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SwissADME Predictions of Phytoconstituents Present in *Hygrophila auriculata*

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Abstract

Background: Within the broad category of phytochemicals, including steroids, alkaloids, and flavonoids, the ancient herbaceous plant *Hygrophila auriculata* exemplifies their diversity. Studies on these bioactive chemicals, drug-likeness, and pharmacokinetics are necessary since they impart different levels of pharmacological action. **Aim:** To use the SwissADME tool to assess the pharmacokinetic characteristics and drug-likeness of a few chosen phytochemicals from *H. auriculata*. **Materials and Methods:** To predict factors including gastrointestinal absorption, blood-brain barrier permeability, bioavailability score, and adherence to drug-likeness filters like Lipinski's Rule of Five, the phytoconstituents from *H. auriculata* were submitted to *in silico* analysis using SwissADME. The *in vitro* anti-inflammatory activity of *H. auriculata* extracts was also studied by checking the inhibition of protein denaturation. The extracts were mixed with bovine serum albumin (BSA) at different concentrations, and the absorbance was measured at 660 nm with aspirin as the reference standard. **Results and Discussion:** The majority of the substances had good physicochemical qualities and high gastrointestinal absorption, according to the SwissADME investigation. There are a lot of drug-likeness principles that phytochemicals follow, and some of them may be able to pass across the blood-brain barrier. These phytoconstituents should be well-bioavailable and structurally appropriate for the creation of oral drugs since they exhibit promising pharmacokinetic characteristics and diversity. The *in vitro* results demonstrated that the extracts exhibited notable inhibition of protein denaturation, supporting their anti-inflammatory potential. **Conclusion:** Pharmacokinetic characteristics of these substances appear promising upon SwissADME evaluation carried out for phytochemicals of *H. auriculata*, giving an impression of similarity with drugs. These results provide further information about the suitability of these active compounds in the formulation of herbal medicines.

Major Findings: The phytoconstituents of *H. auriculata* were predicted by SwissADME to have excellent drug-likeness and bioavailability. Moreover, these compounds were also found to have strong anti-inflammatory activity, thus confirming their therapeutic potential.

Keywords: Gas Chromatography, Green Extraction, *Hygrophila auriculata*, Phytoconstituents Prediction, SwissADME

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1. Introduction

Hygrophila auriculata, also *Asteracantha longifolia* and *Hygrophila spinosa*, is an erect annual plant growing throughout the Indian subcontinent, especially in marshy areas in the plains[1]. *H. auriculata* has been treated differently in chronic diseases in the Dravidian system for a long time by the *Acanthaceae* family. This is due to the incidence of bioactive molecules such as alkaloids, flavonoids, terpenoids, fatty acids, polyphenols, and

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phytosterols in the plant that can be linked with diverse pharmacological actions[2]. It is also rich in nutrients like β-carotene, riboflavin, and essential minerals[3]. Pharmacologically, *H. auriculata* showed antioxidant and antimicrobial activities against various pathogens, differentiated hepatoprotective actions under models of liver toxicity, and wound healing activities supported by molecular docking studies. Generally, it is used in Ayurveda for liver disorders, treatment of wounds, and a miscellany of other surmounting conditions, and ingestion as a functional food in some places in India, which augments its nutrient qualities.

Being widely distributed throughout Asia, this plant has produced significant results as an anti-inflammatory and therapeutic due to phytosterols, flavonoids, terpenoids, and alkaloids as the major active secondary metabolites[4]. Hussain *et al.*,[5] reported that the terpenoid fraction isolated from *H. auriculata* diminished inflammatory markers in lipopolysaccharide-induced septic shock in rats. Contrarily, β-sitosterol-β-D-glucoside extracted from the plant prevented carrageenan-induced inflammation, exhibiting greater affinity toward anti-inflammatory drug targets in molecular docking studies[6]. The plant is used for treating rheumatoid arthritis, jaundice, and urinary disorders[7], and the antioxidant, hepatoprotective, and nephroprotective traits it exhibits support its use against inflammatory ailments.

By *in vitro* and *in silico* studies, *H. auriculata* is considered for the possible treatment of rheumatoid arthritis. *In vitro* studies demonstrated that the extract showed anti-inflammatory properties in the methanolic extract, the effect being comparable with that of indomethacin on carrageenan-induced inflammation. Being not from *H. auriculata*, Jatrorrhizine hydrochloride showed efficacy in collagen-induced arthritis models, stressing the importance of anti-RA (Rheumatoid Arthritis) compounds[8]. It also demonstrated that the isolated HA-06 compound inhibits inflammatory signalling pathways by binding to phospholipase A2 and glucocorticoid receptors, and compounds such as neo-hesperidin dihydrochalcone (NHDC) inhibited pro-inflammatory cytokines, thus implying a similar effect from *H. auriculata* phytochemicals. *In silico* studies buttressed the findings by revealing, through molecular docking, a high binding affinity of HA-06 for important inflammatory targets, with network pharmacology identifying phytochemicals targeting RA-specific pathways[9]. While such studies suggest the therapeutic value of *H. auriculata* in RA, clinical investigations to ascertain its effectiveness and safety in humans need to follow in order to fully understand it, given the limitations of the available drug treatment.

2. Materials and Methods

2.1 Green Extraction

In several natural sources, green extraction with ethanol has been proposed as a sustainable means of isolating the bioactive compounds. These methods minimise environmental impact while optimising the recovery of valuable products. Ethanol proves to be an excellent solvent in various extraction processes due to its versatility and compatibility with different biomass types.

2.1.1 Ethanol as a Green Solvent

- Being considered a green solvent, ethanol has very low toxicity and is readily biodegradable[10].
- Concentration differences in ethanol have been shown to yield significantly different amounts of bioactive compounds, for example, flavonoids and limonoids from lime peel, with maximum yields at 80% ethanol[11].

2.1.2 Efficiency and Sustainability

- Ultrasound-assisted ethanol extraction has been shown to extract higher yields of antioxidant-rich extracts and retain nutritious residual biomass, as exemplified by microalgae studies[12].
- The solvent extraction-crystallisation-evaporation (SECE) method using bioethanol for oil recovery from palm oil wastes very well exemplifies the sustainable applications of ethanol in industrial processes[13].

Ethanol extraction has a multitude of features, but one must analyse solvent recovery and the environmental impact of producing ethanol on a large scale.

2.1.3 Preparation of Plant Extract

Make a coarse powder of the whole dried plant material of *H. auriculata* (Figure 1), and 50g of powder was

taken to macerate with 200ml of ethanol for 3 days. It was then filtered with Muller filter paper and kept inside a conical flask (Figure 2).

2.1.4 Percolation Extraction Method

The extraction by percolation is a classical method for processing traditional medicines; advantages include simplicity and applicability to a wide range of materials. It is especially appropriate for the extraction of thermally labile components. Factors influencing an individual percolation are the solvent composition, impregnation time, percolation rate, and solvent consumption. These extraction methods are crucial to drug discovery and development as they provide samples for the qualitative and quantitative analysis of natural products.

2.2 Evaluation of Phytochemical Composition

2.2.1 Preliminary Phytochemical Screening

The phytochemical standardised screening method was carried out on the ethanolic extract of *H. auriculata* for the purpose of detecting the major class of secondary metabolites. The dried plant material was subjected to ethanolic extraction, and the resulting extract was filtered and concentrated. The concentrated dried extract was re-dissolved in ethanol and subjected to qualitative testing.

Tests for Alkaloids, Flavonoids (Shinoda Test), Phenols and Tannins (Ferric Chloride test), Saponins (Foam Test), Steroids (Liebermann Burchard test), Terpenoids (Salkowski Test), and Total Phenolic Content (TPC) test were performed using standard procedures, and their findings are discussed in Table 1.



Figure 1. Dried plant of *Hygrophila auriculata.*

2.3 Gas Chromatography-Mass Spectrometry (GC-MS)

Gas Chromatography-Mass Spectrometry (GC-MS) is an advanced analytical technique that combines the features of a gas chromatograph and mass spectrometer to identify and quantify different substances within a larger mixture. In pharmaceutical development, it is used to develop and validate methods in pharmaceutical research for the correct measurement of active ingredients[14].

2.3.1 Operating Principles

2.3.1.1 Separation Mechanism

Samples are evaporated, and depending on how they interact with the stationary phase in the column.

2.3.1.2 Mass Spectrometry

After separation, identification of compounds is done by their mass-to-charge ratios, providing more detailed structural information. Role of Mass Spectrometry: After separation, mass spectrometry identifies compounds by analysing the mass-to-charge ratios, thus furnishing more detailed structural information[15].

2.3.2 Technological Advancements

2.3.2.1 Increased Sensitivity

One of the recent innovations is the multi-reflection time-of-flight mass spectrometry (MRT), which has increased the sensitivity and dynamic range so far, with the last traces of analytes being spotted in complicated matrices[16]. Since it is a very strong tool in GC-MS, the matrix effects and issues of method validation do crop up. Therefore, further research and development are a must to fully exploit its usage in various fields.



Figure 2. Green extract of the plant *Hygrophila auriculata.*

Gas Chromatography-Mass Spectrometry was performed on Perkin Elmer Clarus SQ8C instrumentation, which has a high-performance system. It gives an intuitive response for sensitivity and reliability in analytical applications. The substances are separated with a DB-5 MS capillary column, which is a standard nonpolar column widely used for different applications, such as those derived using this dimension from the products given due to its selectivity for volatile and semi-volatile organic compounds. This column is of the length of 30 meters, ID of 0.25 mm; the film thickness is 0.25 µm; thus, it provides an excellent balance between resolution, efficiency, and analysis time on the sample. Helium (He) is the carrier gas for the analyses because of its inert properties, diffusion properties, and ability to give constancy of flow to allow the proper separation peaks and repeatability. Injection volume was 1 µl for extremely sensitive detection with no wastage. Sample ID is IPSG HA-1 2910I, for which reference standards can be traced. Within the assembly, settings take up to a condition of chromatographic separation with very fine details and sensitive detection by mass spectrometry, making it very suitable for qualitative and quantitative studies on heterogeneous mixtures.

Retention time marked the peaks in the GC-MS chromatogram (Figure 3) of the ethanol extract of *H. auriculata*. Their retention time and their amount of presence can be seen listed in Table 2. Through qualitative analysis, 43 compounds in the ethanolic extract were identified.

2.4 SwissADME Analysis

The SwissADME serves as a computational tool for the evaluation of physicochemical and pharmacokinetic properties (Table 3), drug-likeness, and medicinal chemistry friendliness of various molecules. It is regarded as one of the simpler methods for determining the profiles of drug-likeness of compounds by the Lipinski rule, under which scientists were in search of orally active compounds[17]. It was developed by the Swiss Institute of Bioinformatics as a freely available web-based tool for evaluating small molecules' pharmacokinetic, drug-likeness, and medicinal chemistry properties[18]. It has predictive models for several pharmacokinetic parameters like solubility, lipophilicity, and bioavailability, using which researchers can estimate how well drug candidates will be absorbed, distributed, metabolised, and eliminated from the body[19]. The in-house techniques comprising BOILED-Egg, iLOGP, and Bioavailability Radar fulfil rapid and reliable predictions concerning physicochemical properties. Application of SwissADME includes studies on antibacterial N-heterocyclic carbene-silver complexes[20] and virtual screening of bioactive small molecules[21]. Thus, it was made easier for both specialists and non-specialists to predict the key parameters of drug discovery in no

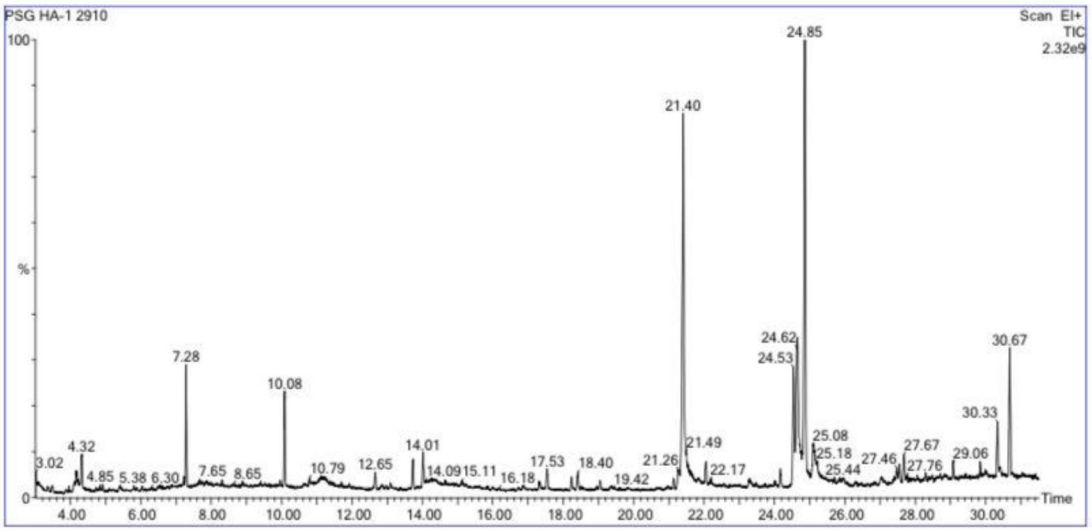


Figure 3. GC–MS chromatogram of the ethanolic extract of *Hygrophila auriculata* showing the detected phytoconstituents.

time, which serves as an invaluable tool in early-stage drug development.

2.4.1 Physicochemical Properties

The first section shows canonical SMILES of the two-dimensional chemical structure. The bioavailability radar synopsis exerts six physicochemical properties in comparing the pharmacological similarity of query compounds: LIPO (Lipophilicity), SIZE, POLAR (Polarity), INSOLU (Insolubility), INSATU (Instauration), and FLEX (Flexibility). These sections clean up molecular and physicochemical properties such as molar refractivity, TPSA, number of rotatable bonds, number of H-bond acceptors, number of H-bond donors, number of heavy atoms, number of aromatic heavy atoms, and fraction csp^3 (Table 4).

The Bioavailability Radar offers the first observation of drug-likeness for a molecule. The pink region marks the optimum range for each property (lipophilicity: XLOGP3 from −0.7 to +5.0, size: MW from 150 to 500 g/mol, polarity: TPSA from 20 to 130Å2, solubility: log S not more than 6, saturation: fraction of carbons in sp^3 not less than 0.25, flexibility: rotatable bonds not greater than 9). In the example above, the compound is predicted to be orally bioavailable and BBB penetrant because all six parameters lie within the limited range (Figure 4), and the compound is predicted to be orally bioavailable but not BBB penetrant because of the high UNSATU (Insaturation)-beyond the limited range (Figure 5).

2.4.2 Water Solubility

A solute quantity transforms the solubility of a particular solute in a solution into that factor by which the concentration can never increase beyond the saturation concentration in the solution[22]. The term SwissADME applies two topological methods in the prediction of water solubility: one is the ESOL model, and the other is like (Solubility class: Log S Scale: Insoluble<-10, poorly<-6, moderately<-4, soluble<-2, very<0, highly). They are even somewhat different from the original basic general solubility equation[23]. Because they destroy the melting point factor, but, on the other hand, they stand best in correlation to field experimental values, with $R^2 = 0.69$ and 0.81. The third SwissADME predictor has been created by SILICOS-IT, which corrects the linear coefficient by molecular weight ($R^2 = 0.75$). It states that the fractional logarithm of molar solubility in water (log S) expresses all means predicted and included by SwissADME, concentration estimates in mol/l and mg/ml, as well as qualitative solubility classes (Tables 5a, 5b and 5c).

2.4.3 Pharmacokinetics

Considering the absorption values (GI absorption) put forth concerning the plot between WLOGP and TPSA here, the elliptical Egan egg-that is generally populated by molecules of easy absorption-will prove handy as an actual predictive model for passive GI absorption and prediction of brain access by passive diffusion and, subsequently, for the BOILED egg (Brain or Intestinal Estimate D permeation). Thus, for drug discovery and research, the BOILED Egg model provides instantaneous and rapid passive GI absorption prediction, which is faster than a few simulations actually performed in a dynamic manner (Table 6). Molecules lying in white orientation, if within the white area, would, in theory, be absorbed by the

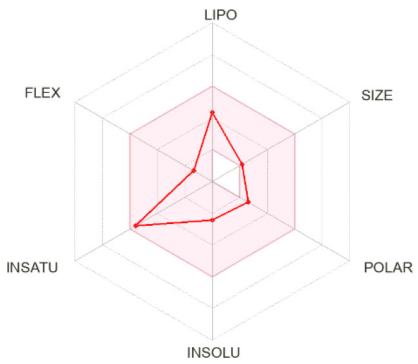


Figure 4. Bioavailability Radar of 2,5-dimethyl phenylacetic acid.

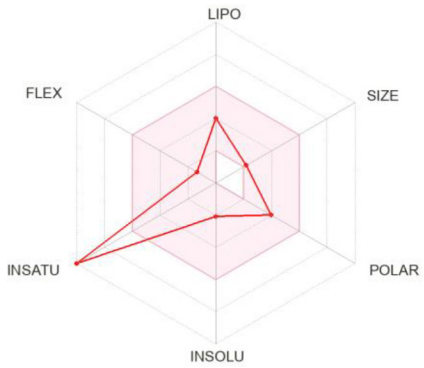


Figure 5. Bioavailability Radar of 5-formylsalicylic acid.

gastrointestinal tract, whereas those in the yellow region (representing the yolk) are expected to diffuse into the brain[24]. Whether compounds are substrates or non-substrates of P-glycoprotein (P-gp, considered the most important ATP-binding cassette transporter or ABC-transporter) is an essential determinant for elucidating the active efflux at biological membranes like that of the gastrointestinal wall: either into the lumen/intestinal lumen on one side or out of the brain on the other[25,26]. In metabolic biotransformation, Cytochromes P450 (CYP), a superfamily of isoenzymes, function by oxidising drugs[27]. Some authors consider that between 50% and 90% of commercial drugs are substrates of five major isoforms: CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4[28]. SwissADME can determine if one particular compound is a P-gp substrate or an inhibitor of most CYP isoenzymes. An SVM, a Support Vector Machine theory-driven algorithm, is employed, ensuring that the input data sets are pre-processed by rigorous cleaning processes from huge databases of known substrates and non-substrates or inhibitors and non-inhibitors[29]. SVM turned out to be more successful than any other machine-learning technique for any other binary classification. The model classifies qualitatively in a "Yes" or "No" answer fashion, irrespective of whether any given molecule, with a promise of higher probability, is a P-gp substrate (or inhibitor) or a P-gp non-substrate (or non-inhibitor)[30].

2.4.4 Medicinal Chemistry

Here is where part one flies on the side of medicinal chemists who strive day by day for drug discovery. The pattern recognition approaches supplement each other to find a set of fragments bearing some tolerance. PAINS (pan assay-interfering compounds, also called frequent-hitters or promiscuous compounds) are molecules whose sub-structure shows high screens regardless of an assay protein target (Table 7). Such fragments have been considered for false-positive biological outputs, going through six different assays to break down molecules active in at least two assays into 481 repeated fragments, thought to be leads for promiscuous compounds. SwissADME issues a warning when any such moieties have been found in the molecule under inspection. Lead likeness was set up in order not to disallow leads exhibiting exceptional affinity from HTS to be worked further during lead optimisation. Being currently unoptimized, lead compounds exist for chemical transformations that generally bring about a diminution in size and likely expose them in that they are more lipophilic than hydrophilic compared to drug-like molecules. Lead optimisation, being so far based on rules, mostly deals with molecules with molecular weight somewhere between 100 and 350 Da, ClogP lying between 1 and 3.0, considered preferably great and superior to those of drug-like counterparts.

2.4.5 Drug-likeness

Drug-likeness checks how well a molecule can truly act as an oral drug on the grounds of parameters such as bioavailability and pharmacokinetics. SwissADME has five rule-based filters-Lipinski (Pfizer), Ghose (Amgen), Veber (GSK), Egan (Pharmacia), and Muegge (Bayer)-for assessing drug-likeness by examination of key physicochemical properties. An infringement of any of these rules can presage certain pharmacokinetic-related concerns. The Abbott Bioavailability Score can also predict the oral bioavailability of a compound in rats or Caco-2 permeability and classifies the compounds into four probabilistic classes (11%, 17%, 56%, and 85%)[31](Table 8).

2.4.6 Lipophilicity

Melanie Kah and colleagues[32] claimed that lipophilicity is one of the most important intrinsic parameters of a molecule and is generally positively correlated with its bioactivity. log $P_{o/w}$ is the classical descriptor for the Lipophilicity. Occasionally referred to as the chief physicochemical property of drugs and molecules in pharmacodynamics and pharmacokinetics, lipophilicity controls ADMET for a drug, i.e., absorption, metabolism, distribution, excretion, or toxicity[33-36]. There are five methods to analyse lipophilicity of a compound: XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP, in SwissADME. XLOGP3 is an atom-based method with correction factors and a knowledge-based library[37], while WLOGP furthers the purely atomistic method based on a fragmental scheme[38]; MLOGP used 13 molecular descriptors as input in a model of linear topological nature[39]; SILICOS-IT combined 7 topological descriptors and 27 fragments in a hybrid method; iLOGP is a physics-based method that computes free energies of solvation in n-Octanol and water using GB/SA, i.e., based on generalized-born and

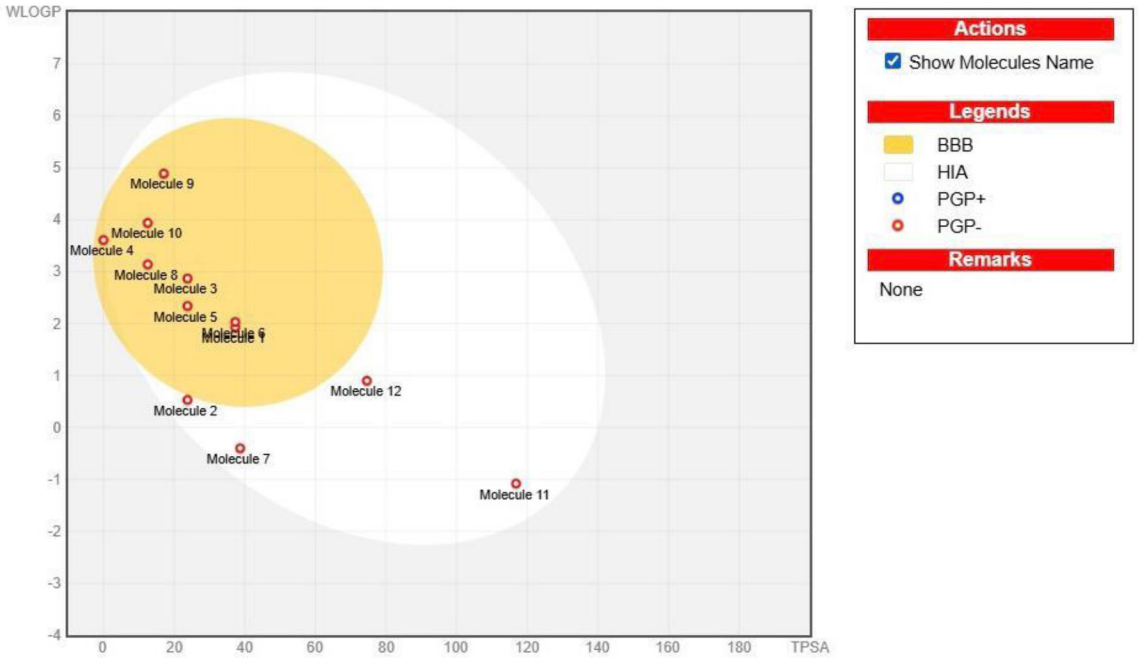


Figure 6. SwissADME BOILED-Egg model predicting gastrointestinal absorption and blood–brain barrier permeability of selected phytoconstituents.

solvent accessible surface area. Consensus log $P_{o/w}$ is the arithmetic average of the values predicted by the five suggested approaches (Table 9).

2.5 BOILED-Egg Model

The BOILED-Egg model (Figure 6) in SwissADME is a predictive graphical tool that evaluates compounds for HIA and BBB penetration with respect to two essential molecular properties: WLOGP (lipophilicity) and TPSA (Topological Polar Surface Area). In this model, compounds are reported on a 2D graph in which the white area (egg white) signifies the possibility of a compound being absorbed by the GI, whereas the yellow area (egg yolk) provides for the penetration of the compound through the BBB. Molecules exhibited in either area are pharmacokinetically favourable for oral and/or CNS activity. Due to its ultimate and useful nature, early-stage drug discovery widely utilises this tool for preeminent visual bioavailability and brain accessibility assessment of drug candidates.

2.6 *In Vitro* Test Analysis

2.6.1 Protein Denaturation Using Bovine Serum Albumin (BSA)

The reaction mixture contained ethanolic extract of *H. auriculata* at different concentrations and 1% of aqueous solution of bovine serum albumin (BSA). To prepare 1% BSA solution, 0.5ml of Bovine serum albumin and 50ml of W/V cold distilled water were taken. The mixture is stirred continuously to obtain a clear component.

2.6.2 Assay Using Bovine Serum Albumin

Bovine Serum Albumin (BSA) is commonly used in proteinase inhibitory tests. Although it interacts with many proteins and inhibitors, BSA can serve as a proteinase substrate in the assay. Such assays are meant to study how different substances inhibit proteinase activity, as various studies have demonstrated.

2.6.3 BSA as a Protein Substrate in Protein Assays

Frequently, BSA is used as a substrate in proteinase assays to analyse how inhibitors can negatively affect certain substances. For example, in the inhibition of *Candida albicans* Sap2 proteinase activity, BSA hydrolysis was used to check inhibition by antibodies; however, the specific antibodies showed no significant inhibition[40]. Similarly, the BSA substrate was used to demonstrate inhibition of elastase and trypsin by lens proteins[41].

2.6.4 Inhibition by Some BSA Preparations

On the other hand, some commercial BSA preparations have evidently inhibited some

Table 1. Preliminary phytochemical screening of the ethanolic extract of *H. auriculata*

Phytochemical Parameter	Test Method	Observation	Result
Alkaloids	Mayer's / Dragendorff's	Cream/orange precipitate	Present (+)
Flavonoids	Shinoda test	Pink/red colour	Present (+)
Phenolics / Tannins	Ferric chloride test	Blue-black colour	Present (+)
Saponins	Foam test	Stable persistent foam	Present (+)
Steroids	Liebermann–Burchard test	Green colour	Present (+)
Terpenoids	Salkowski test	Reddish-brown colour	Present (+)
Total Phenolic Content (TPC)	Folin–Ciocalteu method	High concentration of phenolic compounds	Present (+)

Table 2. GC–MS identified phytoconstituents present in the ethanolic extract of *H. auriculata* along with their reported pharmacological activities

Sr. No.	Phyto-constituents	RT	Height	Peak Area	Pharmacological Activity
1	2,5-Dimethylphenylacetic Acid	4.164	110,427,448	7,355,904.5	Anti-Inflammatory Activity
2	Azetonitrile	4.324	191,841,072	10,056,026	Not Well-Defined Activity
3	Octanenitrile	4.324	191,841,072	10,056,026	Limited Direct Activity
4	Cyclohexane (1-methylpropyl)	4.324	191,841,072	10,056,026	No Intrinsic Activity
5	Hexanenitrile, 5-methyl	7.280	625,797,568	16,757,030.0	No Specific Activity
6	6-Bromohexanoic Acid	10.081	489,114,208	14,651,948	Anti-Bacterial and Anti-Fungal Properties
7	Ethanol 2,2-diethoxy	17.534	107,134,424	4,921,519.0	Specific Activity Depends on Derivatisation
8	Oxirane, octyl-	21.401	1,896,691,712	118,009,320.0	Serves as a Precursor
9	6-Tetra Decanone	21.401	1,896,691,712	118,009,320.0	Anti-Inflammatory, Anti-Fungal, Anti-Microbial Properties
10	Caryophyllene oxide	24.852	2,160,505,600	101,201,656.0	Anti-Cancer, Anti-Inflammatory, Anti-Fungal Properties
11	Diaziquone	25.192	92,199,472	6,545,030.0	Anti-Cancer Activity
12	5-Formylsalicylic Acid	30.674	656,125,120	27,397,308.0	Anti-Inflammatory, Anti-Oxidant Properties

reactions, like inhibiting erythrocyte agglutination in serological tests. Interpreting assay results may become difficult if inhibitors are mediated by the BSA preparation; thus, one must exercise great care in the selection and screening of the BSA batch for use in an experiment[42].

2.6.5 BSA and Protein Complex

Being able to form complexes with other proteins, such as α1-antitrypsin, BSA loses its capacity to bind to other constituents and inhibit functions. This interaction is essential in antimicrobial peptide activity inhibition, where the BSA/α1-antitrypsin complex inhibits peptide activity[43]. While BSA is useful in proteinase assays, its interactions with other proteins and its capacity to inhibit must be considered. Inhibitors in BSA preparations or complex formation by BSA with other proteins could affect the outcomes of the assays, thus placing more caution upon experimental designs and interpretation.

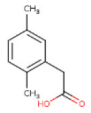
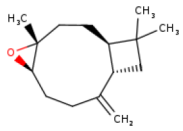
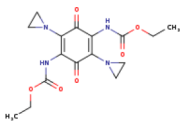
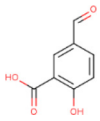
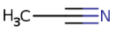
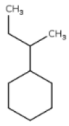
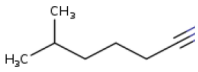
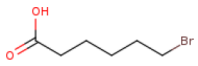
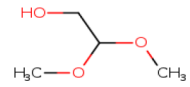
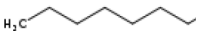
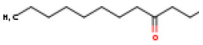
2.6.5.1 Sample Mixture

A 0.5-ml total mixture is prepared by combining 0.2 ml of 1 % BSA with 2 ml of ethanolic extract of *H. auriculata* at varying concentrations and 2.8ml of phosphate buffer (pH 7.4).

2.6.5.2 Standard Mixture

The full mixture of 0.5ml is assembled from 0.2ml of 1% BSA, 2ml of standard aqueous drug aspirin, and 2.8ml of phosphate buffer (pH 7.4).

Table 3: Molecular properties and structural characteristics of major phytoconstituents identified from *H. auriculata*.

Phyto Constituens	Mol. Weight	Mol.Formula	Smile Notation	Structure
2,5-Dimethyl Phenylacetic Acid	164.2	C10H12O2	Cc1ccc(cc1CC(=O)O)C	
Azetonitrile	41.05	C2H3N	CC#N	
Octanenitrile	125.21	C8H15N	CCCCCCCC#N	
Cyclohexane (1-methyl propyl)	140.27	C10H20	CCC(C1CCCCC1)C	
Hexanenitrile, 5-methyl	111.18	C7H13N	N#CCCCC(C)C	
6-bromo hexanoic acid	195.05	C6H11BrO2	BrCCCCCC(=O)O	
Ethanol 2,2-diethoxy	106.12	C4H10O3	OCC(OC)OC	
Oxirane, octyl-	156.27	C10H20O	CCCCCCCCC1CO1	
6-Tetra decanone	212.37	C14H28O	CCCCCCCCC(=O)CCCCC	
Caryophyllene oxide	220.35	C15H24O	C=C1CC[C@H]2O[C@@]2(CC[C@@H]2[C@@H]1CC2(C)C)C	
Diaziquone	364.35	C16H20N4O6	CCOC(=O)NC1=C(N2CC2)C(=O)C(=C(C1=O)N1CC1)NC(=O)OCC	
5-formylsalicylic acid	166.13	C8H6O4	O=Cc1ccc(c(c1)C(=O)O)O	

2.6.5.3 Control Mixture

The full-volume mixture of 0.5 mL is composed of 0.2 mL of 1% BSA, 2.8 mL of phosphate buffer (pH 7.4), and 1.5 mL of triple-distilled water.

2.6.6 Proteinase Inhibitory Action

The reaction mixture (5ml) containing 0.2% of 1% BSA, 2.8ml of phosphate buffer, and 2ml of ethanolic extract of *H. auriculata* and standard aspirin mixture was incubated at 37°C for 30 minutes. After 30 minutes, the pH of all the reaction mixtures was measured using a pH meter, and it was checked whether the pH was 7.4. The reaction mixture was then adjusted to this pH using a 0.1% concentrated solution. HCl to maintain the same pH (pH = 7.4). Heat the reaction mixtures in a water bath at 70°C for 15 minutes. After cooling, the absorbance was measured at 660nm using a UV Spectrometer (using triple-distilled water as a blank)[44].

2.6.7 Formula for Calculating the Percentage of Inhibition

The percentage of inhibition of protein denaturation was calculated using the formula below:

Percentage Inhibition = (Absorbance of control – Absorbance of sample) x 100 / Absorbance of control. The findings are presented in Table 10 below.

3. Results

3.1 Preliminary Phytoconstituent Screening

The ethanolic extract of *H. auriculata* showed the presence of various classes of secondary metabolites, which are usually linked to pharmacological activities.

3.2 Gas Chromatography-Mass Spectrometry (GC-MS)

The qualitative analysis of the extract showed the presence of 43 compounds in the ethanolic extract, out of which 12 phytoconstituents having the largest peak height and peak area were subjected to further studies.

Table 4. SwissADME-predicted physicochemical descriptors of selected phytoconstituents from *H. auriculata*

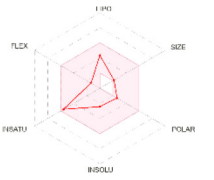
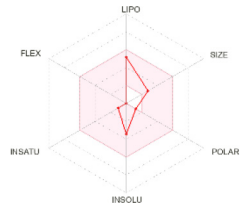
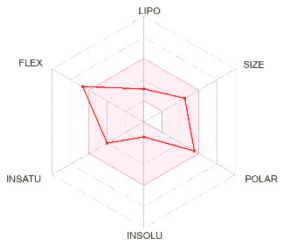
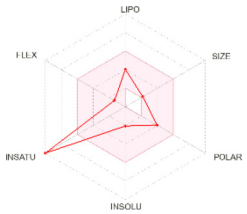
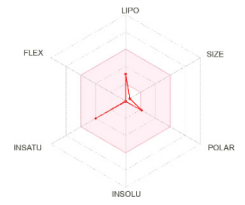
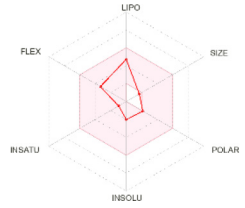
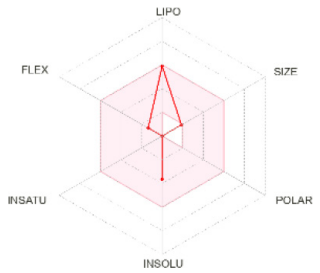
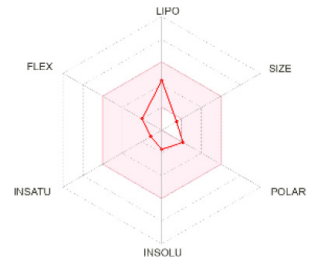
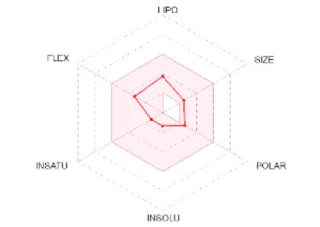
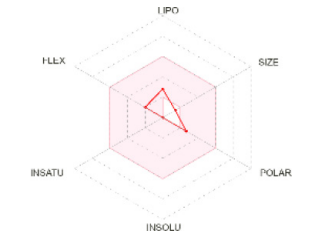
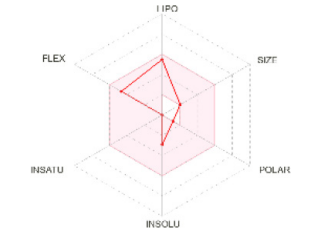
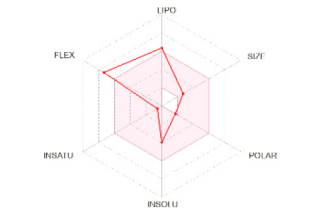
Phyto-constituent	Bioavailability Radar	Results
2,5-Dimethyl Phenylacetic Acid		In this example, the chemical in this instance is expected to be bioavailable when taken orally.
Azetonitrile		The compound's low solubility in this instance is expected to result in a modest oral bioavailability.
Octanenitrile		In this example, the chemical in this instance is expected to be bioavailable when taken orally.
Cyclohexane (1-methylpropyl)		It is anticipated that the chemical in this instance will not be orally bioavailable due to its excessive flexibility and lipophilicity.
Hexanenitrile, 5-methyl		Since the chemical is lipophilic, it is anticipated that it will not be orally bioavailable in this instance.
6-bromo hexanoic acid		Because the carboxyl group is ionised in this instance, the molecule is expected to have a moderate oral bioavailability.

Table 4. Continued...

Phyto-constituent	Bioavailability Radar	Results
Ethanol 2,2-diethoxy		In this example, the chemical in this instance is expected to be bioavailable when taken orally.
Oxirane, octyl-		In this example, the chemical in this instance is expected to be bioavailable when taken orally.
6-Tetradecanone		In this example, the chemical in this instance is expected to be bioavailable when taken orally.
Caryophyllene oxide		In this example, the chemical in this instance is expected to be bioavailable when taken orally.
Diaziquone		Because they are insoluble and lipophilic, the chemicals in this case are projected not to be orally bioavailable.
5-Formylsalicylic acid		Because of its restricted solubility and ionisation, the chemical in this instance is expected to have a modest oral bioavailability.

3.3 SwissADME Analysis

SwissADME evaluation comprehensively assessed the lipophilicity, aqueous solubility (ESOL, Ali, and SILICOS-IT models), drug-likeness, bioavailability, and key pharmacokinetic properties of *H. auriculata* phytoconstituents, providing insight into their oral absorption potential and overall drug candidacy.

Table 5. SwissADME-predicted lipophilicity parameters (Log P) of phytoconstituents identified from *H. auriculata*

Table 5a. ESOL Model – Solubility Prediction

Phytoconstituent	Log S (ESOL)	mg/mL	mmol/L	Solubility Class
2,5-Dimethyl Aminoacridine	-2.43	6.17E-03	7.76E-03	Soluble
Acetoxime	-0.98	3.40E-01	7.82E-01	Very soluble
Oxamemic	-2.02	1.20E-01	9.36E-03	Soluble
Cyclohexane methoxypropylamine	-3.63	3.31E-02	3.02E-02	Soluble
Heptanoic acid	-1.69	2.29E+00	4.02E-02	Soluble
Hexanoic acid	-1.37	8.35E+00	4.28E-02	Soluble
Ethanol, 2-chloro-	0.07	1.25E+02	1.18E+00	Highly soluble
Octane, octylamine	-2.93	1.84E-01	1.18E-03	Soluble
6-Tetradecanoic acid	-3.98	2.02E-02	1.04E-04	Soluble
Caryophyllene	-3.45	7.84E-02	3.45E-04	Soluble
Acetamide	-1.43	1.37E+01	3.57E-02	Soluble
3-trimethylsilyl salicylic acid	-2.09	1.35E-01	8.18E-03	Soluble

Table 5b. Ali Model – Solubility Prediction

Phytoconstituent	Log S (Ali)	mg/mL	mmol/L	Solubility Class
2,5-Dimethyl Aminoacridine	-5.24	4.91E-01	9.05E-03	Soluble
Acetoxime	-0.03	3.83E-01	9.33E-01	Very soluble
Oxamemic	-2.9	1.36E-02	1.27E-05	Soluble
Cyclohexane methoxypropylamine	-4.57	3.74E-03	2.67E-05	Soluble
Heptanoic acid	-2.28	5.81E-01	5.39E-02	Soluble
Hexanoic acid	-1.14	7.71E+00	3.95E-02	Soluble
Ethanol, 2-chloro-	0.25	1.83E+02	1.53E+00	Soluble
Octane, octylamine	-4.07	1.33E-02	8.53E-05	Soluble
6-Tetradecanoic acid	-5.76	3.67E-04	1.73E-06	Moderately soluble
Caryophyllene	-3.51	6.83E-02	3.10E-04	Soluble
Acetamide	-1.98	3.78E+00	1.04E-02	Soluble
3-trimethylsilyl salicylic acid	-2.74	3.05E-02	1.83E-03	Soluble

Table 5c. SILICOS-IT Model – Solubility Prediction

Phytoconstituent	Log S (SILICOS-IT)	mg/mL	mmol/L	Solubility Class
2,5-Dimethyl Aminoacridine	-2.94	1.88E-01	1.15E-03	Soluble
Acetoxime	-0.1	3.22E-01	7.82E-01	Soluble
Oxamemic	-2.74	2.28E-01	1.82E-03	Soluble
Cyclohexane methoxypropylamine	-2.52	4.27E-01	3.04E-03	Soluble
Heptanoic acid	-1.94	1.27E+00	1.14E-02	Soluble
Hexanoic acid	-2.13	1.43E+00	7.35E-03	Soluble
Ethanol, 2-chloro-	0.06	1.20E+02	1.14E+00	Soluble
Octane, octylamine	-3.15	1.11E-01	7.13E-04	Soluble
6-Tetradecanoic acid	-5.06	1.84E-03	8.67E-06	Soluble
Caryophyllene	-3.51	6.81E-02	3.09E-04	Soluble
Acetamide	-2.06	3.20E+00	8.77E-03	Soluble
3-trimethylsilyl salicylic acid	-1.14	1.21E+01	7.92E-02	Soluble

Table 6. SwissADME-predicted pharmacokinetic properties, including GI absorption, BBB permeability and P-gp substrate status of selected phytoconstituents

Phyto-constituents	GI Absorption	BBB Permeant	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Log K_p (cm/s)
2,5-Dimethyl Phenylacetic Acid	High	Yes	No	No	No	No	No	No	-5.8
Azetonitrile	High	No	No	No	No	No	No	No	-6.56
Octanenitrile	High	Yes	No	No	No	No	No	No	-5.11
Cyclohexane (1-methyl propyl)	Low	Yes	No	No	No	Yes	No	No	-3.72
Hexanenitrile, 5-methyl	High	Yes	No	No	No	No	No	No	-5.45
6-bromo hexanoic acid	High	Yes	No	No	No	No	No	No	-6.76
Ethanol 2,2-diethoxy	High	No	No	No	No	No	No	No	-7.37
Oxirane, octyl-	High	Yes	No	No	No	No	No	No	-4.34
6-Tetra decanone	High	Yes	No	Yes	No	No	No	No	-3.59
Caryophyllene oxide	High	Yes	No	No	Yes	Yes	No	No	-5.12
Diaziquone	High	No	No	No	No	No	No	No	-8.54
5-formylsalicylic acid	High	No	No	No	No	No	No	No	-6.21

Table 7. Drug-likeness and medicinal chemistry friendliness parameters of selected phytoconstituents

Phyto-constituents	Pains	Brenk	Lead Likeness	Synthetic Accessibility
2,5-Dimethyl Phenylacetic Acid	0	0	1	1.5
Azetonitrile	0	0	1	2.36
Octanenitrile	0	0	1	1.64
Cyclohexane (1-methylpropyl)	0	0	2	2.29
Hexanenitrile, 5-methyl	0	0	1	1.38
6-bromo hexanoic acid	0	1	1	2.19
Ethanol 2,2-diethoxy	0	1	1	1.93
Oxirane, octyl-	0	1	2	2.22
6-Tetradecanone	0	0	3	2.04
Caryophyllene oxide	0	2	2	4.35
Diaziquone	1	3	2	4.05
5-formylsalicylic acid	0	1	1	1.17

3.4 *In Vitro* Analysis of Anti-inflammatory Activity

The ethanolic extract of *H. auriculata* exhibited a clear concentration-dependent increase in *in vitro* anti-inflammatory activity, with progressively higher percentage (Table 10) inhibition observed as the extract concentration increased, indicating significant anti-inflammatory potential at higher doses.

Table 8. SwissADME-predicted drug-likeness rule filter assessment (Lipinski, Veber, Egan and Muegge) and bioavailability scores of selected phytoconstituents from *H. auriculata*

Phyto-Constituents	Lipinski	Veber	Egan	Muegge	Bioavailability score
2,5-Dimethyl Phenylacetic Acid	0	0	0	1	0.85
Azetonitrile	0	0	0	3	0.55
Octanenitrile	0	0	0	2	0.55
Cyclohexane (1-methylpropyl)	1	0	0	2	0.55
Hexanenitrile, 5-methyl	0	0	0	2	0.55
6-bromo hexanoic acid	0	0	0	1	0.85
Ethanol 2,2-diethoxy	0	0	0	2	0.55
Oxirane, octyl-	0	0	0	2	0.55
6-Tetradecanone	0	1	0	2	0.55
Caryophyllene oxide	0	0	0	1	0.55
Diaziquone	0	0	0	0	0.55

Table 9. Consensus Log P values and comparison of lipophilicity models for selected phytoconstituents based on SwissADME predictions

Phyto-constituents	ILOGP	XLOGP3	WLOGP	MLOGP	SILICOS-IT	Consensus Log $P_{o/w}$
2,5-Dimethyl Phenylacetic Acid	1.68	2.11	1.93	2.29	2.49	2.1
Azetonitrile	0.84	-0.02	0.53	-0.37	-0.19	0.16
Octanenitrile	2.3	2.75	2.87	2.07	2.27	2.45
Cyclohexane (1-methylpropyl)	2.87	4.84	3.61	4.43	3.26	3.8
Hexanenitrile, 5-methyl	1.99	2.15	2.34	1.74	1.67	1.98
6-bromo hexanoic acid	1.71	1.03	2.03	1.79	1.58	1.63
Ethanol 2,2-diethoxy	1.39	-0.59	-0.4	-0.66	-0.35	-0.12
Oxirane, octyl-	3.12	4.1	3.14	2.45	3.58	3.28
6-Tetradecanone	3.85	5.64	4.89	3.8	4.92	4.62
Caryophyllene oxide	3.15	3.56	3.94	3.67	4.07	3.68
Diaziquone	2.36	-0.02	-1.08	-1.55	-0.26	-0.11
5-formylsalicylic acid	0.84	1.56	0.9	0.38	0.89	0.92

Table 10. % Inhibition of the ethanolic extract of *H. auriculata* at different concentrations

Sr. No.	Concentration	Absorbance	% Inhibition
1	50	0.453	11
2	100	0.414	18.66
3	200	0.396	22.20
4	400	0.355	30.25
5	600	0.332	34.77
6	800	0.214	57.9
7	1000	0.196	61.4

4. Discussion

In silico studies carried out using SwissADME on *H. auriculata* phytoconstituents gave insight into their pharmacokinetic and drug-likeness profiles. Most of the selected compounds attained high gastrointestinal absorption rates and thereby suggest good oral bioavailability.

Compounds such as 2,5-Dimethyl Phenylacetic Acid, Octanenitrile, and Caryophyllene oxide were shown to possess the ability to cross the blood-brain

barrier, thus hinting towards possible CNS activities. The drug-likeness against different rules, such as Lipinski, Veber, Egan, and Muegge, showed most of the phytochemicals broke very few of those rules, with compounds such as 2,5-Dimethyl Phenylacetic acid, 5-Formylsalicylic acid, and 6-bromo hexanoic acid showing a good bioavailability (0.85) within the acceptable range for oral drug physicochemical properties.

Consensus log $P_{o/w}$ values for lipophilicity showed moderate to good lipophilicity levels for the few compounds studied, supporting good absorption and distribution properties. These compounds include Octanenitrile (2.45), Caryophyllene oxide (3.68), and 6-Tetradecanone (4.62). Generally ranging between 1.1 and 2.3 for most of the compounds, synthetic accessibility scores also hint that these phytochemicals could be good candidates for further synthetic modification and optimisation in medicinal chemistry.

Altogether, these results demonstrate that the phytoconstituents of *H. auriculata* satisfy the essential pharmacokinetic and medicinal chemistry parameters suitable for early-stage drug development. Profiling of select phytochemicals of *H. auriculata* using SwissADME showed promising pharmacokinetic properties and drug-likeness. Because of high gastrointestinal absorption, suitable lipophilicity, and least violation by drug-likeness filters, many of these phytochemicals have mutually supported the consideration as drug candidates for oral administration. This highly efficient *in silico* work must be further explored as a drug lead in pharmaceutical research of natural products.

In vitro anti-inflammatory study of the ethanol extract of *H. auriculata* showed a clear dose-dependent inhibition of protein denaturation. The 1000 µg/mL dose of the extract gave 61.4% inhibition, which means there was good stabilisation of protein under the inflammation conditions.

5. Conclusion

Given that traditional pharmacokinetic predictions do not encompass the entirety of the consideration, this article puts forth the view of *H. auriculata* as the missing link between traditional medicine and modern drug discovery, wherein *in silico* tools such as SwissADME would fast-track the prioritisation of phytochemicals with real translational promise. The convergence of computational predictions with experimental evidence shows that the therapeutic potential of metabolites must be viewed together with the need to integrate phytochemistry, pharmacoinformatics, and pharmacology within a single workflow. Hence, future endeavours must go beyond *in silico* assessment to conduct preclinical validation in a more organised fashion, ensuring that the most promising molecules get an efficient formulation development and clinical evaluation. Such an approach showcases how ethnopharmacological resources, when coupled with digital screening platforms, can meaningfully support the pipeline of next-generation drug candidates. The present study also revealed the ability of *H. auriculata* to strongly inhibit protein denaturation *in vitro* and thus confirmed the existence of the plant's anti-inflammatory activity. The results add to the evidence of its traditional therapeutic use and pharmacological relevance.

6. Acknowledgement

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Author Contribution

Saranya Devi CS contributed to the research design, performed the SwissADME analysis, and was primarily responsible for developing and writing the overall manuscript. Sangeetha M and Anudeepa J provided continuous scientific guidance, supervision, and critical review of the research work. Mohanram S and Harikrishnan S contributed to the experimental research work, particularly the *in vitro* assessments, and assisted in formatting and organising the manuscript. All authors have read and agreed to the published version of the manuscript.