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Research Article

A Review on Evaluation of antidepressant and In Silico Pharmacokinetics & Pharmacological Activities of *Albizia lebbbeck(L)*

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ABSTRACT

Depression existence a state of sadness may be defined as a neurotic disorder characterized by mental and functional activity, reduction in activity effort in thinking, loss of concentration, agitations in appetite, sleeping, and feelings of sadness, impossibility and generation of suicidal tendencies. It is a common and recurrent disorder causing significant morbidity and mortality worldwide. The antidepressant complexes used against depression are reported to be used also for treating pain, anxiety syndromes etc. They have been grouped in five different categories such as Tricyclic antidepressants (TCAs), Selective serotonin-reuptake inhibitors (SSRIs), Monoamine oxidase inhibitors (MAOIs), Serotonin-nor epinephrine reuptake inhibitor (SNRI) and Non-TCA antidepressants based on their mode of action. Most of the antidepressants have been reported to possess adverse effects on the well-being of operators. The present review article efforts on an updated current of antidepressants, their mechanism of actions, pathophysiology of these compounds, their side effects and the strategies to contest the drug induced toxicity. *Albizia lebbbeck (L.) Benth* is an significant traditional tree found throughout India. All part of this tree is considered as popular medication and used for treatment of various disease. Present investigate effort was supported out to identify the bioactive compound by phytochemical screening and to evaluate anti-inflammatory potential of aqueous leaf extract of *A. lebbbeck*. The phytochemical transmission of the leaf of *A. lebbbeck* shows the presence of alkaloid, flavonoid, tannin, phenol, saponin, glycoside and free amino acid.

KEYWORDS: Antidepressant drugs, Depression, Neurotransmitters, MAOIS, Psychoneurotic Disorder. etc

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INTRODUCTION: Depression is a common mental disorder that presents with depressed mood, loss of interest or pleasure, feeling of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentrations. Depression is a common and recurrent disorder accounting for significant morbidity and mortality worldwide. Depression affects approximately 8-12 per cent of the global population and is currently the leading cause of disability worldwide. In addition to certain conditions like difficulties in job, relationships, natural disasters, finances, child birth, catastrophic injury, loss of life of loved ones and menopause.^[1] Depression in general has three main forms such as

- i. Psychotic depression characterized by severe depression,
- ii. Postpartum depression characterized by perturbations in the levels of hormones and physical features after child birth and
- iii. Seasonal Affective Disorder (SAD) concerning specially the winter months with less sunlight.^[2] There is no single known cause of depression. Rather, it likely results from a combination of genetic, biochemical, environmental, and psychological suggesting a genetic link. However, depression can occur factors. Some types of depression tend to run in families, in people without family histories of depression as well.^[3]

Antidepressants and their classification

Imipramine was discovered in 1958 as an antidepressant regimen.^[4] The antidepressants have been divided into five groups:

- i. Tricyclic antidepressants (TCAs),
- ii. Selective serotonin-reuptake inhibitors (SSRIs),
- iii. Monoamine oxidase inhibitors (MAOIs),
- iv. Serotonin-norepinephrine reuptake inhibitor (SNRI) and
- v. Non-TCA antidepressants.

Pathophysiology of depression

There are no useful biomarkers or imaging abnormalities to determine pathophysiology of depression during life time. The post-mortem study of brain does not reveal any consistent structural or neurochemical abnormality. Majority of the currently available medications were discovered empirically. Most current theories are based on "amine hypothesis."^[5] The most important hypothesis of mood disorder is related to the alterations in the levels of biogenic amines.^[6] It states that depression is caused by a functional deficiency of catecholamines, particularly norepinephrine (NE), whereas mania is caused by a functional excess of catecholamines at the critical synapses in the brain. The occurrence of depression has been found to be associated with the alterations in the levels of biogenic amines in the brain such as NE, dopamine (DA) and epinephrine, indolamine, serotonin, 5- hydroxy tryptamine (5-HT) and two catecholamines.

Pharmacological treatment of depression

Since Kuhn introduced imipramine in the 1950s, the availability of antidepressant drugs has expanded

greatly, not only in terms of number, but also, and especially, in terms of diversity in the associated pharmacological effects. The first-generation antidepressants, the tricyclic antidepressants (TCAs) and MAO inhibitors (MAOIs), increase the concentrations of 5-HT and/or NE and are effective in alleviating the symptoms of depression. Although both types of drugs have been used with great success for many years, there are several undesirable side effects that limit their application. TCAs act on many other transmitter systems in the CNS and periphery, eg, the histaminergic or acetyl cholinergic systems,^[7] leading to sedation, hypotension, blurred vision, dry mouth, and other unwanted effects. In addition, TCAs may be life-threatening and fatal in overdose, especially due to their effects on the cardiovascular system.^[8] Also, the irreversible MAOIs have their own problems, such as an interaction with tyramine (the so-called "cheese effect"), which causes potentially lethal hypertension.^[6] The main problem with the less severe side effects is a reduction in compliance, patients often do not take a sufficient dosage for an adequate period of time and thus remain in an "undertreated" state. The effect of antidepressants on the NE and 5-HT receptor systems has been known for a long time, and the decreased sensitivities of β -adrenoceptors and cortical 5-HT_{2A} receptors have often been suggested to be a prerequisite for antidepressant action.^[9]

Mechanism

Neurotransmitters are endogenous chemicals that transmit signals across a synapse from one neuron to another 'target' neuron. Brain neurotransmitters might not be secreted in adequate amounts to alleviate mood disorders. The chemicals like serotonin, melatonin, and dopamine are the most important in brain for sense. Once the nerves are robbed of those neurotransmitters, they can't send messages to different nerves which leads to depression.^[10] The messages that are passed through the neurons are exhibited as emotions, behavior, temperature, appetite, or several alternative functions. The information sent depends on that neurons area unit activated and what a part of the brain is excited. Low levels of serotonin and norepinephrine within the conjunction area leads to depression. Hence medications like antidepressant used to treat this works by increasing the number of bound neurotransmitters in that particular part of the brain which enables to transmit the message. Each type of antidepressant works on brain with little difference, all antidepressant medications influence the neurotransmitters how to work in the brain, especially serotonin and norepinephrine,^[11] thus controlling the balance of the neurotransmitters.^[12]

SSRIs (selective serotonin reuptake inhibitors) and SNRIs (serotonin norepinephrine reuptake inhibitors) have different mechanisms of action. SSRI has three different serotonin reuptake inhibitors those are fluoxetine, paroxetine and sertraline.^[13] These have selective effect for both citalopram and fluvoxamine on the serotonin reuptake pump. It leads to primary increase in serotonin at the cell body and dendrites. So, SSRIs act by blocking the serotonin reuptake pump (5-HTT).^[14] Whereas SNRIs presumably block both 5-

HTT and the norepinephrine transporter (NET). Blocking these transporters prevents the neuron from vacuuming up excess neurotransmitters, permitting a lot of to stay within the synapse and stimulate postsynaptic receptors. SSRIs have important effect on NE as well, and the SNRIs behave much more like SSRIs. We extend levels of all 3 monoamines (serotonin, monoamine neurotransmitter, and dopamine), ought to be prescribing MAOIs (monoamine enzyme inhibitors). MAOIs aren't re-uptake blockers at all; they increase neurotransmitter levels by inhibiting MAO, associate enzyme that breaks down all 3 monoamines. Thus, MAOIs increase the amount of all 3 neurotransmitters thought crucial in depression, these are efficacy advantage over others. Tricyclic and tetracyclic antidepressants ease depression by affecting naturally occurring chemical messengers.^[15]

Cyclic antidepressants usually block the results of 2 neurotransmitters known as serotonin and norepinephrine these are available in the brain. This

looks to assist brain cells send and receive messages. The roles these chemicals have treat the depression. Serotonin receptor modulators utilized in the treatment of irritable intestine syndrome. Serotonin plays a major role within the initiation of peristaltic and humor reflexes, and in modulation of visceral sensations.^[16] Lithium is used for manic depression. Manic-depressive patients' expertise severe mood changes, starting from associate degree excited or frenzied state to depression or unhappiness. Until higher models of depression area unit devised, establishing the mode of action of antidepressants are trouble. The present focus has been on alterations to straightforward vegetative cell models primarily based around monoamine neurotransmitter and vasoconstrictive. Clearly, these models don't seem to be sufficient to fully make a case for the clinical effects of antidepressants. Additional complicated models, taking under consideration alternative transmitters, adaptive changes at the amount of the sequence.

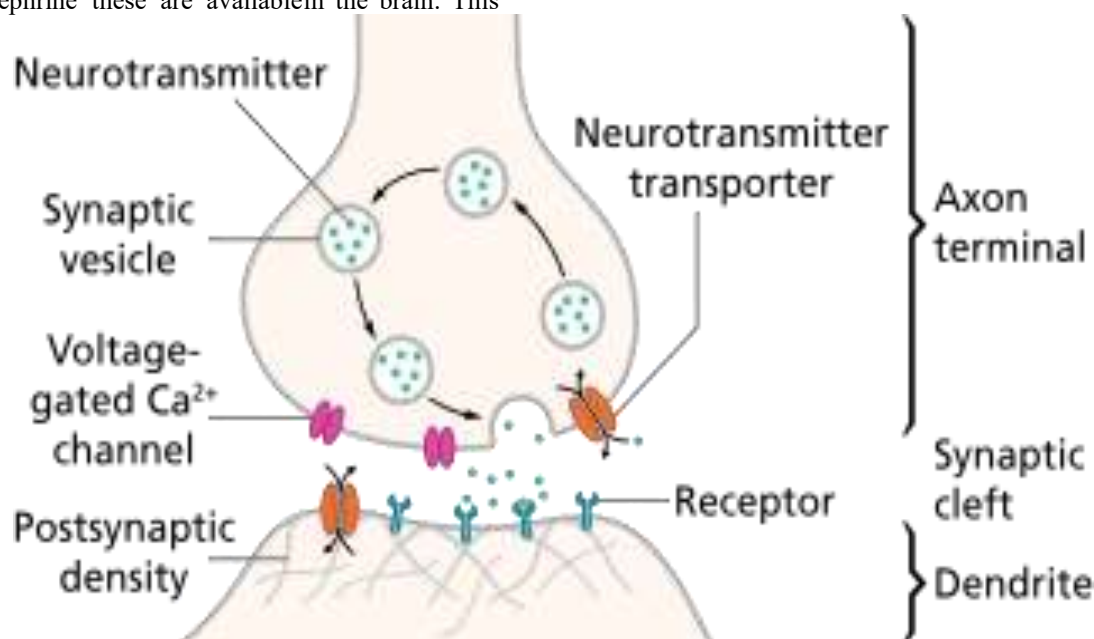


Fig 1: Mechanism of Action of Antidepressant Drug.

Side Effects

Antidepressants cause include nausea, vomiting, dizziness, headache, irritability, sleep disturbance, nightmares, psychosis, and seizures. In a child or adolescent must balance the risk of suicidal with the clinical need for the drug. Antidepressants leads to psychiatric disorders. Antidepressants accrued to change the behavior and thinking in children and adolescents. The primary medicament you are attempting may fit fine. Patients who are started on therapy should be closely observed for unusual changes in behavior.

Herbal drugs play important role in healthcare programs in treatment of various diseases including depression disorders. In India ayurveda is traditional medicinal system, assigns much importance to the pharmacological aspects of many plants. The term

ayurveda in Sanskrit consists of two words 'AYUR' 'meaning life and 'Veda' 'meaning knowledge or science thus. Ayurveda is science of life. Ayurveda is considered as the up Veda of Atharva which deals with different type of herb, plant, the anatomy and physiology of different organ of body and principles of treatment of diseases. Plant kingdom is rich of various medicinal species having their effect on nervous system. They are used or abused for medicinal or narcotic purpose, some of them like opium. pilocarpus and Brahmi have potential therapeutic uses also. Now a day 's pharmacological spectrum and biological efficiency of such herbal drugs can be suitably established due to development of various neuropharmacological testing of herbal drugs with effect on CNS¹⁷

HERB USED FOR DEPRESSION

Healing with herbs has a story as long as the human history itself, Neanderthal to tombs shows the presence of aromatic herbs-ones that are currently documented as medicinal herbs. Using herbs or their parts: leaves, roots, rhizomes, flowers, seeds, as well as their extracts or natural material isolated metabolites can act both as a prophylaxis or a cure disease and enhance general organs functioning especially immunologic system. Many herbs have a role in curing mood disorders. Natural cures (drugs) have different active compounds that may help to treat the condition holistically acting on the body of the patient, the more that depression affects the whole body, causing multi-organ dysfunction. The need for effective and well tolerated remedies for depression has influenced investigators to analysis of herb drugs and natural products which are traditionally used for depression treatment. The use of herbs or their parts: leaves, roots, rhizomes, flowers, seeds, natural strains as well as extracts or isolated metabolites is becoming more and more popular. Natural origin plays a role in treatment of health problems, and also in case of serious diseases such as depression. *Albizzia lebbeck* is a tropical species that belongs to *Albizzia* genus, mostly growing to an average height of 24 m, trunk width of 50 cm, and seed pods that contain 6–12 seeds. The plant is widely distributed in Australia, Asia, Africa, and Southern America¹⁸ The seeds of the plant demonstrate anti-tumour, antifungal, and antibacterial activities against HepG2 hepatoma cells, fungi *Rhizoctonia solans*, and *E. coli*.¹⁹ The leaves of the plant contain phytochemicals such as flavonoids, tannins, alkaloids, triterpenoid saponins, and cardiac *Albizzia lebbeck* is native to India, Pakistan, Thailand, Nepal, Bangladesh, Indonesia, Australia, Malaysia and naturalized in many other tropical and subtropical areas [1-2].

It is introduced as common road-side tree and is cultivated in West Indies, Africa, North and South America. It is dominant in semi-ever green vine forest it grows in a wide range of climates, covering an annual rainfall range of 600 - 2500 mm. It also has been grown successfully in areas with an annual rainfall as low as 400 mm. It grows in Himalayan valleys up to 1600 in. The species is adapted to a wide range of soil types, from acid soils to alkaline and saline conditions. glycosides that have therapeutic value.²⁰ *Albizzia lebbeck* is native to India, Pakistan, Thailand, Nepal, Bangladesh, Indonesia, Australia, Malaysia and naturalized in many other tropical and subtropical areas [1-2]. It is introduced as common road-side tree and is cultivated in West Indies, Africa, North and South

Ethnobotany

The ethnobotanical records reports the plant as astringent, used for treatment of boils, flu, gingivitis, pectoral problems, tumors, lung problems ²⁶ psychoactive ²⁷ The bark is used for the treatment of inflammation ²

Active Constituents

America. It is dominant in semi-ever green vine forest it grows in a wide range of climates, covering an annual rainfall range of 600 - 2500 mm. It also has been grown successfully in areas with an annual rainfall as low as 400 mm. It grows in Himalayan valleys up to 1600 in. The species is adapted to a wide range of soil types, from acid soils to alkaline and saline conditions ²¹ *A. lebbeck* (L.) Benth. is a moderate to large deciduous tree that reaches 18– 30 m in height with a trunk 50 cm to 1 m in diameter. Leaves are found to be bipinnate having length of 7.5–15 cm with 2-4 pairs of pinnae (50-100 mm long) and each pinna with 6–18 leaflets (up to 50 mm long). Foliage is pale green when young and gray-green at maturity. Flowers are white to cream colored, hemispheric pompons, having numerous 2.5– 3.8 cm long stamens and are very fragrant. The fruit is a pod, 15–30 cm in length and 2.5-5.0 cm in width, containing six to twelve seeds ²² It grows in wide range of climates. Mainly develops in rain forests and is adapted to wide range of soil types from acidic to alkaline and saline conditions ²³. The tree develops a straight pole when grown in dense forests, but is spreading and low branching in the open. Trees annually produce an abundance of seed from papery pods. It is used as an avenue tree, sometimes used to shade coffee and tea. Saponins and tannins in the bark can be used for making soap and in tanning, respectively. Bee keepers like the species for the light-colored honey its nectar provides, and the tree hosts the lac insect. Because of its soil-binding ability it is useful for soil conservation plantings ²⁴

Synonyms²⁵

- *Acacia lebbeck* (L.) Willd.
- *Acacia macrophylla* Bunge
- *Acacia speciosa* (Jacq.) Willd.
- *Albizzia latifolia* B. Boivin
- *Albizzia lebbeck* (L.) Benth. var. *leucoxydon* Hassk.
- *Albizzia lebbeck* (L.) Benth. var. *pubescens* Haines

Local Names

English names: Lebbeck, Lebbek Tree, Flea Tree, Fry wood, Koko and Woman's tongues Tree.

Sanskrit: Sirisha, Bhandi

Urdu: Tinia

Hindi: Siris, Saras

Telugu: Dirisinam

Tamil: Vakai Siridam

Kannada: Begemara

Malayalam: Neomexicana

Bengali/ Assamese: Sirish

The plant contains cardiac glycosides, flavonoids, saponins, tannins²⁹ The flowers contain various sterols, leaves contain pipelicolic acid derivatives, root contains echinocystic acid³⁰ The bark contains tannins, friedelin and β - sitosterol. Seeds contain crude protein, calcium, iron, phosphors, niacin and ascorbic acid. Amino acid composition of the protein is: arginine, histidine,

isoleucine, leucine, lysine, methionine, phenylalanine³¹

STUDY REPORT-LEBBECKOSIDE Physiochemical Properties

Two-dimensional structure of the Compound **Lebbeckoside** was retrieved from the literature.

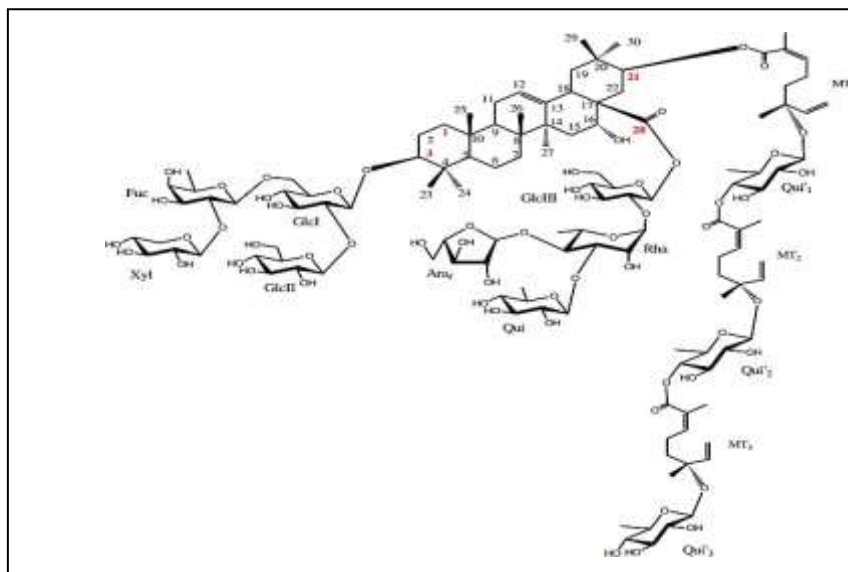


Fig 1: 2D structure of the compound

Three-dimensional structure of the compound Lebbeckoside was developed using the Marvin sketch and energy minimization was carried using

Avogadro. Best stable three-dimensional conformer of the compound was obtained and saved as PDB file for further use.

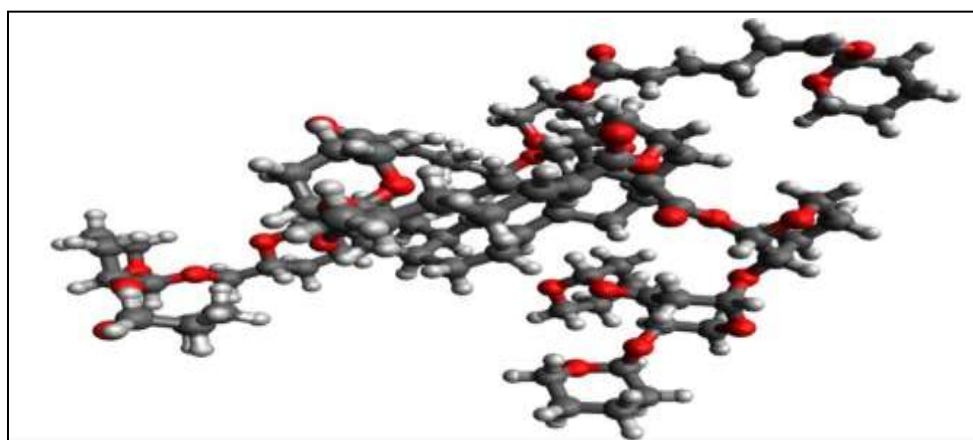


Fig 2: Three-dimensional structure of the compound

Table 1: Physiochemical Properties

Formula	Molecular weight	No of Rings (nRing)	No of rotatable bonds (nRot)	Log Po/w	No of H-bond Acceptor (nHA)	No of H-bond Donor (nHD)	Total polar surface area Å ²
C ₁₁₈ H ₁₈ 6O ₅₄	2467.18084	15	40	8.623	27.00	0	280.570

Table 2: Solubility and Lipophilicity Properties

Log S mg/ml	Log Po/w	Lipinski rule of 5	QED	SAscore
-5.947	8.623	Rejected	0.014	7.623

- Number of hydrogen bond acceptors. Sum of all O and N. Optimal: 0~12, based on Drug-LikeSoft rule.
- Number of hydrogen bond donors. Sum of all OHs

and NHs. Optimal: 0~7, based on Drug-Like Soft rule.

- Number of rotatable bonds. In some situation Amide

C-N bonds are not considered because of their high rotational energy barrier. Optimal: 0~11, based on Drug-Like Soft rule.

- Number of rings. Smallest set of smallest rings. Optimal: 0~6, based on Drug-Like Soft rule.
- The logarithm of aqueous solubility value. The first step in the drug absorption process is the disintegration of the tablet or capsule, followed by the dissolution of the active drug. Low solubility is detrimental to good and complete oral absorption, and early measurement of this property is of great importance in drug discovery.

Results interpretation: The predicted solubility of a compound is given as the logarithm of the molar concentration (log mol/L). Compounds in the range from -4 to 0.5 log mol/L will be considered proper.

LogP:

The logarithm of the n-octanol/water distribution coefficient. log P possess a leading position with considerable impact on both membrane permeability and hydrophobic binding to macromolecules, including the target receptor as well as other proteins like plasma proteins, transporters, or metabolizing enzymes.

QED: A measure of drug-likeness based on the concept of desirability. QED is calculated by integrating the outputs of the desirability functions based on eight drug-likeness related properties, including MW, log P, NHBA, NHBD, PSA, Nrotb, the number of aromatic rings (NAr), and the number of alerts for undesirable functional groups. Here, average descriptor weights were used in the calculation of QED.

Results interpretation: The mean QED is 0.67 for the attractive compounds, 0.49 for the unattractive compounds and 0.34 for the unattractive compounds considered too complex.

Empirical decision: > 0.67: excellent (green); ≤ 0.67: poor (red)

SA score:

Synthetic accessibility score is designed to estimate ease of synthesis of drug-like molecules, based on a

combination of fragment contributions and a complexity penalty. The score is between 1 (easy to make) and 10 (very difficult to make). The synthetic accessibility score (SAscore) is calculated as a combination of two components:

$$\text{SAscore} = \text{fragmentScore} - \text{complexityPenalty}$$

Results interpretation: high SAscore: ≥ 6, difficult to synthesize; low SAscore: < 6, easy to synthesize

Empirical decision: ≤ 6 : excellent (green); > 6: poor (red)

The Lipinski's Rule of Five, also known as the Rule of Five or simply RO5, is a guideline in drug discovery and development to assess the drug-likeness and pharmacokinetic properties of chemical compounds.

The Rule of Five provides a set of criteria that suggest whether a compound is likely to have good oral bioavailability and permeability across cell membranes, which are important factors for a compound to be considered as a potential drug candidate. The criteria are as follows:

Molecular Weight: The molecular weight should be less than or equal to 500 daltons. This criterion helps ensure that the compound is small enough to be efficiently absorbed in the gastrointestinal tract.

Lipophilicity (LogP): The octanol-water partition coefficient (LogP) should be less than or equal to 5. This parameter indicates the compound's hydrophobicity and its ability to cross cell membranes.

Hydrogen Bond Donors: The number of hydrogen bond donors (counting all nitrogen-hydrogen and oxygen-hydrogen bonds) should not exceed 5. This criterion helps assess the compound's ability to form hydrogen bonds with target proteins.

Hydrogen Bond Acceptors: The number of hydrogen bond acceptors (counting all nitrogen and oxygen atoms) should not exceed 10. This criterion is related to the compound's capability to interact with target proteins via hydrogen bonding.

- Total Polar surface area no greater than 140 Å²

PROPERTIES	LEBBECKOSIDE
ABSORPTION	
Human intestinal absorption	Yes >30%
Caco-2 permeability	-4.357 log cm/s
MDCK Permeability	7.9e-06 cm/s , Medium
DISTRIBUTION	
P-glycoprotein inhibitor	Yes (excellent)
Blood-brain barrier penetration	Yes
Plasma Protein Binding	91.083%
METABOLISM	
CYP3A4 substrate	Yes
CYP3A4 inhibition	Mildly
CYP2C19 inhibition	Yes
CYP2D6 substrate	No
CYP2D6 inhibition	No

CYP2C9 inhibition	No
EXCRETION	
T1/2 (half-life period)	0.000 hrs
Clearance rate	7.080 ml/min/kg

Its of ADME/T tests

PROPERTIES	LEBBECKOSIDE
ABSORPTION	
Human intestinal absorption	Yes >30%
Caco-2 permeability	-4.357 log cm/s
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METABOLISM	
CYP3A4 substrate	Yes
CYP3A4 inhibition	Mildly
CYP2C19 inhibition	Yes
CYP2D6 substrate	No
CYP2D6 inhibition	No
CYP2C9 inhibition	No
EXCRETION	
T1/2 (half-life period)	0.000 hrs
Clearance rate	7.080 ml/min/kg
TOXICITY	
Ames test	(---) non toxic
Rat Oral Acute Toxicity	(++) Toxic
Skin Sensitization	(+++) Toxic
Carcinogenicity	(---) Non toxic
Respiratory toxicity	(---) Non toxic
Hepatotoxicity (H-HT)	(+) medium toxic

HIA: Human intestinal absorption. As described above, the human intestinal absorption of an oral drug is the essential prerequisite for its apparent efficacy. What's more, the close relationship between oral bioavailability and intestinal absorption has also been proven and HIA can be seen as an alternative indicator for oral bioavailability to some extent.

Result interpretation: A molecule with an absorbance of less than 30% is considered to be poorly absorbed. Accordingly, molecules with a HIA >30% were classified as HIA- (Category 0), while molecules with a HIA < 30% were classified as HIA+ (Category 1). The output value is the probability of being HIA+, within the range of 0 to 1.

Empirical decision: 0-0.3: excellent (green); 0.3-0.7: medium (yellow); 0.7-1.0(++): poor (red)

Caco-2 Permeability:

Before an oral drug reaches the systemic circulation, it must pass through intestinal cell membranes via passive diffusion, carrier-mediated uptake or active transport processes. The human colon adenocarcinoma cell lines (Caco-2), as an alternative approach for the human

intestinal epithelium, has been commonly used to estimate in vivo drug permeability due to their morphological and functional similarities. Thus, Caco-2 cell permeability has also been an important index for an eligible candidate drug compound.

Results interpretation: The predicted Caco-2 permeability of a given compound is given as the log cm/s. A compound is considered to have a proper Caco-2 permeability if it has a predicted value >-5.15 log cm/s.

Empirical decision: > -5.15: excellent (green); otherwise: poor (red)

MDCK Permeability:

Madin-Darby Canine Kidney cells (MDCK) have been developed as an in vitro model for permeability screening. Its apparent permeability coefficient, Papp, is widely considered to be the in vitro gold standard for assessing the uptake efficiency of chemicals into the body. Papp values of MDCK cell lines are also used to estimate the effect of the blood-brain barrier (BBB).

Results interpretation: The unit of predicted MDCK

permeability is cm/s. A compound is considered to have a high passive MDCK permeability for a $P_{app} > 20 \times 10^{-6}$ cm/s, medium permeability for $2-20 \times 10^{-6}$ cm/s, low permeability for $< 2 \times 10^{-6}$ cm/s.

Empirical decision: $> 2 \times 10^{-6}$ cm/s: excellent (green), otherwise: poor (red)

Pgp-inhibitor:

The inhibitor of P-glycoprotein. The P-glycoprotein, also known as MDR1 or ABCB1, is a membrane protein member of the ATP-binding cassette (ABC) transporters superfamily. It is probably the most promiscuous efflux transporter, since it recognizes a number of structurally different and apparently unrelated xenobiotics; notably, many of them are also CYP3A4 substrates. Results interpretation: Category 0: Non-inhibitor; Category 1: Inhibitor. The output value is the probability of being Pgp-inhibitor, within the range of 0 to 1.

Empirical decision: 0-0.3: excellent (green); 0.3-0.7: medium (yellow); 0.7-1.0(++): poor (red)

BBB Penetration:

Drugs that act in the CNS need to cross the blood-brain barrier (BBB) to reach their molecular target. By contrast, for drugs with a peripheral target, little or no BBB penetration might be required in order to avoid CNS side effects.

Result interpretation: The unit of BBB penetration is cm/s. Molecules with $\log_{BB} > -1$ were classified as BBB+ (Category 1), while molecules with $\log_{BB} \leq -1$ were classified as BBB- (Category 0). The output value is the probability of being BBB+, within the range of 0 to 1.

Empirical decision: 0-0.3: excellent (green); 0.3-0.7: medium (yellow); 0.7-1.0(++): poor (red)

Plasma Protein Binding:

Plasma protein binding. One of the major mechanisms of drug uptake and distribution is through PPB, thus the binding of a drug to proteins in plasma has a strong influence on its pharmacodynamic behavior. PPB can directly influence the oral bioavailability because the free concentration of the drug is at stake when a drug binds to serum proteins in this process.

Result interpretation: A compound is considered to have a proper PPB if it has predicted value $< 90\%$, and drugs with high protein-bound may have a low therapeutic index.

Empirical decision: $\leq 90\%$: excellent (green); otherwise: poor (red).

Distribution of the compound under systemic circulation is necessary for considering any compound as a drug. In order to achieve a complete circulation and targeted delivery any compound should possess the basic ability to move around circulatory system for complete distribution. P-glycoprotein substrate signifies

the ability of a compound to penetrate inside any cellular organelles. Inability to react with P-glycoprotein proves the anti-sedimentation nature of the compound inside any cell. With good plasma binding & BBB penetration the drug has better chance for using it as local distribution throughout the body.

Caco-2 permeability is an important parameter in drug discovery and development because it provides information on a compound's potential for oral absorption. Compounds with high Caco-2 permeability are more likely to be absorbed efficiently across the intestinal epithelium, increasing their chances of reaching systemic circulation and exerting their desired pharmacological effects. Here the compound possess low Caco2 permeability.

The more negative the $\log K_p$ the less skin permeant the molecule.

Metabolic nature of the compound is predicted using ADME SIB portal and ADMESAR 2.0 sever. Cytochromes P450 (CYPs) are a monooxygenase superfamily of enzymes that contain heme as a cofactor. These proteins oxidise steroids, fatty acids, and xenobiotics in mammals, and are vital for chemical clearance as well as hormone synthesis and breakdown. The drug that suppresses CYP2C19 are likely to raise the plasma concentration of drugs. On the otherhand, they can be considered as inhibitors of these enzymes that is helpful during various treatments like epileptic seizures, Candidiasis, Bipolar disorder, and other psychological conditions.

Clearance rate:

The clearance of a drug. Clearance is an important pharmacokinetic parameter that defines, together with the volume of distribution, the half-life, and thus the frequency of dosing of a drug.

Result interpretation: The unit of predicted CL penetration is ml/min/kg. >15 ml/min/kg: high clearance; 5-15 ml/min/kg: moderate clearance; <5 ml/min/kg: low clearance.

Empirical decision: ≥ 5 : excellent ; < 5 : poor

T1/2 Half-life:

The half-life of a drug is a hybrid concept that involves clearance and volume of distribution, and it is arguably more appropriate to have reliable estimates of these two properties instead.

Result interpretation: Molecules with $T_{1/2} > 3$ were classified as $T_{1/2}^-$ (Category 0), while molecules with $T_{1/2} \leq 3$ were classified as $T_{1/2}^+$ (Category 1). The output value is the probability of being $T_{1/2}^+$, within the range of 0 to 1.

Empirical decision: 0-0.3: excellent; 0.3-0.7: medium; 0.7-1.0: poor

The compound's excretion properties also reveal moderate clearance rate, implying that it may or may not induce persistent damage to the organ system by sedimentation.

Finally, toxicity assessment was carried out using ADMETlab2.0 to analyse and estimate the level of toxicity, towards different panel of tests including Carcinogenicity, Respirational toxicity and Hepatotoxicity.

AMES Toxicity

The Ames test for mutagenicity. The mutagenic effect has a close relationship with the carcinogenicity, and it is the most widely used assay for testing the mutagenicity of compounds. Result interpretation: Category 0: AMES negative (-); Category 1: AMES positive (+). The output value is the probability of being toxic, within the range of 0 to 1.

Empirical decision: 0-0.3: excellent (green); 0.3-0.7: medium (yellow); 0.7-1.0(++): poor (red)

Rat Oral Acute Toxicity:

Determination of acute toxicity in mammals (e.g. rats or mice) is one of the most important tasks for the safety evaluation of drug candidates.

Result interpretation: Category 0: low-toxicity, > 500 mg/kg; Category 1: high-toxicity; < 500mg/kg. The output value is the probability of being toxic, within the range of 0 to 1.

Empirical decision: 0-0.3: excellent (green); 0.3-0.7: medium (yellow); 0.7-1.0(++): poor (red)

Skin Sensitization:

Skin sensitization is a potential adverse effect for dermally applied products. The evaluation of whether a compound, that may encounter the skin, can induce allergic contact dermatitis is an important safety concern.

Result interpretation: Category 1: Sensitizer; Category 0: Non-sensitizer. The output value is the probability of being toxic, within the range of 0 to 1.

Empirical decision: 0-0.3: excellent (green); 0.3-0.7: medium (yellow); 0.7-1.0(++): poor (red)

Carcinogenicity:

Among various toxicological endpoints of chemical substances, carcinogenicity is of great concern because of its serious effects on human health. The carcinogenic mechanism of chemicals may be due to their ability to damage the genome or disrupt cellular metabolic processes. Many approved drugs have been identified as carcinogens in humans or animals and have been withdrawn from the market.

Result interpretation: Category 1: carcinogens; Category 0: non-carcinogens. Chemicals are labelled as active (carcinogens) or inactive (non-carcinogens) according to their TD50 values. The output value is the probability of being toxic, within the range of 0 to 1. Empirical decision: 0-0.3: excellent (-); 0.3-0.7: medium; 0.7-1.0(++): poor (+++)

Respiratory toxicity:

Among these safety issues, respiratory toxicity has become the main cause of drug withdrawal. Drug-induced respiratory toxicity is usually underdiagnosed because it may not have distinct early signs or symptoms in common medications and can occur with significant morbidity and mortality. Therefore, careful surveillance and treatment of respiratory toxicity is of great importance.

Result interpretation: Category 1: respiratory toxicants; Category 0: non-respiratory toxicants. The output value is the probability of being toxic, within the range of 0 to 1.

Empirical decision: 0-0.3: excellent (-); 0.3-0.7: medium (+); 0.7-1.0(++): poor (+++)

H-HT

The human hepatotoxicity. Drug induced liver injury is of great concern for patient safety and a major cause for drug withdrawal from the market. Adverse hepatic effects in clinical trials often lead to a late and costly termination of drug development programs.

Result interpretation: Category 0: H-HT negative (-); Category 1: H-HT positive (+). The output value is the probability of being toxic, within the range of 0 to 1.

Empirical decision: 0-0.3: excellent (green); 0.3-0.7: medium (yellow); 0.7-1.0(++): poor (red) Further LD 50 value of the compound was estimated using a variety of toxicity models including Rat, Mouse and Fish.

Table 2: Results of LD 50 value of the compound estimated with rat toxicity model

Rat IP LD50 (mg/kg)	Rat IV LD50 (mg/kg)	Rat Oral LD50 (mg/kg)	Rat SC LD50 (mg/kg)
61,850	23,780	196,300	0,181

Note:

LD50-CLASS
≤ 50 - fatal if swallowed (I)
$5 < LD \leq 50$ - fatal if swallowed (II) $50 < LD \leq 300$ – Toxic if swallowed
$300 < LD \leq 2000$ – Harmful
$2000 < LD \leq 5000$ – May be harmful
$LD > 5000$ – Non toxic

PA	PI	Bio-activity
0,828	0,009	Antineoplastic
0,790	0,003	Transcription factor NF kappa B stimulant
0,790	0,003	Transcription factor stimulant
0,793	0,006	Caspase 3 stimulant
0,682	0,014	Glyceryl-ether monooxygenase inhibitor
0,660	0,009	Hepatoprotectant
0,660	0,017	Hypolipemic
0,647	0,008	Beta glucuronidase inhibitor
0,650	0,023	Immunosuppressant
0,626	0,011	Alcohol O-acetyltransferase inhibitor
0,590	0,010	Mycothiols-S-conjugate amidase inhibitor
0,580	0,008	Caspase 8 stimulant
0,576	0,011	Chemopreventive
0,587	0,028	Apoptosis agonist
0,566	0,022	Antifungal
0,556	0,013	Bilirubin oxidase inhibitor
0,553	0,022	Dermatologic
0,497	0,011	Wound healing agent
0,497	0,015	Myc inhibitor
0,497	0,015	P-glycoprotein substrate
0,480	0,040	Immunostimulant
0,444	0,018	Antineoplastic (lung cancer)
0,447	0,022	Antibacterial
0,435	0,011	Protein synthesis inhibitor
0,440	0,017	Hepatic disorders treatment
0,523	0,108	CYP2H substrate
0,455	0,049	Cholesterol antagonist
0,432	0,041	Membrane permeability enhancer
0,398	0,014	Phospholipase A1 inhibitor
0,413	0,030	Gestagen antagonist
0,412	0,036	Prostate disorders treatment
0,412	0,047	Interleukin 2 agonist
0,491	0,142	Antieczematic
0,387	0,049	CYP17 inhibitor
0,406	0,084	Antiviral (Rhinovirus)
0,330	0,011	Nitric oxide antagonist

0,333	0,015	Antiacne
0,353	0,061	Antimetastatic
0,375	0,096	CYP3A substrate
0,302	0,023	Antioxidant
0,373	0,110	Antiinflammatory
0,350	0,091	Lactase inhibitor
0,260	0,011	Antineoplastic antibiotic
0,294	0,051	Proliferative diseases treatment
0,293	0,059	RNA synthesis inhibitor
0,288	0,058	Antineoplastic (breast cancer)

Pa (probability "to be active") estimates the chance that the studied compound is belonging to the sub-class of active compounds. Pi (probability "to be inactive") estimates the chance that the studied compound is belonging to the sub-class of inactive compounds. Pa greater than 7 Confirm the bioactivity and Pa greater than 5 indicates the Probable occurrence of the bioactivity. Pa less than 3 indicates the inactiveness of the particular compound towards that bioactivity

Pharmacological Activities of Albizia Lebbeck (L.) Benth.

The various parts of this plant possess a wide range of pharmacological activities such as antimicrobial, analgesic, anti-inflammatory, immunomodulatory, anti-arthritis, antiasthmatic, antioxidant, antidiarrhoeal, anticonvulsant, mast cell stabilization, anti-anaphylactic, steroidogenic, nootropic, antifertility, antihistaminic, antitumor, antiulcer etc.

Antibacterial and Antifungal Activity of pods, seeds, flowers and roots

Shakir Ahmad Shahid et al.³² studied the in vitro antibacterial and antifungal activities crude methanolic extracts of pods, seeds, flowers and roots of Albizzia lebeck Benth. and Acacia leucophloea (Roxb.) Willd. Antibacterial study was evaluated for six bacterial species of both gram positive and gram-negative types including *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella typhi*, *Proteus mirabilis* and *Bacillus subtilis*. When compared with gentamicin and Gemifloxacin it indicated that the plant extracts have potent activity against all tested microorganisms. The antifungal activity of the extracts was evaluated against six fungal strains including *Aspergillus parasiticus*, *Aspergillus Niger*, *Candida albicans*, *Aspergillus effusus*, *Fusarium solani* and

Antimicrobial activity of seeds

S.H.K.R. Prasad et al.³³ investigated the antimicrobial activity of the methanolic and chloroform extracts of seeds of Albizzia lebeck(L.) Benth. against *Escherichia coli*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Aspergillus niger*, *Aspergillus fumigatus* and *Candida albicans*, Both solvent extracts were found to be effective against all the tested organisms.

Antidiarrheal activity of stem bark

Neelam Balekar et al.³⁴ performed a study to substantiate the traditional claim of the antidiarrhoeal

activity of ethanolic stem bark extract of Albizzia lebeck Linn. in rats. Castor oil-induced diarrhea, castor oil magnesium sulphate-induced enteropooling, and gastrointestinal motility test using charcoal meal models were examined. The extract inhibited peristaltic movements in charcoal meal test, intestinal fluid secretions in castor oil as well as magnesium sulphate induced enteropooling which confirmed its antidiarrhoeal activity, might be due to its high flavonoid content.

Analgesic and Anti-Inflammatory of bark

Achinto Saha et al.³⁵ studied the analgesic and anti-inflammatory of the extract of the bark of Albizzia lebeck Benth. obtained by cold extraction of mixture of equal proportions of petroleum ether, ethyl acetate and methanol. In rat paw edema model induced by carrageenan, the extract at the 400 mg/kg dose level showed 36.68% ($p < 0.001$) inhibition of edema volume at the end of 4h. In the acetic acid-induced writhing test, the extract at the 200 and 400 mg/kg dose level showed 39.9 % and 52.4 % inhibition of writhing, respectively. In radiant heat tail-flick method the crude extract reduced 40.74% ($p < 0.001$) and 61.48% ($p < 0.001$) elongation of tail flicking time 30 minutes after.

Analgesic and Anti-Inflammatory of bark

N. Prakash Babu et al.³⁶ the anti-inflammatory activity of different organic solvent extracts of Albizzia lebeck bark using the carrageenan, dextran, cotton pellet and Freund's complete adjuvant induced rat models. The extracts of petroleum ether, chloroform and ethanol were administered at the concentrations of 100, 200 and 400 mg/kg body weight. The petroleum ether and ethanol extracts at 400 mg/kg, showed maximum inhibition of inflammation induced by carrageenan (petroleum ether—48.6%; ethanol—59.57%), dextran (petroleum ether—45.99%; ethanol—52.93%), cotton pellet (petroleum ether—34.46%; ethanol—53.57%) and Freund's adjuvant (petroleum ether—64.97%; ethanol—68.57%).

Antiarthritic activity

Nimish Pathak et al.³⁷ studied the anti-arthritis activity of methanolic bark extract of Albizzia lebeck by Freund's complete adjuvant induced- arthritis induce arthritis model in rats and bone erosion turnover was studied by analyzing various markers of bone erosion like histological and radiological analysis of the joints. It was concluded that Albizzia lebeck methanolic

extract (AL) possesses strong anti-arthritis property by modulating bone erosion.

Anti-asthmatic activity of stem bark

S. Kumar et al.³⁸ conducted the anti-asthmatic activity of *Albizzia lebbek* on 81 patients at I.P.D. and O.P.D. level. Stem bark decoction in a dose of 50 ml thrice daily for 6 weeks, supported by light diet. A significant increase in PEF and considerable decrease in total leukocyte count, eosinophil count and E.S.R. were observed. From the study conducted, it was found that 56 % (28) cases has shown good response, 38 % (19) cases shown fair response, 6 % cases shown poor response and 31 cases were dropouts. It was concluded that formulation can be used as an effective drug in Bronchial asthma with detailed observational studies.

Anti-Asthmatic and Anti-Anaphylactic Activity of bark and flower

R.M. Tripathi et al.³⁹ evaluated the anti-asthmatic and anti-anaphylactic activity of the decoction of the bark and flower of *Albizzia lebbek*. The decoctions were found to protect the guinea pig against histamine as well as acetylcholine induced broncho-spasm. Chronic treatment with bark decoction has also protected the sensitized guinea pigs against antigen challenge. However, there was no significant effect on the rat mesenteric mast cell count and had not protected the mast cell from the disruption induced by compound 48/80. The drug inhibited the rate of disruption of mast cells induced by antigen in sensitized albino rats. The antiasthmatic and antianaphylaxis activities of the drug cannot be wholly due to smooth muscle relaxant, antihistamine or antispasmodic activity nor are mediated through stability of mast cells or adrenal gland. The effect seems to be due to inhibition of phenomenon of sensitization.

Steroidogenic Effect

Pratibha Tripathi et al.⁴⁰ studied the steroidogenic effect of alcoholic extract of *Albizzia lebbek*. The dose effect relationship was studied and 200 mg/Kg. of body weight had been found to be maximum effective dose in terms of stimulation of adrenals and rise in plasma cortisol. Vitamin C and Cholesterol content of adrenals has been estimated after the administration of the drug and a strictly significant fall was noted as compared to control. Thus the steroidogenic action of *A. lebbek* was inferred and action was explained to be like Adreno corticotrophic hormone.

Nootropic activity of leaves

S.D. Chintawar et al.⁴¹ studied the effect of saponin containing n-butanolic fraction extracted from leaves of *Albizzia lebbek* on learning and memory in albino mice using passive shock avoidance paradigm and the

elevated plus maze. Significant improvement was observed in the retention ability of the normal and amnesic mice as compared to their respective controls. They also studied the effects of butanolic fraction on the behavior influenced by serotonin (5-HT), noradrenaline and dopamine. The brain levels of serotonin, gamma-aminobutyric acid and dopamine were also estimated and correlated the behavior with neurotransmitter levels. The brain concentrations of GABA and dopamine were found to be decreased, whereas the 5-HT level was increased. The data indicate the involvement of monoamine neurotransmitters in the nootropic action of butanoic fraction of *A. lebbek*.

Nootropic and anxiolytic activity of Albizzia lebbek leaves

H.D. Une et al.⁴² studied the effect of n-butanolic fraction extracted from dried leaves of *Albizzia lebbek* containing saponin on cognitive behavior and anxiety in albino mice. Elevated plus maze was used for both nootropic and anxiolytic activity. The nootropic activity was evaluated by recording the effect on the transfer latency, whereas anxiolytic activity was evaluated by studying its effect on the duration of occupancy in the closed arm. Results showed the significant improvement in the retention ability of the normal and amnesic mice as compared to their respective controls. Animals treated with butanolic fraction spent more time in the open arm in a dose-dependent manner. The data suggested involvement of gamma-aminobutyric acid (GABA) in the nootropic and anxiolytic activity of saponins.

Antifertility activity of pods

Rakesh Chaudhary et al.⁴³ evaluated the antifertility activity of triterpenes isolated from *Albizzia lebbek* (L.) Benth pods in male albino rats. Testicular sperm count, epididymal sperm count and motility were assessed. Biochemical and histological analysis was performed in blood samples and reproductive organs. A significant reduction in the weight of testis, epididymides, seminal vesicle and ventral prostate were observed. Testicular sperm count, epididymal sperm count and motility were significantly reduced when compared to controls. spermatogenesis was depressed in various stages. Production of primary spermatocytes, secondary spermatocytes and step-19 spermatids declined. The size of seminiferous tubules reduced. Cross sectional surface area of Sertoli cell as well as its counts was found to be reduced significantly, Leydig cell nuclear area and number of mature Leydig cells were decreased. Serum testosterone level showed significant reduction after triterpenes feeding. Biochemical parameters of tissues i.e. protein, sialic acid, glycogen, cholesterol content of testis and seminal vesicular fructose showed significant reduction.

Anti-histaminic activity of bark

Islam Mohammed Nurul et al.⁴⁵ evaluated that the bark extract of *Albizzia lebbek* inhibit histamine signaling in TDI-sensitized rats through suppression of H1R and HDC gene transcriptions. Compounds that suppress

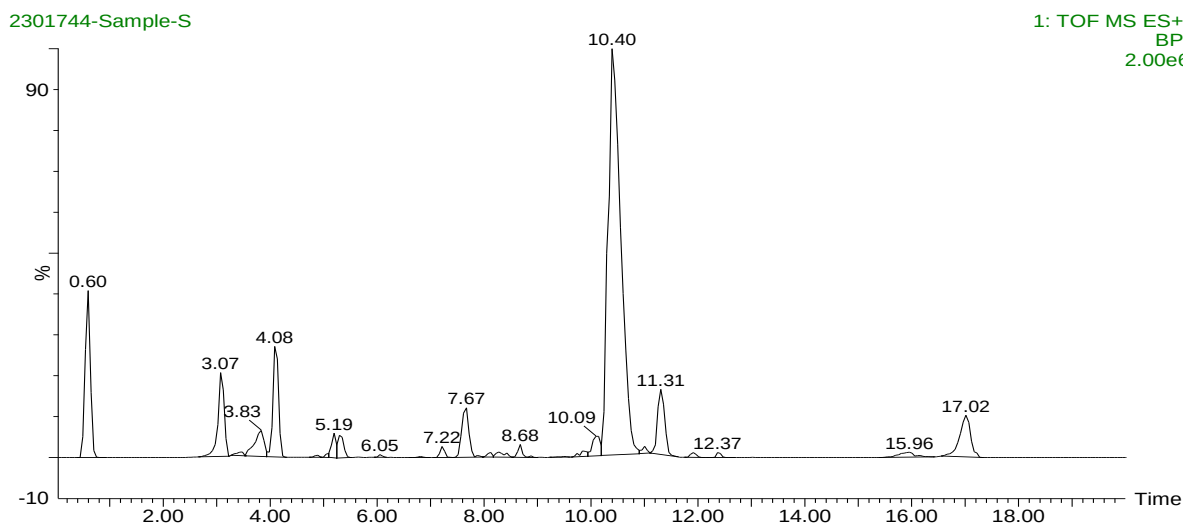
histamine signaling should be promising candidates as anti-allergic drugs. Pretreatment with the extract suppressed TDI- induced H1R and HDC mRNA elevations as well as [³H] mepyramine binding, HDC activity, and histamine content in the nasal mucosa. The extract also suppressed TDI.

Sample Preparation: 10mg of the sample extract is dissolved in 2mL of ethanol. Filtered and injected.

Instrumentation: The Acquity H-class UPLC (Waters Corporation, Milford, MA, USA) was employed, which had an integrated vacuum degasser, automatic sample manager (Serial # C10UPA554M, Waters Corporation, Singapore), ultra-performance binary solvent manager (Serial # C10UPB081A, Waters Corporation, Singapore), and injection volume range of up to 100 µL with an optional extension loop. A C18 stationary phase (BEH C18, 50 x 1.0mm, 1.7µ) was used for chromatographic separation. A photodiode array detector (DAD) was employed in conjunction with a Xevo G2-XS QToF (Serial # YFA1548, Waters Corporation, Wilms low, UK) for mass spectrometric

(MS) detection.

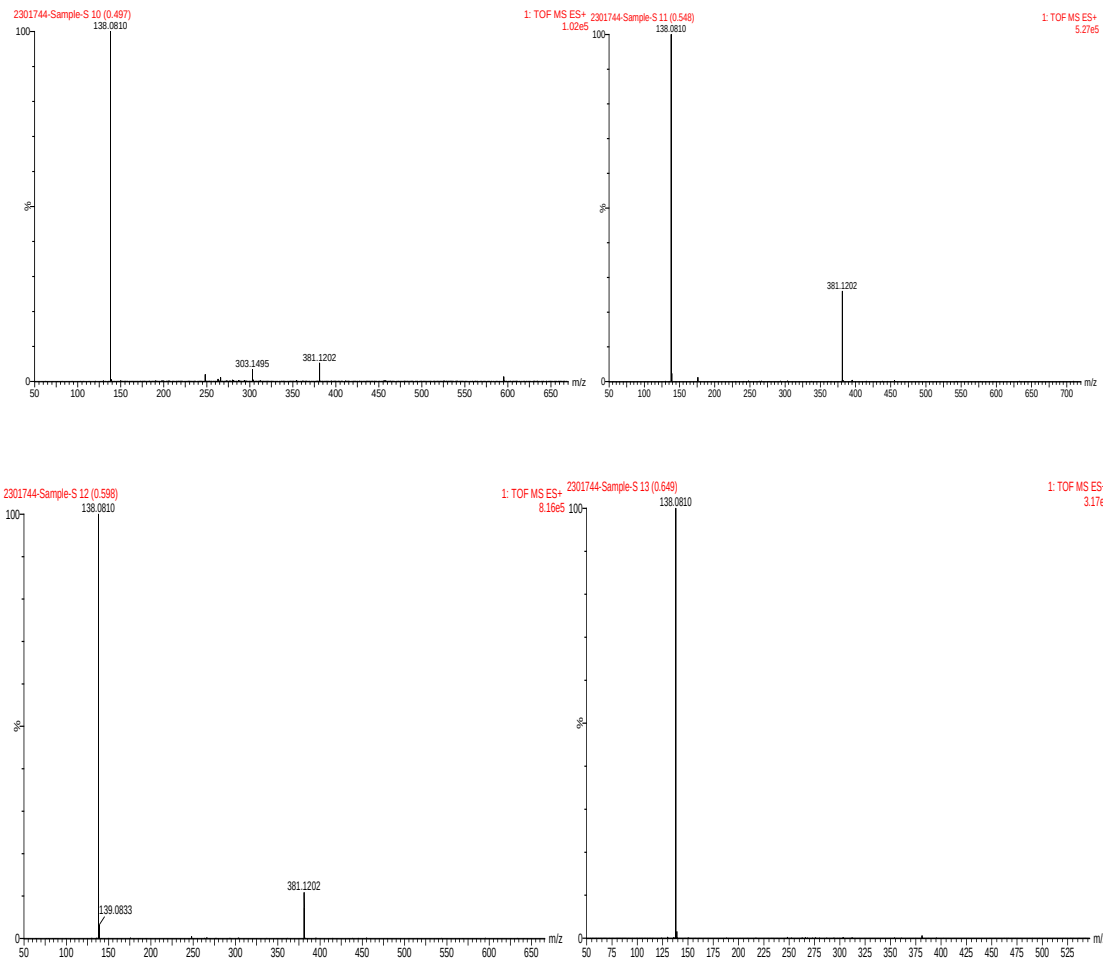
Method: The Mobile Phase is made up of 0.1% Formic acid in Water as an aqueous phase (A) and acetonitrile as an Organic modifier (B), and it is delivered at a flow rate of 0.2 mL/min in the following gradient: initially %B is kept at 2% for 1 minute; 1 to 6 minutes (2 to 50% B), 6 to 12 minutes (50 to 95% B), held for 4 minutes, 16 to 17 minutes (95 to 2% B) and held at 2% for 3 minutes. The sample was injected in a volume of 5 µL. The column oven temperature was kept at an optimal level throughout the chromatographic run (22°C). For MS detection, a positive and negative polarity electrospray combined ionization (ESCI) source was used. The optimal instrument and acquisition parameters were as follows: 50 L/hr. cone gas (nitrogen) flow; 750 L/hr. desolvation gas (nitrogen) flow; 450°C probe temperature; 30 V sampling cone voltage; 150°C source temperature; 80 V source offset voltage; the collision energy ramp varies from 6 eV-50eV (Argon, collision gas), and a mass range of 50 to 2000 m/z. To acquire and process data, Waters Corporation's Mass Lynx software (V4.1, Milford, MA, USA) was used.



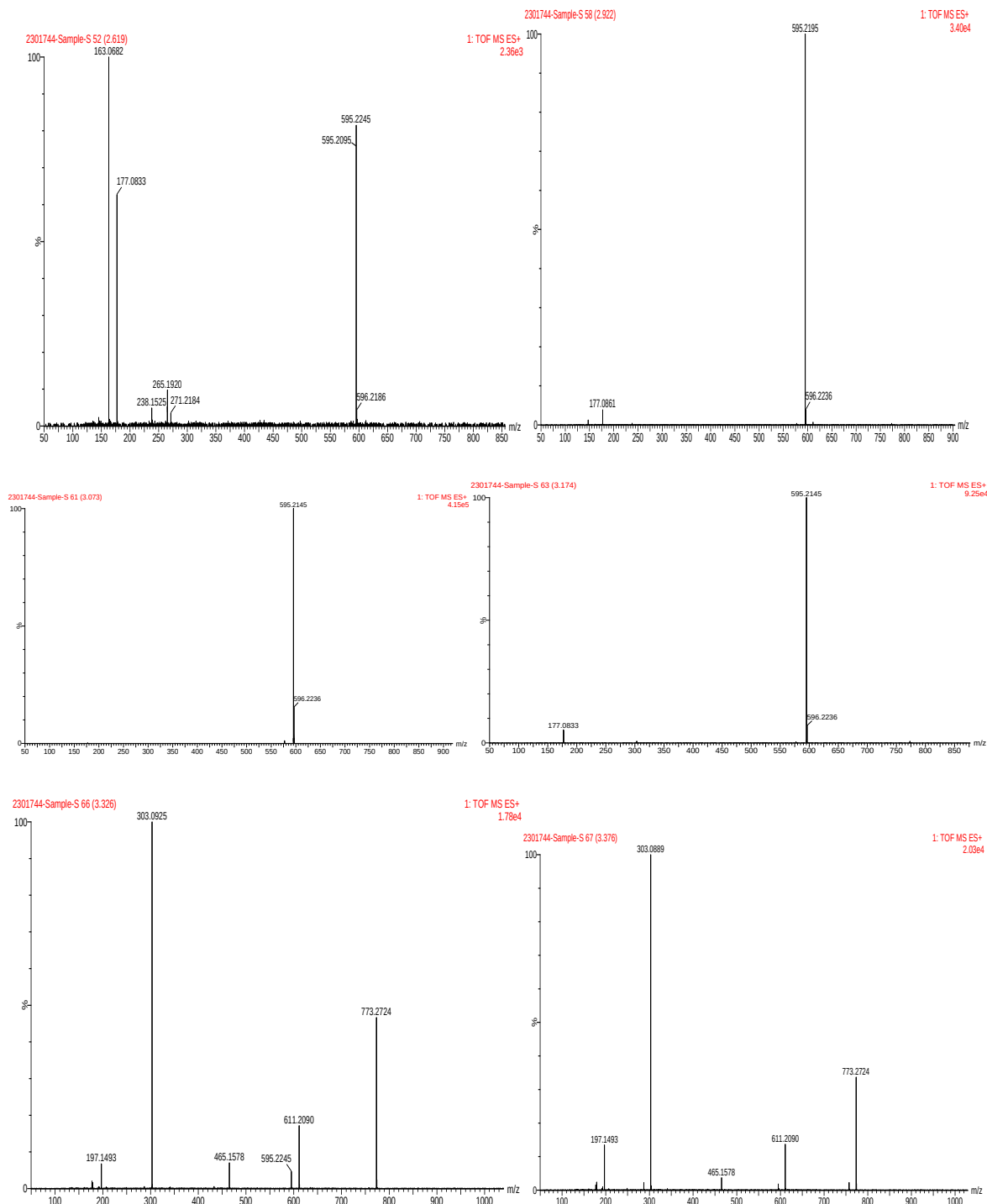
Time	Height	Area	Area%
0.598	816051	90824.992	9.056
3.073	409394	55420.043	5.526
3.477	18160	2659.553	0.265
3.831	127334	25992.775	2.592
4.084	540274	66578.109	6.638
4.892	9977	960.128	0.096
5.094	20586	1378.885	0.137
5.195	120814	11290.926	1.126
5.296	110485	14310.630	1.427
6.054	12579	981.667	0.098
6.811	5306	445.548	0.044
7.215	53481	5262.465	0.525
7.670	241980	36950.754	3.684
8.124	23023	2348.780	0.234
8.276	25214	5227.887	0.521
8.680	62982	5660.298	0.564

List of Proposed Compounds in Sample SP-2 by LCMSMS Study in Progenesis Database

Sl.no	Name	RT(min)	Precursor m/z	Adduct	Formula	Ontology
1	Mycosporine glutaminol	0.497	303.1495	[M+H] ⁺	C13H22N2O6	Cyclohexenones
2	Lactobionic Acid	0.548	381.1202	[M+H] ⁺	C12H22O12	Fatty acyl glycosides of mono- and disaccharides
3	Salvinorin A	0.548	455.1655	[M+Na] ⁺	C23H28O8	Diterpene lactones
4	Poncirin	0.649	595.2145	[M+H] ⁺	C28H34O14	glycosides
5	Methyl cinnamate	2.619	163.0682	[M+H] ⁺	C10H10O2	Cinnamic acid esters
6	3Trimethylsilylpropionic acid	2.922	147.0732	[M+H] ⁺	C6H14O2S	Carboxylic acids
7	1,7,7-trimethylbicyclo	3.477	197.1493	[M+H] ⁺	C12H20O2	Bicyclic monoterpenoids
8	Anthothecol	4.235	519.1595	[M+H] ⁺	C28H32O7	Limonoids
9	Naratriptan HCl	5.346	336.1738	[M+H] ⁺	C17H26ClN3O2S	3-alkylindoles
10	2-heptadecanone	6.71	277.2512	[M+H] ⁺	C17H34O	Ketones



A Review on Evaluation of antidepressant and In Silico Pharmacokinetics & Pharmacological Activities of Albizzia lebeck(L)



CONCLUSION

Understanding the biology of major depression is a challenging scientific problem with enormous sociological and clinical relevance. The discovery of antidepressant drugs and the investigation of their mechanism of action has revolutionized our understanding of neuronal functioning and the possible mechanisms underlying depression. There is no doubt that the monoaminergic system is one of the cornerstones of research, but any hypothesis for the pathophysiology of depression must take into account the many interactions with other brain systems and the complexity of the regulation of the CNS function. In

spite of all the progress that has been achieved in the last decades, we must be aware that there are still today considerable problems in understanding and treating severe depression, and knowing the cause of treatment-resistant depression. From the conducted review work on the plant *Albizia lebeck* Benth (L.) it can be concluded that the various researches had already been carried out for the evaluation of diverse number of pharmacological activities associated with different parts of the plant. So it has already been established to be an important medicinal plant which is widely found throughout the country. Future work on the isolation of various active constituents of the plant may provide

distinct contribution to the field of medicinal research. And also, the plants present in some of chemical constituents Like cyclohexane's, fatty acyl glycosides of mono-disaccharides, diterpene lactone, glycosides, cinnamic acid, esters, carboxylic acids, bicyclic monoterpenoids, limonoids, 3-alkylindoles, ketones.

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