effective | No |
| C Log P | 4.65 |
| Solubility | -5.73 |
| Molecular Weight | 472 |
| Drug Likeliness | -1.63 |
| Drug Score | 0.24 |

**TABLE 5: BINDING AFFINITY RESULTS AFTER DOCKING STUDIES**

| Sl No | Ligand | Protein | Binding Affinity(kcal/mol) |
|---|---|---|---|
| **1** | D – Catachin | IL 3 | -6.6 |
| | | IL 4 | -6.8 |
| | | IL 5 | -8.0 |
| | | IL 9 | -6.0 |
| | | IL 10 | -6.3 |
| | | IL 13 | -7.1 |
| | | TNF –α | -6.6 |
| **2** | Melacidin | IL 3 | -7.2 |
| | | IL 4 | -6.3 |
| | | IL 5 | -8.1 |
| | | IL 9 | -7.0 |
| | | IL 10 | -6.0 |
| | | IL 13 | -7.5 |
| | | TNF-α | -6.5 |
| **3** | Lebbecacidin | IL 3 | -7.2 |
| | | IL 4 | -7.0 |
| | | IL 5 | -8.3 |
| | | IL 9 | -7.1 |
| | | IL 10 | -6.3 |
| | | IL 13 | -7.9 |
| | | TNF-α | -7.8 |
| **4** | Leucocynidin | IL 3 | -7.0 |
| | | IL 4 | -6.5 |
| | | IL 5 | -7.5 |
| | | IL 9 | -6.7 |
| | | IL 10 | -6.2 |
| | | IL 13 | -7.1 |
| | | TNF-α | -6.2 |

No literature references described about the drug candidature of these compound. It is assumed that Lebbecacidin is having much external hydrogen bonding energy that leads to better binding than any other Ligands. Like other Ligands Lebbecacidin also shows good drug score with 0.83 and molecular weight 290.

## DISCUSSION AND CONCLUSION:

The Ayurveda literature mentions that Shirish can also be used in Asthma, so a detailed study was made to explore the concept and to find out the scientific cause behind. A two-fold attempt has been made that is in silico studies and clinical studies on Asthma and Shirish. In in-silico studies of the compounds of bark of A. lebbeck have been done and their bio- activity, toxicity and molecular properties have been assessed. Also the compounds have been filtered by Lipinski's rule of five. The filtered compounds have been considered for further analysis.

The pathway of Asthma has been studied and some of the major genes responsible for causing asthma such as IL-3, IL-4, IL-5, IL-9, IL-10, IL-13 and TNF-α were identified and selected. On screening the filtered compounds we found D-catechin, Melacidin, Lebbecacidin, Leucocynidine had a comparably better drug score. So, we docked these compounds with the major precursor proteins to check their binding affinity. Based on binding energy and hydrogen bond formation, docking results were analyzed by using Auto Dock tools-1.5.1. All the results were compared to find the best ligand which had inhibited the property of genes responsible for the cause of the disease. Based on this observation, Lebbecacidin is found to be most potent ligand among the other Ligands that binds with IL-5 at the minimum binding energy of -8.3 kcal/mol.

### Ethical statement

For the clinical study of the trial drug permission has been taken from Institutional Ethical Committee Govt. Ayurvedic College & Hospital, Jalukbari, Guwahati, Assam India. Reference No; IEC/13, 20-24. Dated 4/9/13.

**ACKNOWLEDGEMENTS:** Thus the *in silico* studies validated experimental analysis in the present study which further helped in identifying the potent molecule which can be used as a drug for the treatment of bronchial asthma. This method reduces the time and cost in designing a drug in laboratory and subsequently studies can be validated before it enters the clinical trials. The study gave us a transparent view of the role of the proper compound of the herb initially used which could be later employed to another similar pathway disorder.

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