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Harshita Seth
Department of Biotechnology, Sri Agrasen Kanya PG College, Bulanala, Varanasi, Uttar Pradesh, India

Vibha Agrawal
Department of Biotechnology, Sri Agrasen Kanya PG College, Bulanala, Varanasi, Uttar Pradesh, India

Ananya Singh
Department of Biotechnology, Sri Agrasen Kanya PG College, Bulanala, Varanasi, Uttar Pradesh, India

Avinash Kumar Chaurasiya
Department of Biotechnology, Sri Agrasen Kanya PG College, Bulanala, Varanasi, Uttar Pradesh, India

Akhileshwar Kumar Srivastava
Department of Biotechnology, Sri Agrasen Kanya PG College, Bulanala, Varanasi, Uttar Pradesh, India

Corresponding Author:
Akhileshwar Kumar Srivastava
Department of Biotechnology, Sri Agrasen Kanya PG College, Bulanala, Varanasi, Uttar Pradesh, India

Biochemical property of phytochemical and molecular docking studies on *Bombax ceiba* compounds against TAU protein in Alzheimer's disease

Harshita Seth, Vibha Agrawal, Ananya Singh, Avinash Kumar Chaurasiya and Akhileshwar Kumar Srivastava

Abstract
The Tau protein plays a pivotal role in the organization and reinforcement of microtubules, which are essential for the normal functioning of neurons and the brain. Under diseased conditions, several pathological alterations occur in the tau protein. These changes lead to the aggregation of tau protein and the formation of neurofibrillary tangles (NFT) and paired helical filaments (PHF), which are common hallmarks of Alzheimer's disease and other tauopathies. Bioactive compound derived from the medicinal plant *Bombax ceiba* were examined for their potential in targeting the tau protein, with the objective of assessing their effectiveness in combating Alzheimer's disease. In this research article, we focus on the major bioactive constituents of plant *Bombax ceiba* in some solvent's methanol, ethanol, and water along with binding affinity of selected bioactive compounds: Lupeol (PubChem CID 259846), Beta-Sitosterol (PubChem CID 222284), and Quercetin (PubChem CID 5280343), in comparison to the binding affinity of the standard drug Donepezil (PubChem CID 3152). The results showed that that bioactive compounds like Alkaloids, Cardiac Glycosides, Flavonoids, Phenolic compound, sugar (carbohydrate), Tannins, and Saponins are mostly present in ethanol, normal (water), boil (water), and methanol, whereas amino acid are not present in any of it. The extract derived from the leaves of the plant species exhibited notable antioxidant potential as determined through the DPPH (2, 2-diphenyl-1-picrylhydrazyl) radical scavenging assay. In antioxidant analysis, Ethanol exhibits the highest percentage of inhibition against the standard solution (vitamin C). During docking among the three selected ligands, lupeol exhibited the highest binding affinity value of -5.24, while the binding affinity of the standard drug was -4.98.

Keywords: Alzheimer's disease, interaction partners, tau protein, *Bombax ceiba*

Introduction
Alzheimer disease stands as the most common form of dementia, counting for 60-70% of cases. Today, more than 55 million people suffer from dementia in the whole world, over 60% of whom live in middle-and low-income countries. Every year, there are about 10 million new cases. Dementia is currently the seventh leading cause of death among older people globally [1].

While Alzheimer's disease is the major contributor to dementia, [2] a range of potential indicators are currently under examination, including vascular complications, metal ions, oxidative stress, protein irregularities, alterations in mitochondrial populations. This study presents an all-surrounding model of Alzheimer's biomarkers [5] in range with the most recent disease categorization [3]. For three decades, researchers have been concentrating their efforts on therapies aimed at addressing amyloid β [4]. Amyloid positivity was solely associated with older age, clinical setting, and carrying the APOE epsilon 4 gene in isolation [6].

Numerous reports counted that tau protein is also responsible for AD where it forms the neurofibrillary tangles. [7] Tau protein appears to be better associated with the inflexibility of cognitive decline than amyloid β [8]. Tau is an unfolded protein that shows no tendency for aggregation by itself [9]. The accumulation of tau in Alzheimer's disease is associated with both the spatial and temporal development of neurodegeneration and the appearance of clinical symptoms [10]. The buildup of PHFs and NFTs disrupts normal functions, triggers apoptosis, and results in the loss of neurons. This manifests as cognitive decline and, in the later stages of the disease, leads to mortality.

The reasons behind this transformation of tau protein haven't been completely clarified [11]. In both normal and abnormal conditions, tau interacts with various proteins that can either support their proper function or contribute to their pathological changes [12]. These partner proteins and the associated molecular pathways can either kickstart and push tau pathology [5] or serve a neuroprotective role by decreasing abnormal tau proteins or inflammation [13].

A broadly utilized treatment for Alzheimer's disease is Donepezil, often recognized as Aricept [14]. This medication belongs to the class of acetylcholinesterase inhibitors [15]. The FDA firstly sanctioned the use of Donepezil in 1996. In 2014, an extended-release version of Donepezil gained approval when used with Memantine for the management of moderate to severe Alzheimer's dementia [13].

There are leads suggesting that donepezil might have a connection with the tau protein. This study used techniques like surface plasmon resonance (SPR) and molecular modelling to figure out how donepezil attaches to the tau protein [16]. Molecular docking was employed to further understand this interaction. As the temperature was raised, it was noted that the affinity between donepezil and tau protein strengthened. This was evident from the decrease in the equilibrium constant, indicating that the binding of donepezil to the tau protein became more fit at elevated temperatures.[17] Some clinical studies assess the effect of AChEIs on neurodegeneration, donepezil [18].

For a long time, numerous herbs have been used as pain relievers and even today we depend on the healing properties of herbal remedies. Only a few drugs from plant are available for Alzheimer's disease [19]. In this research we have selected *Bombax ceiba* to detect anti-Alzheimer's effect. This plant belongs to the family Bombacaceae. It is commonly known as Kapok Tree or Red Silk Cotton tree. This plant extract also has exhibits antioxidant and pharmacological activities. Studies prove that it is used in various disease like diarrhoea, asthma, boils, wounds, leprosy, pimples and many other skin diseases [20]. It is an anthelmintic remedy since ancient time [21]. It shows pharmacological studies like hypotensive, antioxidant, analgesic, anti-inflammatory, antipyretic, etc. [20] This plant mainly contains alkaloids, Tannins, Saponins, flavonoids, Cardiac Glycosides [22], Phenolic compound, Quercetin, [23] Lupeol, b-sitosterol [24] and other constituents from different parts of plant.

Materials and Methods

The present work was focused on the phytochemical analysis and molecular compound against tau protein, 6N4P.pdb, responsible for Alzheimer's disease. The protein sequence was retrieved from NCBI (National Centre for Biotechnology Information) by using (www.ncbi.nlm.nih.gov) and the 3D Structure of the protein from PDB by using URL (http://www.rcsb.org/PDB). Ligands against this protein were selected from the plant (*Bombax ceiba*) and they were retrieved from PubChem database (PubChem (nih.gov)).

Filtration method was used to extract the powdered leaf into green solution using three different solvents; distilled water, ethanol and methanol. The different plant extracts were subjected to qualitative phytochemical screening for Alkaloids, Cardiac Glycosides, Flavonoids, Phenolic compound, Amino acid, Sugar (carbohydrate), Tannins, and Saponins. Chemicals used for phytochemical analysis are Ethanol (CH_3CH_2OH), methanol (CH_3OH), iodine (I_2), glacial acetic acid (CH_3CO_2H), ferric Chloride (FeCl3), concentrated sulphuric acid (H2So4), ninhydrin Solution ($C_9H_6O_4$), Sodium hydroxide (NaOH), Dil. Hydrochloric acid (Hal), alcoholic a-naphthol [25]. DPPH assay (α, α-diphenyl-β-picrylhydrazyl).

Maceration method was use to extract the powdered leaf into a brownish paste using three different solvents; distilled water, ethanol and methanol. The different plant extracts were subjected to qualitative phytochemical screening for alkaloids, flavonoids, saponins, carbohydrates, tannins and anthraquinones. Quantitative phytochemical analysis was done using a Gas chromatography - Mass Spectroscopy machine.

Structural details of the protein, 6N4P

The protein sequence for 6N4P (Figure 1), retrieved from PDB is known as Microtubule-associated protein tau contains a complex of 2 biomacromolecules A, B [auth C] and 6 residues. The protein structural weight is 1.62 Kad.

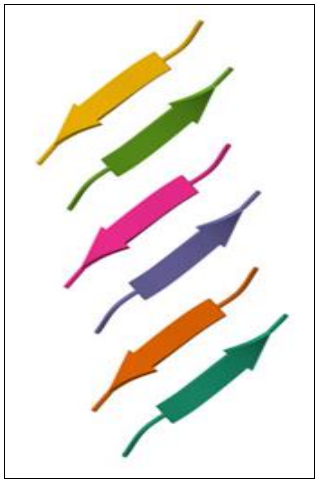

Fig 1: 3D-structure of tau protein

Structural details of the ligands

On the basis of literature, the ligand was taken from Medicinal plant, *Bombax ceiba* [10]. These selected ligands were recruit from PubChem Database in 3D.sdf format. The 3D-crystal structure of Donepezil [Aricept], standard drug PubChem CID: 3152 (Figure 2a) and phytochemical: Lupeol (PubChem CID: 259846) (Figure 2b), Beta-Sitosterol (PubChem CID: 222284) (Figure 2c), Quercetin (PubChem CID: 5280343), (Figure 2d).

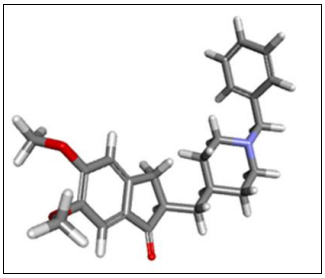

Fig 2a: The 3D-structure of donepezil

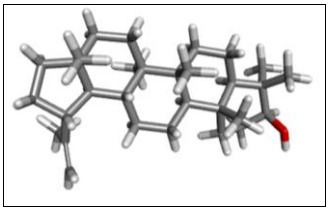

Fig 2b: The 3D-structure of lupeol

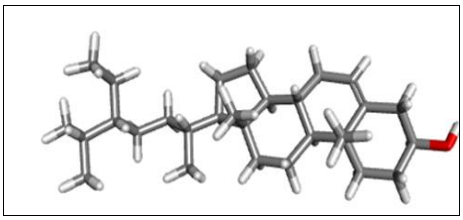

Fig 2c: The 3D-structure of beta-sitosterol

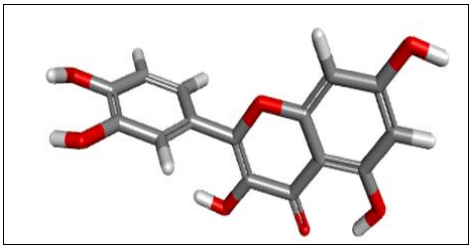

Fig 2d: The 3D-structure of quercetin

Phytochemical Analysis

Plant Materials: The plant materials were cleaned and left to air dry until complete evaporation of moisture occurred. The dried leave was processed into a coarse powder. This powdered sample was then carefully preserved in a sterile glass container, and kept until required for analysis in the laboratory [26].

Preparation of crude leave extract: Approximately 20 grams of powdered plant leaf material underwent separate extractions with 250 millilitres of different solvents: methanol, ethanol, and water, selected based on their respective polarities. This extraction process was conducted over a period of 24 hours. Subsequently, the resulting extracts were transferred to beakers and subjected to heating on a hot plate at 30-40 ºC until all solvents were completely evaporated. The resulting dried extracts were then stored in a refrigerator at 4 ºC for future utilization in phytochemical analysis [26].

Qualitative phytochemical analysis: The extracts were tested for the presence of bioactive components by using following standard Phytochemical analysis methods [27].

Phytochemical analysis [28]

- **Alkaloids (Iodine test):** In 1ml or 5 drops extract add few drops of iodine. Blue colour appears if we boil it, it disappears then appear [28].
- **Cardiac Glycosides:** In 1ml extract add 1.5ml glacial acetic acid, few drops of 5% Ferric chloride and few drops of concentrated H2So4 (by pipette), blue colour appears [28].
- **Protein /Amino acid:** In 1ml of extract add two drops of ninhydrin solution, purple colour appears [28].
- **Flavonoids:** In 1ml of extract add 2ml of 2% NaOH, few drops of dil. HCl, pink to crimson colour appear [28].
- **Phenolic:** In 1 ml extract add few drops of 5% ferric chloride solution, dark green/bluish black colour appear [28].
- **Tannins:** In 1 ml of extract add 3 ml distilled water and 3-4 drops of 10% ferric chloride blue green colour appear [29].
- **Saponins:** In 0.5 ml extract add 2 ml water vigorously shaken persistent from for 10 minutes appear [29].
- **Sugar test:** Dissolve 1ml extract in distilled water & filter it. Filtrate was treated with 2 drops of alcoholic a-naphthol solution in a test tube, shake and add conc. Sulphuric acid from the side of the test tube. Development of a violet ring at the junction of two liquid confirmed the presence of carbohydrates and glycosides [28].

Fig 3a: Drying of leave

Fig 3b: Filtration of extract

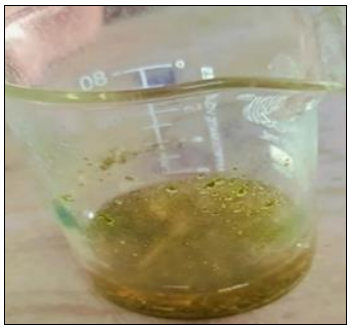

Fig 3c: Filtrate

Fig 3d: Boiling

Fig 3e: Extract

Fig 3f: Phytochemical test

Antioxidant DPPH Assays of Plant Extract: The DPPH assay measures radical scavenging activity. 1, 1 Diphenyl 2-picryl Hydroxyl is a stable free radical that turns yellow when scavenged by antioxidants. This reduction is quantified by measuring absorbance at 517nm, indicating the hydrogen donating ability of the compounds [30].

Procedure: Prepared 0.01% DPPH solution in absolute alcohol. Prepare a standard solution of vitamin C (25 mg/ml). Incubated the solution in the dark for 30 minutes at room temperature. Mix 100µl of sample with 2ml of DPPH solution. Again, incubate in the dark for 30 minutes at room temperature. Measure absorbance at 517nm using a UV visible spectrophotometer.

Calculation for Antioxidant Activity:

% Antioxidant activity = (Absorbance at blank) - (absorbance at test)/ absorbance at blank × 100 [31]

Molecular Docking of Compounds: The AutoDockTools-1.5.7 is used to obtain receptor-ligand complexes based on their minimum binding energy, which represents the strength of binding between the ligands and the receptor. Discovery Studio software was employed for the visualization of the binding modes between the 6N4P protein and the ligands.

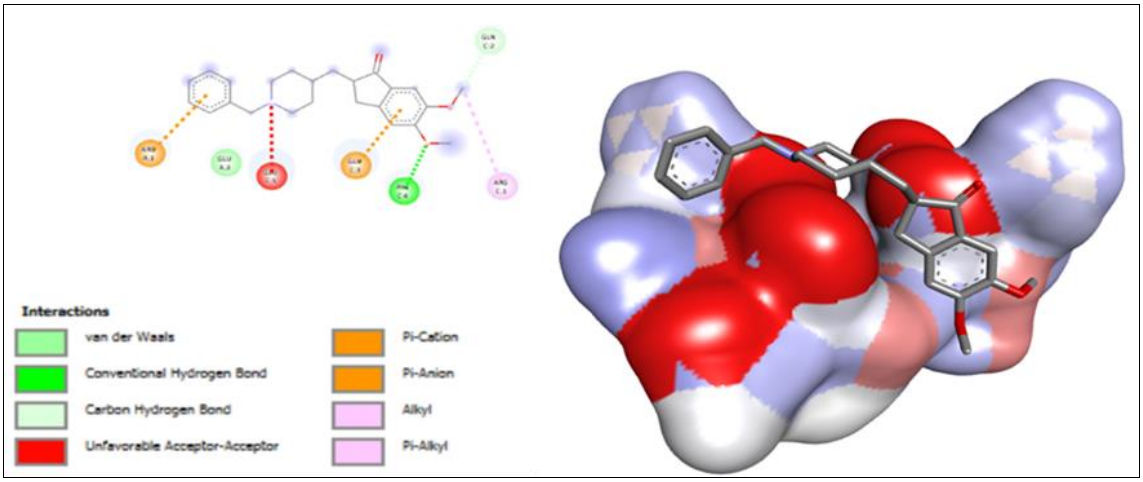

Fig 4a: Visualization of 3D and 2D structures of the interacting residues of 6N4P protein with Donepezil.

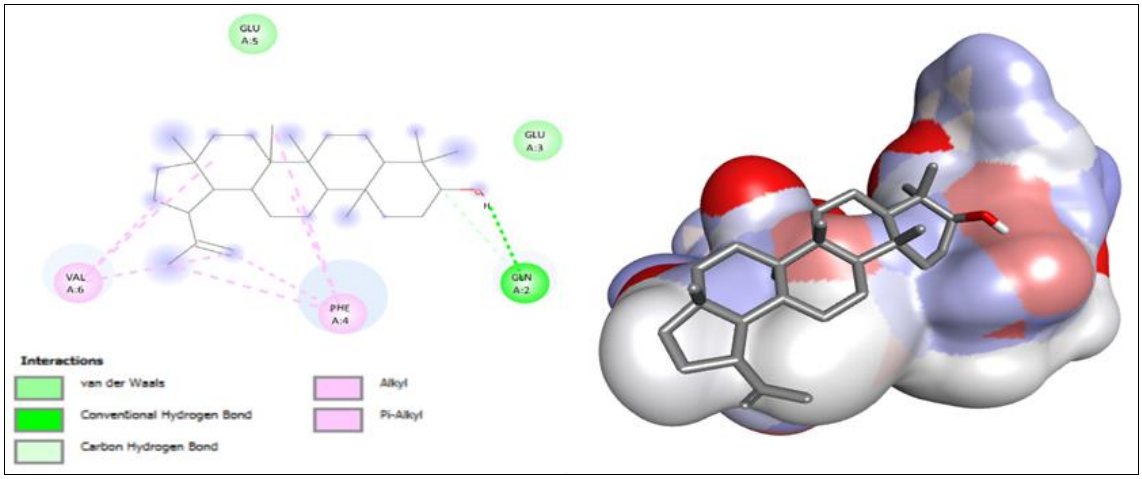

Fig 4b: Visualization of 3D and 2D structures of the interacting residues of 6N4P protein with Lupeol.

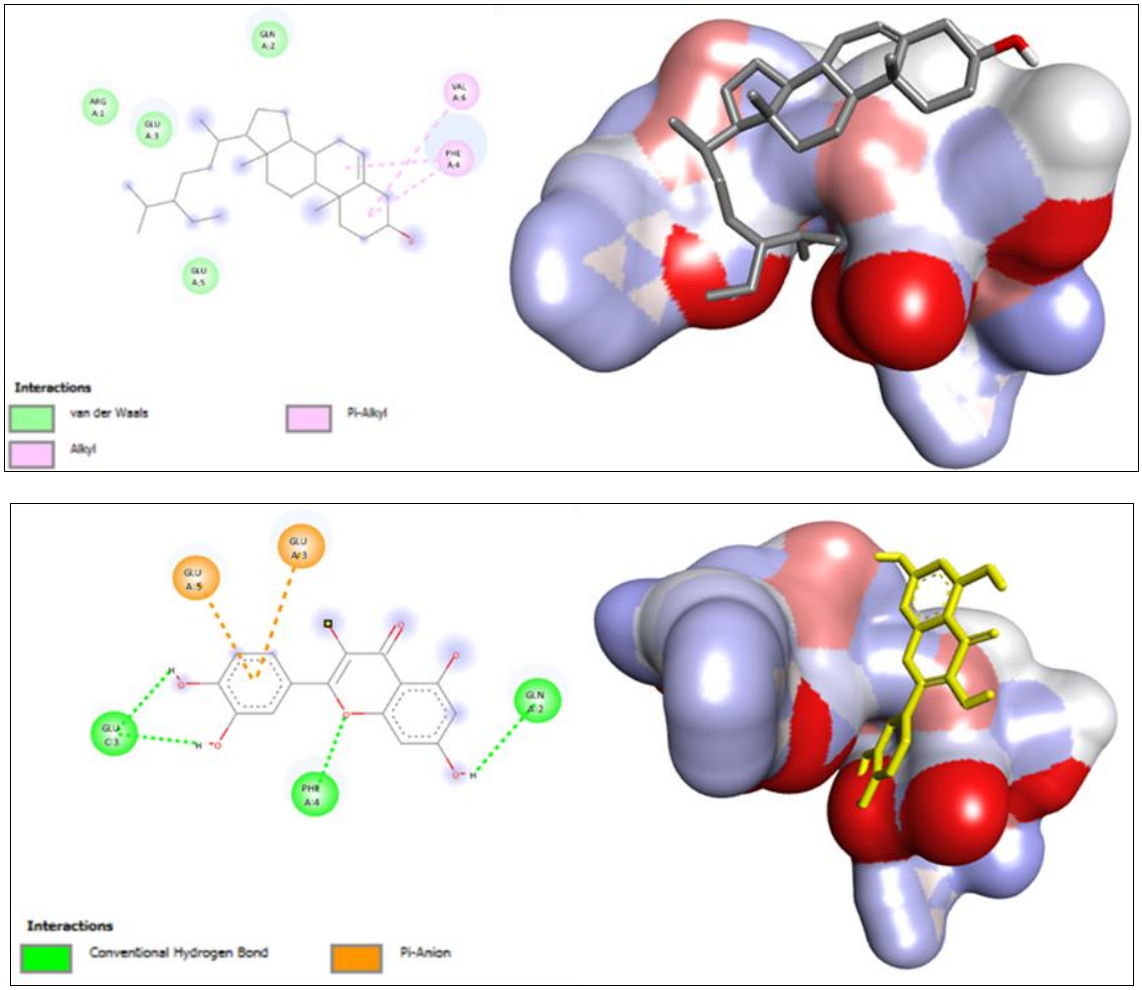

Fig 4d: Visualization of 3D and 2D structures of the interacting residues of 6N4P protein with Quercetin

Results

Table 1: Detection of phytochemicals

Phytochemical	Result in methanol extract	Result in ethanol extract	Result in water (normal, boil)
Alkaloids	Positive	Positive	Positive
Cardiac Glycosides	Positive	Positive	Positive
Amino acid / protein	Negative	Negative	Negative
Flavonoids	Positive	Positive	Positive
Phenolic compound	Positive	Positive	Positive
Tannins	Positive	Positive	Positive
Saponins	Positive	Positive	Positive
Sugar	Positive	Positive	Positive

Table 2: Standard solution of vitamin c

B S. No.	Vollum e of vitamin C solution (ul)	Vitamin Content (mg)	Volume of Water (ul)	Volume of DPPH (ml)	OD Absorbance at 517nm	% Inhibition
1.	5	1.25 mg	995	2.00	0.060	93.17%
2.	10	2.5 mg	990	2.00	0.040	95.44%
3.	20	5mg	980	2.00	0.043	95.33%
4.	40	10mg	960	2.00	0.041	95.33%
5.	80	20mg	920	2.00	0.041	95.33%
6.	100	25mg	900	2.00	0.056	93.62%

Antioxidant DPPH Assays of plant extract

Table 3a: For Volume of extract 100ul

S. No	Volume of extract (100ul)	DPPH (ml)	Absorbance at 517nm	% inhibition
1	Ethanol	2.00	0.090	89.76%
2	Methanol	2.00	0.434	50.62%
3	Cold water	2.00	0.088	79.1%
4	Boil water	2.00	0.170	80.65%

Table 3b: For Volume of extract 200ul

S. No	Volume of extract (200ul)	DPPH (ml)	Absorbance at 517nm	% Inhibition
1	Ethanol	2.00	0.131	85.96%
2	Methanol	2.00	0.714	18.77%
3	Cold water	2.00	0.063	92.83%
4	Boiled water	2.00	0.186	78.83%

ADMET analysis: Result obtains from online server Swiss ADME showed the best drug related properties such as Physicochemical, Pharmacokinetics, Solubility and Drug Likeness. The results are shown below

Table 4: Analysis of Pharmacokinetics Properties of compounds by SwissADME

S.NO.	Properties	Donepezil	Lupeol	Beta-Sitosterol	Quercetin
1	GI absorption	High	Low	Low	High
2	BBB permeant	Yes	No	No	No
3	P-gp substrate	Yes	No	No	No
4	Log K_p (skin permeation)	-5.58 cm/s	-1.90 cm/s	-2.20 cm/s	-7.05 cm/s

Table 5: Analysis of Water Solubility of compounds by SwissADME

S. No.	Solubility	Donepezil	Lupeol	Beta-Sitosterol	Quercetin
1	Log *S* (ESOL)	-4.81	-8.64	-7.90	-3.16
	Solubility	5.87e-03 mg/ml; 1.55e-05 mol/l	9.83e-07 mg/ml; 2.30e-09 mol/l	5.23e-06 mg/ml; 1.26e-08 mol/l	2.11e-01 mg/ml; 6.98e-04 mol/l
	Class	Moderately soluble	Poorly soluble	Poorly soluble	Soluble
2	Log *S* (Ali)	-4.81	-10.22	-9.67	-3.91
	Solubility	5.92e-03 mg/ml; 1.56e-05 mol/l	2.58e-08 mg/ml; 6.05e-11 mol/l	8.90e-08 mg/ml; 2.15e-10 mol/l	3.74e-02 mg/ml; 1.24e-04 mol/l
	Class	Moderately soluble	Insoluble	Poorly soluble	Soluble
3	Log *S* (SILICOS-IT)	-6.90	-6.74	-6.19	-3.24
	Solubility	4.78e-05 mg/ml; 1.26e-07 mol/l	7.69e-05 mg/ml; 1.80e-07 mol/l	2.69e-04 mg/ml; 6.49e-07 mol/l	1.73e-01 mg/ml; 5.73e-04 mol/l
	Class	Poorly soluble	Poorly soluble	Poorly soluble	Soluble

Table 6: Analysis of Drug likeness of compounds by SwissADME

S. No.	Properties	Donepezil	Lupeol	Beta-Sitosterol	Quercetin
1	Lipinski	Yes, 0 Violation	Yes; 1 violation: MLOGP>4.15	Yes; 1 violation: MLOGP>4.15	Yes, 0 violation
2	Ghose	Yes	No; 3 violations: WLOGP>5.6, MR>130	No; 3 violations: WLOGP>5.6, MR>130	Yes
3	Veber	Yes	Yes	Yes	Yes
4	Egan	Yes	No; 1 violation: WLOGP>5.88	No; 1 violation: WLOGP>5.88	Yes
5	Muegge	Yes	No; 2 violations: XLOGP3>5, Heteroatoms<2	No; 2 violations: XLOGP3>5, Heteroatoms<2	Yes
6	Bioavailability Score	0.55	0.55	0.55	0.55

Table 7: Showing binding affinity between protein (6N4P) and the ligands:

Ligand	Interacting residues	Bonding	binding energy kcal/mol
Donepezil	ARG1 GLU3 GLU5 GLU3 PHE4 ARG1 GLN2	Pi-Cation Van der Waals Unfavourable acceptor-acceptor Pi-anion Conventional hydrogen bond Alkyl Carbon hydrogen bond	-4.98
Lupeol	GLU3 GLU5 GLN2 PHE4 VAL6	Van der Waals Van der Waals Conventional hydrogen bond Alkyl Alkyl	-5.24
Beta-Sitosterol	ARG1 GLN2 GLU3 GLU5 VAL6	Van der Waals Van der Waals Van der Waals Van der Waals Alkyl	-4.71

	PHE4	Alkyl	
Quercetin	GLN2 GLU3 PHE4 GLU5 GLU3	Conventional hydrogen bond Conventional hydrogen bond Conventional hydrogen bond Pi-anion Pi-anion	-4.66

Discussion

The analysis presented in Table 1 reveals the detection of phytochemicals across different solvents. Bioactive compounds including Alkaloids, Cardiac Glycosides, Flavonoids, Sugar Phenolic compounds, Tannins, and Saponins were predominantly found in ethanol, normal (water), boil (water), and methanol. However, amino acids were not detected in any of the solvents.

The analysis presented in Table 2 reveals the high % inhibition of the Standard solution of vitamin c, [32] indicating its potent antioxidant behaviour. Tables 3a and 3b represent the % inhibition of different solvents. In Table 3a, with a volume of extract of 100ul and Table 3b, with a volume of extract of 200ul, the % inhibition was observed as ethanol (89.76% and 85.96%), methanol (50.62% and 18.77%), Boil water (80.65% and 78.83%) and Cold water (79.1% and 92.83%).

Tables 4, 5, and 6 display diverse properties of the ligands derived from Swiss ADME analysis such as Pharmacokinetics Properties of compounds, Water Solubility and Drug likeness. The analysis suggests significant similarities between the standard drug Donepezil and the chosen ligands Lupeol, Beta-Sitosterol, and Quercetin.

Table 7 provides the binding energy (kcal/mol) values for the ligands and the protein. The binding energies for the ligands were determined through analysis. Donepezil exhibited a binding energy of -4.98 kcal/mol. Lupeol displayed a slightly stronger binding energy at -5.24 kcal/mol. Beta-Sitosterol showed a binding energy of -4.71 kcal/mol, while Quercetin exhibited a binding energy of -4.66 kcal/mol. These values provide insights into the strength of interaction between the respective ligands and their target proteins.

Conclusion

The research focused on investigating the prominent bioactive constituents of the *Bombax ceiba* plant using various solvents such as methanol, ethanol, and water. Additionally, it explored the binding affinities of selected ligands, namely lupeol, Beta-Sitosterol, and Quercetin, comparing them to the standard drug Donepezil. The results revealed that crucial bioactive compounds, including Alkaloids, Cardiac Glycosides, Flavonoids, Phenolic compounds, Tannins, and Saponins, were predominantly present in ethanol, normal water, boil water, and methanol. Interestingly, amino acids were absent in all of these solvents.

Furthermore, the leaf extract of the *Bombax ceiba* plant demonstrated significant antioxidant potential, as confirmed by the DPPH radical scavenging assay. Notably, ethanol exhibited the highest percentage of inhibition against the standard vitamin C solution in the antioxidant analysis.

In the molecular docking study, lupeol displayed the highest binding affinity value of -5.24, surpassing the binding affinity of the standard drug Donepezil, which was -4.98.

In conclusion, the research provides valuable insights into the bioactive composition of *Bombax ceiba* and highlights the notable antioxidant capabilities of its leaf extract. The findings also underscore the potential of selected ligands, particularly lupeol, as promising candidates for further exploration in drug development. This study contributes significantly to our understanding of the therapeutic potential of *Bombax ceiba* and its constituent compounds.

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Conflict of Interest

Authors have no any conflict of interest.

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