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RESEARCH ARTICLE

Exploring the antiviral activity of *Adhatoda beddomei* bioactive compounds in interaction with coronavirus spike protein

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Abstract

This study explores the pharmacokinetic properties, drug-likeness, and molecular docking potential of bioactive compounds from *Adhatoda beddomei* as potential inhibitors of the coronavirus spike protein. Using SwissADME, we evaluated the pharmacokinetic profiles and drug-likeness of compounds such as Naringenin, Epicatechin, Morin, Quercetin, and Epigallocatechin. The results indicate high gastrointestinal absorption and favorable drug-likeness profiles, though none of the compounds are capable of crossing the blood-brain barrier. Molecular docking studies were conducted to assess the binding affinity of these compounds with the coronavirus spike protein. The spike protein structure was obtained from the RCSB Protein Data Bank and prepared using PyMOL, while the ligand structures were optimized in Discovery Studio. Docking simulations, performed using AutoDock Vina, revealed that Naringenin, Morin, and Quercetin exhibit strong binding affinities, with Naringenin demonstrating the highest binding affinity (-6.8 kcal/mol). These findings suggest that bioactive compounds from *Adhatoda beddomei* possess significant potential as antiviral agents. The integration of pharmacokinetic assessments and molecular docking provides a comprehensive framework for advancing these compounds as therapeutic candidates for treating coronavirus infections. Further studies are recommended to elucidate the mechanisms of action, optimize pharmacokinetic properties, and validate the efficacy in preclinical and clinical settings.

1. Introduction

Adhatoda beddomei, known commonly as Malabar Nut or Vasa, belongs to the Acanthaceae family and is indigenous to the Indian subcontinent. This evergreen shrub, characterized by large lance-shaped leaves and white or purple flowers, has been an integral part of traditional Ayurvedic and Unani medicine (Singh et al., 2015). The plant is rich in bioactive compounds such as vasicine, vasicinone, flavonoids, tannins, saponins, and essential oils, which confer various therapeutic properties. Primarily, Adhatoda beddomei is used to treat respiratory ailments like asthma, bronchitis, and cough, owing to its bronchodilator and expectorant effects (Khursheed et al., 2010). The plant's anti-inflammatory and antioxidant properties further enhance its medicinal value, making it effective in managing conditions such as arthritis and oxidative stress-related diseases (Biharee et al., 2023).

The antimicrobial properties of *Adhatoda beddomei* are particularly noteworthy. It exhibits strong antibacterial activity against both Gram-positive and Gram-negative bacteria, including *Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa* (Marasini et al., 2015). These effects are largely due to the disruption of bacterial cell walls and inhibition of protein synthesis by its bioactive compounds. Moreover, *Adhatoda beddomei* shows significant antifungal activity against pathogens like *Candida albicans* and Aspergillus niger. The antifungal mechanisms involve disrupting the fungal cell membrane integrity and interfering with metabolic processes essential for fungal growth (Joshi et al., 2020; Pa and Mathew, 2012). Preliminary research also suggests that the plant may possess antiviral properties, potentially inhibiting viral replication and enhancing immune responses, which is particularly relevant in the context of emerging viral infections (Gheware et al., 2021).

In the context of the COVID-19 pandemic, there has been increasing interest in exploring traditional medicinal plants for potential therapeutic benefits. *Adhatoda beddomei*, with its broad spectrum of pharmacological properties, presents a

promising candidate for such exploration. Although specific studies on its efficacy against SARS-CoV-2 are still in the preliminary stages, the plant's immunomodulatory effects could help in enhancing the body's defense mechanisms against viral infections. By potentially boosting the immune response, *Adhatoda beddomei* could assist in reducing the severity of COVID-19 symptoms and improve respiratory health. Additionally, its anti-inflammatory and antioxidant properties could mitigate the inflammatory responses and oxidative stress associated with severe COVID-19 cases. Further research is necessary to fully understand and harness the potential of *Adhatoda beddomei* in combating coronavirus infections and to develop effective therapeutic strategies based on its bioactive compounds.

2. Materials and Methods

2.1.Toxicity analysis of Bioactive compounds in *Adhatoda beddomei*

To perform a SwissADME analysis, begin by obtaining the molecular structure of the compound of interest in a suitable format, such as SMILES (Simplified Molecular Input Line Entry System) or MOL file. Access the SwissADME web tool (http://www.swissadme.ch/) and input the compound's SMILES notation or upload the MOL file. Upon submission, the tool provides various predictive models to assess pharmacokinetic properties, drug-likeness, and potential medicinal chemistry friendliness. Select the desired parameters for analysis, which typically include Lipinski's rule of five, bioavailability score, and various pharmacokinetic predictions such as absorption, distribution, metabolism, and excretion (ADME) properties. After running the analysis, review and interpret the results provided by SwissADME, which include detailed information on the compound's drug-likeness, solubility, and potential bioactivity, aiding in the assessment of its suitability for further drug development (Bakchi et al., 2022; Daina et al., 2017; Sympli, 2021). The bioactive compound present in *Adhatoda beddomei* are given in table 1.

2.2. Molecular Docking analysis

To perform molecular docking of a bioactive compound from *Adhatoda beddomei* with the coronavirus spike protein, begin by obtaining the 3D structure of the spike protein from the RCSB Protein Data Bank (PDB. Use PyMOL to visualize and prepare the protein structure, removing water molecules and adding hydrogen atoms. Save the prepared protein as a PDB file. For the ligand, use Discovery Studio to draw or import the structure of Vasicine, optimize its geometry, and save it as a PDB file. Convert both the protein and ligand PDB files to PDBQT format using AutoDock Tools, ensuring the addition of necessary atomic charges and setting rotatable bonds for the ligand. Configure the grid box in ADT to encompass the active site of the spike protein. Run the docking simulation using AutoDock Vina, specifying the protein and ligand PDBQT files and the grid box parameters. After docking, analyze the binding poses and interactions in PyMOL and Discovery Studio, focusing on the binding affinity and key molecular interactions between Vasicine and the spike protein's active site. The binding affinity value in molecular docking studies is typically expressed in kilocalories per mole (kcal/mol). This unit measures the free energy change associated with the binding interaction between the ligand and the protein. In AutoDock Vina and similar software, more negative values indicate stronger and more favorable binding, suggesting that the ligand forms a stable complex with the protein. The more negative binding affinity value implies that less energy is required for the ligand to bind to the protein, which is indicative of a potentially effective inhibitor in the context of drug discovery (Krishna et al., 2013; Tao et al., 2020).

3. Results

3.1. Pharmacokinetics studies of Bioactive compounds

The SwissADME analysis results for Naringenin, Epicatechin, Morin, Quercetin, and Epigallocatechin indicate that all compounds have high gastrointestinal (GI) absorption, suggesting good oral bioavailability. However, none of these compounds are capable of crossing the blood-brain barrier (BBB), which means they are unlikely to have central nervous system effects. Naringenin and Epicatechin are substrates of P-glycoprotein (P-gp), which could affect their absorption and distribution. Naringenin and Morin inhibit the cytochrome P450 enzyme CYP1A2, while Naringenin also inhibits CYP2C19, potentially leading to drug-drug interactions. The Log Kp values for skin permeation are negative for all compounds, with Epigallocatechin having the lowest value (-8.17 cm/s), indicating poor skin permeability (Table 2). This comprehensive pharmacokinetic profile highlights the compounds' potential efficacy and safety considerations in drug development.

3.2. Druglikeness studies of Bioactive compounds

The druglikeness studies, as assessed by Lipinski, Ghose, Veber, Egan, and Muegge rules, provide insight into the pharmaceutical suitability of the compounds Naringenin, Epicatechin, Morin, Quercetin, and Epigallocatechin (Table 3 and Figure 1). Overall, all compounds, except Epigallocatechin, demonstrate favorable druglikeness profiles with no violations of Lipinski's rule of five, indicating their potential as drug candidates. These compounds also adhere to the Ghose, Veber, Egan, and Muegge criteria for druglikeness, further supporting their suitability for drug development. However, Epigallocatechin shows one violation of Lipinski's rule due to the presence of NH or OH groups exceeding the recommended limit, and another violation according to Muegge's rule due to the number of hydrogen bond donors exceeding the threshold. Despite these violations, the compounds exhibit a high bioavailability score of 0.55, indicating promising pharmacokinetic properties. Therefore, while Epigallocatechin may require further optimization to address these violations, the other compounds present themselves as promising candidates for drug development, possessing favorable druglikeness attributes.

3.3. Interaction studies with coronavirus spike protein

The molecular docking studies conducted with the ligands Naringenin, Epicatechin, Morin, Quercetin, and Epigallocatechin against the receptor Spike glycoprotein (PDB: 6VSB) yielded insights into their potential interactions and binding affinities. Among the compounds, Naringenin demonstrated the highest binding affinity with a value of -6.8 kcal/mol, forming interactions with amino acids PHE, LEU, TRP, and SER within the active site of the spike glycoprotein. Morin and Quercetin also exhibited notable binding affinities

of -5.3 kcal/mol and -5.5 kcal/mol, respectively, interacting with key amino acids such as GLN, TYR, ILE, VAL, and LEU. However, Epicatechin and Epigallocatechin displayed comparatively lower binding affinities of -3.1 kcal/mol and -2.7 kcal/mol, respectively, with interactions involving amino acids like SER, PRO, GLU, GLN, and TYR. Despite the variations in binding affinities, all compounds demonstrated interactions with amino acids crucial for stabilizing the ligand-receptor complex. These findings suggest the potential of Naringenin, Morin, and Quercetin as promising candidates for further investigation as inhibitors against the spike glycoprotein of the coronavirus, highlighting their potential therapeutic significance in combating viral infections.

4. Discussion

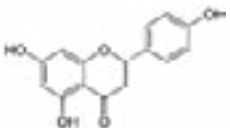
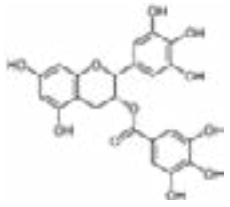
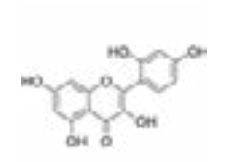
The comprehensive pharmacokinetic, druglikeness, and interaction studies with the coronavirus spike protein provide valuable insights into the potential therapeutic applications of bioactive compounds like Naringenin, Epicatechin, Morin, Quercetin, and Epigallocatechin from *Adhatoda beddomei*. Firstly, the pharmacokinetic profiles suggest that these compounds exhibit favorable oral bioavailability and gastrointestinal absorption, indicating their potential efficacy when administered orally. However, the inability to cross the blood-brain barrier suggests a reduced likelihood of central nervous system effects, which may be advantageous in certain therapeutic contexts, particularly for targeting peripheral conditions (Furtado et al., 2018; Terstappen et al., 2021). The druglikeness assessments underscore the suitability of these compounds for drug development, as they adhere to established pharmaceutical criteria with minimal violations, demonstrating their potential as viable drug candidates. Despite some violations observed in Epigallocatechin, its high bioavailability score suggests promising pharmacokinetic properties, warranting further optimization efforts to address these violations. Overall, these findings highlight the potential of these bioactive compounds for further exploration in pharmacology.

Moreover, the molecular docking studies reveal the interaction profiles of these compounds with the coronavirus spike protein, offering insights into their potential as inhibitors against viral infections (Huang et al., 2020; Papageorgiou and Mohsin, 2020). Notably, compounds like Naringenin, Morin, and Quercetin demonstrate strong binding affinities with key amino acids within the active site of the spike glycoprotein, suggesting their potential as promising candidates for further investigation as antiviral agents. While Epicatechin and Epigallocatechin exhibit comparatively lower binding affinities, their interactions with essential amino acids still underscore their potential therapeutic relevance. In future pharmacological research, these findings can guide the development of novel therapeutics targeting viral infections, particularly against the coronavirus. Further studies could focus on elucidating the mechanisms of action of these compounds, optimizing their pharmacokinetic properties, and exploring their efficacy in preclinical and clinical settings. Additionally, the structural insights obtained from molecular docking studies could inform rational drug design efforts to develop more potent and specific inhibitors against the coronavirus spike protein. Overall, the integration of pharmacokinetic, druglikeness, and interaction studies provides a comprehensive framework for advancing the development of bioactive compounds as potential therapeutics in pharmacology.

5. Conclusion

In conclusion, the pharmacokinetic, druglikeness, and interaction studies of bioactive compounds from *Adhatoda beddomei* present promising potential for treating coronavirus infections. These compounds exhibit favorable pharmacokinetic profiles and strong interactions with the coronavirus spike protein, suggesting their suitability as antiviral agents. Further research and development efforts are warranted to explore their efficacy and optimize their therapeutic potential in combating coronavirus and other viral infections.

Table 1: Bioactive compounds present in Adhatoda beddomei

S.No	Compound	Molecular Formula	Molecular Weight	Structure
1.	Naringenin	$C_{15}H_{12}O_5$	272.25 g/mol	
2.	Epicatechin	$C_{15}H_{14}O_6$	290.27 g/mol	
3.	Morin	$C_{15}H_{10}O_7$	302.2357 g/mol	

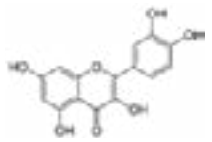
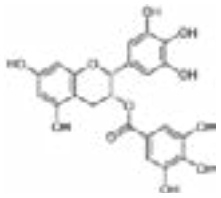
4.	Quercetin	$C_{15}H_{10}O_7$	302.236 g/mol	
5.	Epigallocatechin	$C_{22}H_{18}O_{11}$	458.372 g/mol	

Table 2: Pharmacokinetics studies of Adhatoda beddomei compounds

Pharmacokinetics						
Compounds	**GI absorption**	**BBB permeant**	**P-gp substrate**	**CYP1A2 inhibitor**	**CYP2C19 inhibitor**	**Log Kp (skin permeation)**
Naringenin	High	No	Yes	Yes	No	-6.17 cm/s
Epicatechin	High	No	Yes	No	No	-7.82 cm/s
Morin	High	No	No	Yes	No	-7.05 cm/s
Quercetin	High	No	No	Yes	No	-7.05 cm/s
Epigallocatechin	High	No	No	No	No	-8.17 cm/s

Table 3: Druglikeness studies of Adhatoda beddomei compounds

Druglikeness						
Compounds	**Lipinski**	**Ghose**	**Veber**	**Egan**	**Muegge**	**Bioavailability score**
Naringenin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
Epicatechin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
Morin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
Quercetin	Yes; 0 violation	Yes	Yes	Yes	Yes	0.55
Epigallocatechin	Yes; 1 violation: NHorOH>5	Yes	Yes	Yes	No; 1 violation: H-don>5	0.55

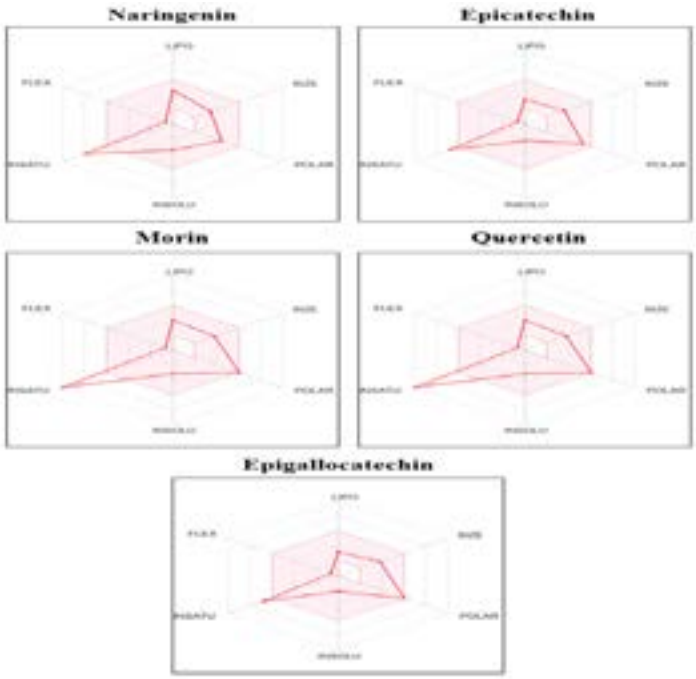


Figure 1: The detection of suitable physicochemical space for oral bioavailability

Table 4: Bioactive compounds amino acid interaction with coronavirus spike glycol protein. PHE (Phenylalanine), LEU (Leucine), TRP (Tryptophan), SER (Serine), PRO (Proline), GLU (Glutamic acid), VAL (Valine), ILE (Isoleucine), GLN (Glutamine), and TYR (Tyrosine)

Ligand	Receptor (PDB: 6VSB)	Amino acid interaction	Binding Affinity (kcal/mol)
Naringenin	Spike glycol protein	PHE, LEU, TRP, PHE, and SER	-6.8 kcal/mol
Epicatechin	Spike glycol protein	SER, PRO, GLU, and VAL	-3.1 kcal/mol
Morin	Spike glycol protein	GLN, TYR, ILE, and ILE	-5.3 kcal/mol
Quercetin	Spike glycol protein	VAL, LEU, and GLU	-5.5 kcal/mol
Epigallocatechin	Spike glycol protein	GLN, GLU, and TYR	-2.7 kcal/mol

Declarations

Ethics approval statement

No ethical approval was required for the current study as it did not deal with any human or animal samples.

Consent to participate

Not applicable

Consent to publish

Not applicable

Data Availability Statement

The data are available from the corresponding author upon reasonable request

Competing Interests

The authors declare that they have no conflict of interest

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Author contribution

Conceptualization, Data curation, Investigation: S.A Formal analysis: I.F Writing—review and editing: S.A. All authors have read and agreed to the published version of the manuscript

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Not Applicable

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