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# Phytochemical Profiling And Molecular Docking Analysis Of Ficus Religiosa Compounds Against B2-Adrenergic Receptor

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***Abstract***

***Objectives:*** *To perform comprehensive phytochemical profiling of Ficus religiosa bark extract using high-resolution liquid chromatography-mass spectrometry (HR-LCMS) and evaluate the binding interactions of identified compounds with β2-adrenergic receptor (PDB ID: 2RH1) through molecular docking analysis, thereby elucidating the molecular basis of its traditional therapeutic applications in respiratory and cardiovascular disorders.*

***Methods:*** *Ficus religiosa bark was extracted using hydroalcoholic solvent followed by sequential fractionation through column chromatography. Phytochemical constituents were identified using HRLCMS with electrospray ionization. All identified compounds underwent molecular docking studies against β2-adrenergic receptor using AutoDock Vina. Drug-likeness was assessed using Lipinski's Rule of Five, while pharmacokinetic properties were predicted using ForceADME platform evaluating gastrointestinal absorption, blood-brain barrier permeability, P-glycoprotein substrate status, and cytochrome P450 inhibition potential.*

***Results:*** *HRLCMS analysis identified 40 bioactive compounds with confidence scores ranging from 90.42% to 99.8%. Molecular docking revealed binding energies from -5.1 to -11.7 kcal/mol, with silibinin demonstrating strongest affinity (-11.7 kcal/mol), followed by ellagic acid (-10.5 kcal/mol) and quercitrin (-10.3 kcal/mol). Five compounds luteolin (-9.9 kcal/mol), apigenin (-9.5 kcal/mol), chrysin (-9.6 kcal/mol), naringenin (-9.3 kcal/mol), and genistein (-9.1 kcal/mol) exhibited optimal balance across binding affinity, zero Lipinski violations, high gastrointestinal absorption, and favorable bioavailability scores (0.55), with minimal cytochrome P450 inhibition.*

***Conclusion:*** *This study provides molecular evidence supporting Ficus religiosa's traditional therapeutic efficacy, identifying five lead flavonoid compounds as promising β2-adrenergic receptor modulators with excellent drug-like properties and favorable pharmacokinetic profiles, warranting further in vitro receptor binding assays and in vivo efficacy evaluation for clinical translation as novel bronchodilators and cardioprotective agents.*

***Keywords:*** *Ficus religiosa; HRLCMS; β2-adrenergic receptor; molecular docking; flavonoids; drug-likeness; ADME prediction; bronchodilators; cardioprotective agents.*

## INTRODUCTION

CVDs and respiratory diseases remain among the most common causes of mortality in the world, impacting over 545 million people and causing almost 30 % of the global deaths. The β2- adrenergic receptor is a major regulator of bronchodilation, vascular tone and some metabolic processes making it a valuable therapeutic target in asthma, chronic obstructive lung disease and hypertension [1]. The available β2-agonist medicines are currently effective but are associated with undesirable side effects such as tachycardia, tremors, and receptor desensitization when used over prolonged periods. The annual healthcare expenditure incurred worldwide to treat these conditions is more than $800 billion [2]. The ever-increasing worries about drug resistance and the necessity of safer treatment choices have been behind the attempt to find new 2-adrenergic receptor modulators out of natural products [3]. At the molecular level, there is little understanding of the effects of traditional medicinal plants on this important receptor protein despite their known effects on respiratory and cardiovascular health [4].

The *Ficus religiosa,* also called the sacred fig or peepal tree has been widely used in Ayurvedic and Unani medicine to treat respiratory diseases, cardiovascular and inflammatory diseases. Phytochemical research has revealed that the plant has many bioactive compounds such as flavonoids such as quercetin, kaempferol, rutin, phenolic acids, tannins, phytosterols as well as various glycosides [5]. These components exhibit several pharmacological effects like bronchodilation, anti-inflammatory effect, antioxidant effect and

cardioprotective effect. The leaves contain compounds that bring about smooth relaxation of muscle and dilation of blood vessels [6]. Previous studies have recorded the existence of substances which are able to change the level of cyclic adenosine monophosphate and inhibit phosphodiesterase enzymes, which are both associated with the activation of 2-adrenergic receptors [7]. Recent pharmacological studies have confirmed that the plant is effective in animal models of asthma and cardiovascular disease and this would suggest compounds that may interact with 2 receptors. However, the precise molecular processes and the way by which these compounds affinity to the receptor have not been investigated with computational procedures [8].

HPLC-MS has now become a critical analytical technique in fine phytochemical profiling, enabling the identification and characterization of complex mixtures of plant metabolites with both high sensitivity and specificity [9]. This method provides accurate data concerning the molecular weights, element composition, and structures of plant compounds by the means of accurate determination of the mass and fragmentation [10]. Together with molecular docking studies, HRLCMS data allows to evaluate detected compounds systematically in their binding strengths and interaction patterns with target proteins. Computational screening techniques offer great advantages such as lower costs, rapid evaluation of many compounds, determination of binding orientations and identification of significant structural features [11]. In the recent past, the reliability of virtual screening to discover potential drug candidates has been enhanced by advances in docking algorithms and scoring systems. This two-step approach of analytic characterization and subsequent computer-based analysis has proved to be effective in accelerating the discovery of natural product drugs and in determining the molecular basis of the conventional medicine application [12].

The objective of the current research is to conduct a thorough phytochemical screening and HRLCMS-based analysis of *Ficus religiosa* extracts in order to identify bioactive compounds and evaluate molecular docking of all identified plant constituents to 2RH1 (PDB ID: 2RH1) to determine their binding capacity and explain the possible mechanisms behind the traditional therapeutic effects of the plant used.

## MATERIALS AND METHODS

### MATERIALS

Methanol (HPLC grade, 99.9% purity) and acetonitrile (HPLC grade, 99.9% purity) were procured from Sciquaint Chemicals, Pune, India. Formic acid (analytical grade, 98% purity) and chloroform (analytical grade, 99.5% purity) were obtained from Research Lab Fine Chem Industries, Mumbai, India. Ethanol (analytical grade, 99.5% purity) was purchased from Neeta Chemicals, Pune, India. Silica gel (60-120 mesh, particle size 0.063-0.200 mm) for column chromatography was procured from Research Lab Fine Chem Industries, Mumbai, India. Dragendorff's reagent, Mayer's reagent, Wagner's reagent, ferric chloride (analytical grade), lead acetate (analytical grade), and Liebermann-Burchard reagent were obtained from Sciquaint Chemicals, Pune, India. Whatman filter paper No. 1 and amber-colored glass containers were procured from local laboratory suppliers. All other chemicals and reagents used in the study were of analytical grade and used without further purification. Distilled water was freshly prepared in the laboratory using a double distillation apparatus. All solvents used for HRLCMS analysis were of HPLC grade to ensure high sensitivity and minimize background interference during mass spectrometric detection.

### METHODS

#### Collection, authentication and preparation of plant material

The trunk bark of the grown tree of *Ficus religiosa* was harvested in March 2024 in local area of Loni BK, Tal-Rahata, Dist- Ahmednagar in Maharashtra. Voucher number BSI/WRC/Cert./2014 Authentication of the plant specimen was performed by Botanical Survey of India, Pune. The trunk bark material collected was carried to the lab and rinsed in a lot of running tap water to remove the soil particles, dust and extraneous matter stuck to it and then it was rinsed with distilled water a number of times. The cleaned pieces of the barks were placed on a clean cotton cloth to remove all the excess water and then cut into smaller pieces of about 2-3 cm size with a sharp blade in order to achieve a uniform drying process. The bark fragments were shade dried in ambient temperature and dried over 15-20 days in a well-ventilated space and without direct exposure to sunlight in order to conserve thermolabile phytoconstituents. The pieces of bark used during the drying process were occasionally turned to ensure that the process was fully dry and to avoid contamination

with microorganisms. The dried bark after being fully dry, i.e. brittle and free of any moisture content, was then reduced in size by using a mechanical grinder, and then sieved through mesh no. 40 to reach a uniform distribution of particle size. The obtained powdered bark product was kept in clean, moisture free, airtight amber-colored glass flasks and kept in a cool dark environment until further extraction and phytochemical studies were done [13,14].

**Extraction of plant material**

The extraction of the powdered *Ficus religiosa* bark (100 g) was performed in a Soxhlet apparatus in 500 mL of hydroalcoholic solvent. The extraction was conducted during a period of 48 hours under controlled temperature to maximize phytoconstituent recovery. Upon extraction, the extract obtained was filtered using Whatman filter paper No. 1 to eliminate the plant debris and particulate matter. The solvent was then evaporated at reduced pressure using a rotary evaporator at 45-50 °C to concentrate the extract into a semi-solid mass. The concentrated hydroalcoholic extract was moved in pre-weighed, amber-colored glass containers and the percentage yield was determined on dry weight basis. The extract was refrigerated at 4 °C until subsequent phytochemical screening and analysis studies [15,16].

**Preliminary Phytochemical Screening**

Standard qualitative chemical tests were used as preliminary phytochemical studies on *Ficus religiosa* bark extract to determine major phytoconstituent classes. Dragendorff's and Mayer's reagents were used to detect alkaloids, Keller-Kiliani and Borntrager tests were used to detect glycosids, Shinoda test and alkaline reagent test were used to detect flavonoids, ferric chloride test was used to detect tannins, foam test was used to detect saponians, ferric chloride, lead acetate tests were used to detect phenolic compounds, Libermann-Burchard test was used to detect steroids, Salkowski test was used to detect terpenoids and All the tests were conducted in three replicates per the standard requirements and the results were documented as positive or negative according to the characteristic changes of colors or the formations of precipitates [17].

**Fractionation by column chromatography**

Column chromatography was used to fractionate the hydroalcoholic *Ficus religiosa* bark extract using silica gel (60-120 mesh) as the stationary phase. The wet packing method was used to pack a glass column to give homogeneous packing and equilibrate it with the initial mobile phase. About 10 g of the concentrated bark extract was adsorbed onto silica gel, dried and carefully loaded into the pre-packed column. The procedure was done on gradient elution with chloroform and ethanol, starting with non-polar, then moving to the polar solvent mixtures. The flow rate was kept constant; 2 mL/min and extract concentration was 100 mg/mL and volume eluted per fraction at 125 mL. Fractions were brought into labeled glass vials in a sequential manner and concentrated using rotary vacuum evaporator at low temperatures. Thin-layer chromatography was used to analyze the concentrated fractions and those fractions with a similar TLC pattern and similar values of retention factor were combined together to be analyzed further [18].

**HRLCMS analysis**

High-resolution liquid chromatography-mass spectrometry was used to identify and characterize phytoconstituents using the pooled fractions that were provided by column chromatography. The high-resolution mass spectrometer with the electrospray ionization source was used to perform the analysis. A 150 mm × 4.6 mm reverse phase C18 column (5 µm particle size) was used to perform the chromatographic separation at 30 °C. The mobile phase was made of a binary gradient system, where solvent A was water that contained 0.1 of formic acid and solvent B, which was acetonitrile that also contained 0.1 of formic acid. The gradient elution program was set up in such a way that it would achieve improved separation beginning with 10 percent B and slowly rising to 95 % B throughout the analysis. The flow rate was adjusted to 0.5 mL/min and the volume of the injection was 10 µL. Mass spectrometry was done under positive and negative ionization modes at m/z 100-1500. Parameters of the source were capillary voltage, cone voltage and desolvation temperature with optimal sensitivity. Nitrogen was taken as nebulizing gas and drying gas [19].

**Interpretation of HRLCMS data**

The obtained HRLCMS data were analyzed with the help of the corresponding mass spectrometry data processing software. The process of identification of the compounds was done using the accurate mass measurement, generation of molecular formula, isotopic distribution patterns, and characteristic mass fragmentation patterns. Each identified compound was recorded with respect to the retention time, molecular ion peaks $[M+H]^+$ or $[M-H]^-$, and diagnostic fragment ions. Making tentative identification of

phytoconstituents was achieved through the comparison of the obtained mass spectral data with the available databases such as PubChem, ChemSpider, METLIN and MassBank. Further identification was done by comparing the pattern of fragmentation and the mass spectral features with previously reported literature on *Ficus religiosa* and other species of Ficus. The correct mass with mass error tolerance of less than 5 ppm was used to assign the molecular formulas. All the identified compounds were recorded along with their retention time, molecular formula, observed m/z, and calculated m/z ions, mass error, and key fragment ions to fully characterize them [20,21].

**Selection of Target Receptor**

The β2-adrenergic receptor was selected as the molecular target based on its crucial role in bronchodilation, vascular smooth muscle relaxation, and metabolic regulation. This G-protein coupled receptor serves as an important therapeutic target for respiratory disorders like asthma and chronic obstructive pulmonary disease, as well as cardiovascular conditions. The crystal structure of human β2-adrenergic receptor was retrieved from the Protein Data Bank (PDB ID: 2RH1) with a resolution of 2.4 Å, selected for its high resolution, complete structural information, and co-crystallized ligand providing reliable binding site data. The traditional use of *Ficus religiosa* bark in managing respiratory and cardiovascular ailments, along with reported bronchodilatory and smooth muscle relaxant activities, provided strong rationale for investigating the interaction of identified phytoconstituents with this receptor. The molecular docking approach would elucidate possible binding modes and interaction patterns of the identified compounds, explaining the molecular basis of therapeutic effects and identifying potential lead compounds for pharmacological evaluation [22].

**Molecular Docking**

Molecular docking studies were performed to evaluate the binding interactions of all identified phytoconstituents with the β2-adrenergic receptor. The three-dimensional crystal structure of human β2-adrenergic receptor (PDB ID: 2RH1) was retrieved from the RCSB Protein Data Bank with a resolution of 2.4 Å. The protein structure was prepared by removing water molecules, heteroatoms, and co-crystallized ligands, followed by addition of polar hydrogen atoms and Kollman charges using AutoDock Tools. The binding site was defined based on the co-crystallized ligand position, and a grid box was generated encompassing the active site residues with appropriate dimensions to allow flexible ligand exploration. Three-dimensional structures of identified compounds were retrieved from PubChem database in SDF format and converted to PDB format. Ligand preparation involved energy minimization, addition of Gasteiger charges, and conversion to PDBQT format. Molecular docking simulations were conducted using AutoDock Vina with exhaustiveness set to 8 and generating multiple binding poses for each compound. The binding affinity was calculated in kcal/mol, and the best-scored pose with lowest binding energy was selected for interaction analysis. The docked complexes were visualized using PyMOL and Discovery Studio Visualizer to identify hydrogen bonds, hydrophobic interactions, π-π stacking, and other non-covalent interactions between ligands and receptor residues. Key interacting amino acids, bond lengths, and interaction types were documented for each compound to understand structure-activity relationships [23,24].

**Drug-likeness and In Silico ADME Prediction**

The pharmacokinetic properties and drug-likeness characteristics of identified phytocompounds were evaluated using ForceADME web server (https://geinforce.com/force-adme/, Geinforce Technology Pvt. Ltd., Pune, India) to assess their pharmaceutical potential as β2-adrenergic receptor modulators. SMILES notations of individual compounds were generated from their chemical structures and submitted to the platform for comprehensive pharmacokinetic profiling. The computational analysis evaluated multiple drug-likeness parameters including Lipinski's rule of five (molecular weight ≤500 Da, LogP ≤5, hydrogen bond donors ≤5, hydrogen bond acceptors ≤10) and Veber's criteria (polar surface area <140 $Å^2$, rotatable bonds ≤10) to predict oral bioavailability. Additional parameters assessed included gastrointestinal absorption capacity, blood-brain barrier permeability, P-glycoprotein substrate status, inhibitory potential against cytochrome P450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4), plasma protein binding affinity, volume of distribution, and skin permeability coefficient. The platform provided bioavailability scores and identified potential liabilities in medicinal chemistry properties, facilitating selection of compounds with favorable pharmacokinetic profiles for potential therapeutic applications in respiratory and cardiovascular disorders [25,26].

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## RESULTS AND DISCUSSION

### Preliminary Phytochemical investigation

Preliminary phytochemical analysis of the *Ficus religiosa* bark extract indicated the presence of various secondary metabolites using standard qualitative chemical tests (Table 1). The extract showed high positive results in flavonoid, tannin and phenolic compounds with alkaloids, glycoside, saponins, steroid and terpenoids being antagonized. The high concentration of flavonoids and the phenolic compounds is especially notable, since the mentioned classes are associated with the powerful antioxidant, anti-inflammatory, and cardioprotective properties. This observation is consistent with the conventional folk medicine uses of *Ficus religiosa* in respiratory and cardiovascular diseases, which gives it a phytochemical foundation to its therapeutic benefits and justifies more detailed characterization by more advanced analytical methods.

**Table 1: Preliminary Phytochemical Investigation of *Ficus religiosa* Bark Extract**

| Phytochemical constituents | Test | *Ficus religiosa* Bark Extract |
|---|---|---|
| **Alkaloids** | Mayer's test | + |
| | Wagner's test | + |
| | Hager's test | + |
| **Glycosides** | General test | + |
| | Keller-Kiliani test | + |
| **Flavonoids** | NaOH test | ++ |
| | $AlCl_3$ test | ++ |
| **Tannins** | $FeCl_3$ test | ++ |
| | Lead acetate test | ++ |
| **Saponins** | Foam test | + |
| **Phenolic compounds** | $FeCl_3$ test | ++ |
| **Steroids** | Liebermann-Burchard test | + |
| **Terpenoids** | Salkowski test | + |

+ = Present (Positive); ++ = Strongly present; - = Absent (Negative)

### HR-LCMS Analysis results

Analysis of *Ficus religiosa* bark extract using high-resolution liquid chromatography-mass spectrometry of the ethanolic fraction demonstrated the successful identification of 23 bioactive compounds with high confidence scores (95.7-99.6) (Table 2, Figure 1). The phytoconstituents were mainly flavonoids such as quercetin, naringenin, luteolin, apigenin, kaempferol and myricetin and the phytosterol, beta-sitosterol. Several hydroxylated flavonoids, which include catechin, epigallocatechin, eriodictyol, and fisetin, indicate that the activity has a high antioxidant potential. The significant compounds such as silibinin, ellagic acid, and resveratrol have been well-reported due to their pharmacological activities such as antipharmacological, cardioprotective and bronchodilatory. The retention times (10.15-15.25 min) are diverse, which confirms a successful chromatographic separation, whereas the mass accuracy and confidence scores are also high, which confirms the reliability of the compound identification and provides a complete phytochemical profile of the ethanolic extract.

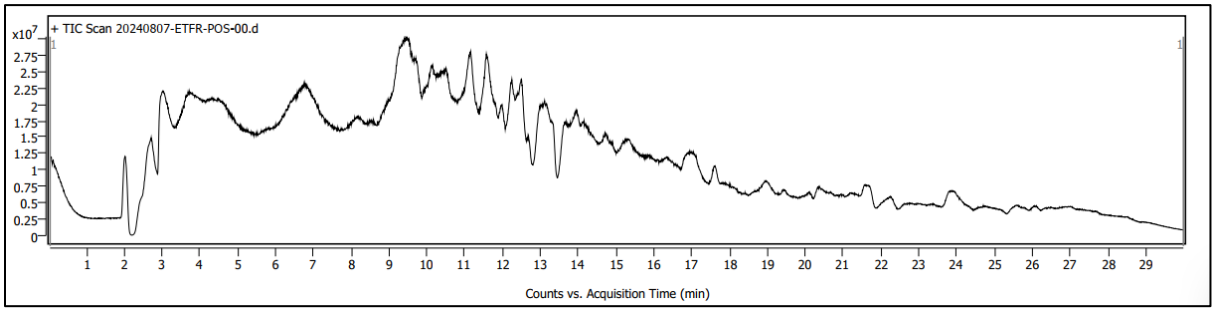


**Figure 1: HR-LCMS report of ethanolic fraction of *Ficus religiosa* bark extract**

**Table 2: List of the compounds identified in the ethanolic fraction of *Ficus religiosa* bark extract.**

| Sr. No. | Compound Name | Retention Time | Mass | Score |
|---|---|---|---|---|
| 1 | Beta-Sitosterol | 10.15 | 414.74 | 98.2 |
| 2 | Quercetin | 12.85 | 464.09 | 98.13 |
| 3 | Naringenin | 14.22 | 272.25 | 97.6 |
| 4 | Luteolin | 11.95 | 286.11 | 96.9 |
| 5 | Cyanidin | 11.65 | 287.08 | 95.7 |
| 6 | Apigenin | 13.65 | 270.12 | 99.1 |
| 7 | Myricetin | 14.95 | 318.04 | 99.3 |
| 8 | Hesperidin | 13.85 | 610.19 | 99.5 |
| 9 | Kaempferol | 13.25 | 286.06 | 97.4 |
| 10 | Chrysin | 14.45 | 254.25 | 96.1 |
| 11 | Isorhamnetin | 12.65 | 316.09 | 99.2 |
| 12 | Galangin | 14.75 | 270.13 | 98.9 |
| 13 | Baicalein | 13.55 | 270.08 | 98.7 |
| 14 | Catechin | 10.55 | 290.27 | 97.8 |
| 15 | Epigallocatechin | 12.95 | 306.18 | 99 |
| 16 | Theobromine | 15.15 | 180.16 | 96.8 |
| 17 | Ellagic Acid | 14.95 | 302.11 | 97.6 |
| 18 | Resveratrol | 12.45 | 228.25 | 98.5 |
| 19 | Fisetin | 13.95 | 286.12 | 99.6 |
| 20 | Eriodictyol | 14.85 | 288.25 | 98.4 |
| 21 | Silibinin | 15.25 | 482.1 | 98.9 |
| 22 | Genistein | 12.85 | 270.11 | 99 |
| 23 | Morin | 14.15 | 302.05 | 98.3 |

The HRLCMS analysis of chloroform fraction identified 17 different compounds with identification scores of 90.42 -99.8% (Table 3, Figure 2). The chloroform extract, unlike the ethanolic fraction, contained mostly aliphatic compounds such as dicarboxylic acids (suberic acid, sebacic acid, dodecanedioxic acid, hexadecanedioxacid), hydroxylated fatty acids (6-hydroxypentadecanedioxacid, cucurbic acid), and fatty acid derivatives (3-oxo-dodecanoic acid, 9,10-dihydroxy-12,13-epox The presence of vitexin and quercitrin is an indication of flavonoid glycosides, whereas imiquimod which is an immune response modifier was surprisingly found. D-lombricine, an amino acid derivative, and other terpenoid-related substances such as 1,4-ipomeadiol indicate that there are a wide range of biosynthetic pathways. The larger retention time range (7.183-19.862 min) than the ethanol fraction suggests a better chemical diversity and differing polarities indicating the usefulness of sequential solvent extraction in extracting different phytochemical classes in *Ficus religiosa* bark.

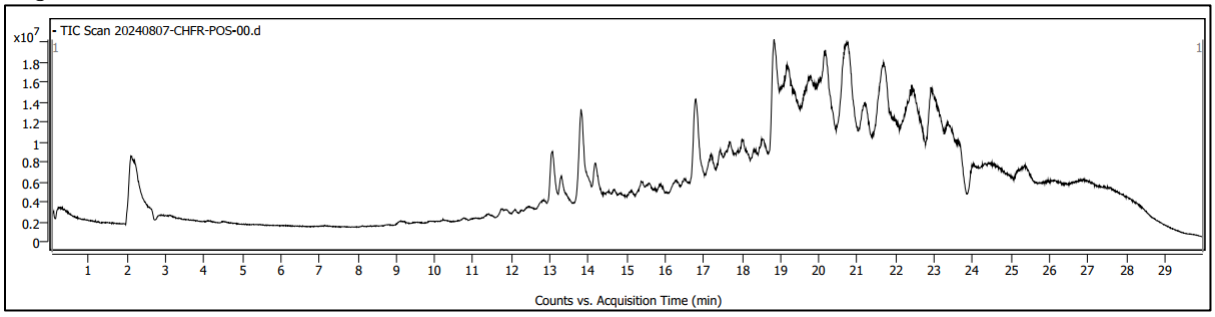


**Figure 2: HR-LCMS report of chloroform fraction of *Ficus religiosa* bark extract**

**Table 3: List of the compounds identified in the chloroform fraction of *Ficus religiosa* bark extract.**

| Sr. No. | Compound Name | Retention Time | Mass | Score |
|---|---|---|---|---|
| 1 | D-Lombricine | 7.183 | 270.0721 | 95.23 |
| 2 | 6-Hydroxypentadecanedioic acid | 10.971 | 288.1936 | 90.42 |
| 3 | 3-(2-Furanyl)-2-propenal | 11.504 | 122.0367 | 99.8 |
| 4 | Quercitrin | 11.766 | 448.1014 | 97.71 |
| 5 | Cucurbic acid | 11.824 | 212.142 | 93.3 |
| 6 | 1,4-Ipomeadiol | 11.893 | 170.0949 | 93.01 |
| 7 | 3-oxo-dodecanoic acid | 12.08 | 214.1574 | 98.6 |
| 8 | trans-4-Hydroxycyclohexanecarboxylate | 12.144 | 144.0789 | 96.88 |
| 9 | Suberic acid | 12.425 | 174.0891 | 94.31 |
| 10 | Vitexin | 12.472 | 432.1064 | 95.38 |
| 11 | Sebacic acid | 13.238 | 202.1206 | 95.2 |
| 12 | Imiquimod | 13.105 | 240.1372 | 91.28 |
| 13 | Dodecanedioic acid | 14.427 | 230.152 | 98.81 |
| 14 | 9,10-Dihydroxy-12,13-epoxyoctadecanoate | 16.257 | 330.2411 | 98.68 |
| 15 | (Â±)-1,4-Nonanediol diacetate | 16.658 | 244.1677 | 99.63 |
| 16 | Ethyl(E,Z)-decadienoate | 16.802 | 196.147 | 96.7 |
| 17 | Hexadecanedioic acid | 19.862 | 286.2146 | 98.9 |

**Results of molecular docking**

Molecular docking analysis of all 40 identified compounds against the β2-adrenergic receptor (PDB ID: 2RH1) revealed varying binding affinities ranging from -5.1 to -11.7 kcal/mol (Table 4). Silibinin exhibited the strongest binding affinity (-11.7 kcal/mol) with 6 hydrogen bonds and extensive hydrophobic interactions involving VAL114, TYR199, TYR308, and multiple phenylalanine residues, suggesting exceptional receptor complementarity. Ellagic acid (-10.5 kcal/mol) and quercitrin (-10.3 kcal/mol) demonstrated similarly robust binding with 9 and 5 hydrogen bonds respectively. Among the flavonoids, luteolin and beta-sitosterol both showed binding energies of -9.9 kcal/mol, while quercetin, apigenin, chrysin, baicalein, and eriodictyol exhibited strong affinities (-9.2 to -9.7 kcal/mol). The consistent involvement of key residues VAL114, PHE290, PHE193, PHE289, and VAL117 across multiple compounds indicates these amino acids constitute critical anchoring points within the binding pocket. Notably, compounds from the chloroform fraction generally displayed moderate binding energies (-5.1 to -7.4 kcal/mol), with D-lombricine uniquely forming 8 hydrogen bonds despite moderate affinity, while aliphatic acids primarily relied on hydrophobic interactions for receptor stabilization.

**Table 4: Molecular Docking Results of Identified Compounds with β2-Adrenergic Receptor (2RH1)**

| Sr. No. | Compound Name | Binding Energy (kcal/mol) | Hydrogen Bonds | Hydrophobic Interactions |
|---|---|---|---|---|
| 1 | Beta-Sitosterol | -9.9 | - | ALA271, LEU275, TYR141, PHE332 |
| 2 | Quercetin | -9.2 | 9 | VAL114, PHE290, VAL117, ALA200 |
| 3 | Naringenin | -9.3 | 5 | VAL114, PHE193, PHE289, PHE290, VAL117 |

| | | | | |
|---|---|---|---|---|
| 4 | Luteolin | -9.9 | 6 | VAL114, PHE193, PHE289, PHE290, VAL117 |
| 5 | Cyanidin | -8.8 | 1 | VAL114, PHE289, PHE290 |
| 6 | Apigenin | -9.5 | 3 | VAL114, PHE193, PHE289, PHE290, VAL117 |
| 7 | Myricetin | -9.4 | 5 | VAL114, PHE193, PHE289 |
| 8 | Hesperidin | -8.9 | 4 | VAL114, PHE193, PHE289 |
| 9 | Kaempferol | -9.3 | 2 | VAL114, PHE289 |
| 10 | Chrysin | -9.6 | 3 | VAL114, PHE193, PHE289, PHE290, VAL117 |
| 11 | Isorhamnetin | -9.1 | 1 | VAL114, PHE289 |
| 12 | Galangin | - | 5 | VAL114, PHE193, PHE289, PHE290, VAL117 |
| 13 | Baicalein | -9.5 | 5 | VAL114, PHE193, PHE289, PHE290, VAL117 |
| 14 | Catechin | -9.1 | 4 | TYR199, VAL114, PHE193, ALA200, VAL117 |
| 15 | Epigallocatechin | -7.6 | 2 | SER329, LYS270, ARG328, ALA271, PRO330 |
| 16 | Theobromine | - | 3 | PHE290, VAL114, VAL117 |
| 17 | Ellagic Acid | -10.5 | 9 | VAL114, PHE193, PHE289, PHE290 |
| 18 | Resveratrol | -8.7 | 2 | VAL114, PHE290, VAL117 |
| 19 | Fisetin | -9.1 | 1 | VAL114, PHE289, PHE290 |
| 20 | Eriodictyol | -9.7 | 8 | VAL114, PHE290, VAL117, ALA200 |
| 21 | Silibinin | -11.7 | 6 | VAL114, TYR199, TYR308, PHE193, PHE290, PHE194, ALA200, VAL117 |
| 22 | Genistein | -9.1 | 4 | VAL114, PHE193, PHE290, VAL117, ALA200 |
| 23 | Morin | -9.3 | 4 | VAL114, PHE289 |
| 24 | D-Lombricine | -6.2 | 8 | - |
| 25 | 6-Hydroxypentadecanedioic acid | -6.4 | 2 | VAL114, VAL117, PHE193, PHE289, PHE290 |

| | | | | |
|---|---|---|---|---|
| 26 | 3-(2-Furanyl)-2-propenal | -5.1 | 3 | TYR185 |
| 27 | Quercitrin | -10.3 | 5 | TYR308, ILE309, LYS305 |
| 28 | Cucurbic acid | -7.4 | 2 | VAL114, VAL117, ALA200, TYR199, PHE290 |
| 29 | 1,4-Ipomeadiol | -6.2 | 4 | VAL114, VAL117, PHE290, ALA200, PHE193 |
| 30 | 3-oxo-dodecanoic acid | -6.6 | 2 | VAL114, VAL117, PHE193, TRP286, PHE289 |
| 31 | trans-4-Hydroxycyclohexanecarboxylate | -5.7 | 2 | VAL114, VAL117, PHE290 |
| 32 | Suberic acid | -5.8 | 2 | VAL114, PHE290 |
| 33 | Vitexin | -9.0 | 10 | TYR199, PHE290, TYR308, VAL114, ALA200 |
| 34 | Sebacic acid | -6.1 | 5 | VAL114, VAL117, PHE289, PHE290 |
| 35 | Imiquimod | -9.1 | 6 | VAL114, PHE290, PHE193, VAL117 |
| 36 | Dodecanedioic acid | -6.9 | 2 | VAL114, VAL117, ALA200, PHE193, TYR199, PHE290 |
| 37 | 9,10-Dihydroxy-12,13-epoxyoctadecanoate | -7.2 | 2 | VAL114, VAL117, ALA200, TRP286, PHE290 |
| 38 | (±)-1,4-Nonanediol diacetate | -6.4 | 4 | VAL114, ALA200, PHE193, TYR199, TRP286, PHE289, PHE290 |
| 39 | Ethyl(E,Z)-decadienoate | -5.4 | - | ALA226, LYS273, PHE223, PHE264, HIS269 |
| 40 | Hexadecanedioic acid | -6.9 | 2 | VAL114, VAL117, ALA200, PHE193, TYR199, PHE290 |

**Drug-likeness and Lipinski's Rule of Five Compliance**

The analysis of the lipinski rule of five (drug-likeness) showed that 35 of 40 compounds had good oral bioavailability with no violation (Table 5). The vast majority of flavonoids such as quercetin, luteolin, apigenin, and kaempferol had good drug-like properties, which manifested themselves through a molecular weight of less than 500 Da, middle lipophilicity (MLogP -1.08 to 2.26), and suitable hydrogen bond parameters. One violated rule was beta-sitosterol because of high lipophilicity (MLogP 6.73) and three violated rules were exhibited by hesperidin. The rules of Veber showed that compounds with TPSA values smaller than 140 Ø and less than 8 rotatable bonds had a high potential of membrane permeability, and this implied good prospects of pharmaceutical development.

**Table 5: Lipinski's Rule of Five and Veber's Rule Parameters for All Compounds**

| Sr. No. | Compound Name | MLog P | Mol. Wt. (g/mol) | HBA | HBD | Violations | TPSA (Å²) | Rotatable Bonds |
|---|---|---|---|---|---|---|---|---|
| 1 | Beta-Sitosterol | 6.73 | 414.71 | 1 | 1 | 1 | 20.23 | 6 |
| 2 | Quercetin | -0.56 | 302.24 | 7 | 5 | 0 | 131.36 | 1 |
| 3 | Naringenin | 0.79 | 274.27 | 5 | 4 | 0 | 90.15 | 1 |
| 4 | Luteolin | 0.16 | 288.25 | 6 | 4 | 0 | 107.22 | 1 |
| 5 | Cyanidin | 0.16 | - | 6 | 4 | 0 | - | 0 |
| 6 | Apigenin | 0.71 | 272.25 | 5 | 3 | 0 | 86.99 | 1 |
| 7 | Myricetin | -1.08 | 318.24 | 8 | 6 | 1 | 151.59 | 1 |
| 8 | Hesperidin | -3.04 | 610.56 | 15 | 8 | 3 | 234.29 | 7 |
| 9 | Kaempferol | -0.03 | 286.24 | 6 | 4 | 0 | 111.13 | 1 |
| 10 | Chrysin | 1.27 | 256.25 | 4 | 2 | 0 | 66.76 | 1 |
| 11 | Isorhamnetin | -0.31 | 316.26 | 7 | 4 | 0 | 120.36 | 2 |
| 12 | Galangin | 0.52 | 270.24 | 5 | 3 | 0 | 90.90 | 1 |
| 13 | Baicalein | 0.52 | 270.24 | 5 | 3 | 0 | 90.90 | 1 |
| 14 | Catechin | 0.24 | 290.27 | 6 | 5 | 0 | 110.38 | 1 |
| 15 | Epigallocatechin | -0.29 | 306.27 | 7 | 6 | 1 | 130.61 | 1 |
| 16 | Theobromine | 0.22 | 194.19 | 3 | 0 | 0 | 61.82 | 0 |
| 17 | Ellagic Acid | -0.50 | 388.24 | 11 | 6 | 2 | 191.05 | 2 |
| 18 | Resveratrol | 2.26 | 228.24 | 3 | 3 | 0 | 60.69 | 2 |
| 19 | Fisetin | -0.56 | 302.24 | 7 | 5 | 0 | 131.36 | 1 |
| 20 | Eriodictyol | 0.24 | 290.27 | 6 | 5 | 0 | 110.38 | 1 |
| 21 | Silibinin | -0.34 | 470.43 | 10 | 5 | 0 | 155.14 | 5 |
| 22 | Genistein | 0.52 | 270.24 | 5 | 3 | 0 | 90.90 | 1 |
| 23 | Morin | -1.08 | 318.24 | 8 | 6 | 1 | 151.59 | 1 |
| 24 | D-Lombricine | -3.26 | 191.18 | 6 | 4 | 0 | 120.85 | 6 |
| 25 | 6-Hydroxypentadecanedioic acid | 2.09 | 288.38 | 5 | 3 | 0 | 94.83 | 14 |
| 26 | 3-(2-Furanyl)-2-propenal | 0.08 | 122.12 | 2 | 0 | 0 | 30.21 | 2 |
| 27 | Quercitrin | -1.84 | 448.38 | 11 | 7 | 2 | 190.28 | 3 |
| 28 | Cucurbic acid | 2.34 | 302.41 | 5 | 3 | 0 | 94.83 | 15 |
| 29 | 1,4-Ipomeadiol | 2.50 | 212.33 | 2 | 2 | 0 | 40.46 | 7 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 30 | 3-oxo-dodecanoic acid | 2.16 | 214.30 | 3 | 1 | 0 | 54.37 | 10 |
| 31 | trans-4-Hydroxycyclohexanecarboxylate | 0.35 | 144.17 | 3 | 2 | 0 | 57.53 | 1 |
| 32 | Suberic acid | 0.93 | 174.19 | 4 | 2 | 0 | 74.60 | 7 |
| 33 | Vitexin | -2.39 | 356.28 | 10 | 7 | 1 | 181.05 | 2 |
| 34 | Sebacic acid | 1.55 | 202.25 | 4 | 2 | 0 | 74.60 | 9 |
| 35 | Imiquimod | 0.46 | 205.26 | 3 | 1 | 0 | 69.62 | 2 |
| 36 | Dodecanedioic acid | 2.13 | 230.30 | 4 | 2 | 0 | 74.60 | 11 |
| 37 | 9,10-Dihydroxy-12,13-epoxyoctadecanoate | 1.85 | 342.47 | 5 | 3 | 0 | 90.29 | 15 |
| 38 | (±)-1,4-Nonanediol diacetate | 2.92 | 272.38 | 4 | 0 | 0 | 52.60 | 12 |
| 39 | Ethyl(E,Z)-decadienoate | 3.48 | 224.34 | 2 | 0 | 0 | 26.30 | 10 |
| 40 | Hexadecanedioic acid | 3.17 | 286.41 | 4 | 2 | 0 | 74.60 | 15 |

**In Silico ADME and Pharmacokinetic Profiling**

Pharmacokinetic results showed that 32 compounds displayed good gastrointestinal absorption, which showed good chances of oral bioavailability (Table 6). Great absorption profiles and bioavailability score of 0.55 were observed in most of these flavonoids and some aliphatic acids had a better score of 0.85. It was found that chrysin, resveratrol and a number of chloroform fraction compounds have blood-brain barrier permeability, which indicated possible CNS actions. It is worth noting that quercetin, kaempferol, apigenin, and baicalein represented CYP1A2 inhibitory potential, and quercetin also inhibited CYP2D6 and CYP3A4, which is why there is a risk of drug-drug interactions. P-glycoprotein substrate prediction P-glycoprotein substrate prediction predicted the presence of naringenin, luteolin, apigenin, and catechin as potential efflux substrates. Most of the compounds passed Ghose, Egan, and Muegge filters, which verify drug-like behavior and in favor of their therapeutic value as 2-adrenergic receptor modulators.

**Table 6: Pharmacokinetics Properties of Identified Compounds**

| **Sr. No.** | **Compound Name** | **GI abs.** | **BBB pen.** | **P-gp sub.** | **CYP 1A2 inh.** | **CYP 2C19 inh.** | **CYP 2C9 inh.** | **CYP 2D6 inh.** | **CYP 3A4 inh.** | **Log Kp (cm/s)** | **Ghose** | **Egan** | **Muegge** | **Bioavail. Score** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Beta-Sitosterol | Low | No | No | No | No | No | No | No | -2.20 | No | No | No | 0.55 |
| 2 | Quercetin | High | No | No | Yes | No | No | Yes | Yes | -7.05 | Yes | Yes | Yes | 0.55 |
| 3 | Naringenin | High | No | Yes | No | No | No | No | No | -6.81 | Yes | Yes | Yes | 0.55 |
| 4 | Luteolin | High | No | Yes | No | No | No | No | Yes | -6.62 | Yes | Yes | Yes | 0.55 |
| 5 | Cyanidin | High | No | Yes | No | No | No | No | Yes | -6.62 | Yes | Yes | Yes | 0.55 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | Apigenin | High | No | Yes | Yes | No | No | No | Yes | -6.17 | Yes | Yes | Yes | 0.55 |
| 7 | Myricetin | Low | No | No | Yes | No | No | No | Yes | -7.40 | Yes | No | No | 0.55 |
| 8 | Hesperidin | Low | No | Yes | No | No | No | No | No | -10.12 | No | No | No | 0.17 |
| 9 | Kaempferol | High | No | No | Yes | No | No | Yes | Yes | -6.70 | Yes | Yes | Yes | 0.55 |
| 10 | Chrysin | High | Yes | No | Yes | Yes | No | No | No | -5.82 | Yes | Yes | Yes | 0.55 |
| 11 | Isorhamnetin | High | No | No | Yes | No | No | Yes | Yes | -6.90 | Yes | Yes | Yes | 0.55 |
| 12 | Galangin | High | No | No | Yes | No | No | Yes | Yes | -6.35 | Yes | Yes | Yes | 0.55 |
| 13 | Baicalein | High | No | No | Yes | No | No | Yes | Yes | -5.70 | Yes | Yes | Yes | 0.55 |
| 14 | Catechin | High | No | Yes | No | No | No | No | No | -7.16 | Yes | Yes | Yes | 0.55 |
| 15 | Epigallocatechin | High | No | No | No | No | No | No | No | -7.51 | Yes | Yes | No | 0.55 |
| 16 | Theobromine | High | No | No | No | No | No | No | No | -7.53 | No | Yes | No | 0.55 |
| 17 | Ellagic Acid | Low | No | Yes | No | No | No | No | No | -8.31 | Yes | No | No | 0.11 |
| 18 | Resveratrol | High | Yes | No | Yes | No | Yes | No | Yes | -5.47 | Yes | Yes | Yes | 0.55 |
| 19 | Fisetin | High | No | No | Yes | No | No | Yes | Yes | -7.05 | Yes | Yes | Yes | 0.55 |
| 20 | Eriodictyol | High | No | Yes | No | No | No | No | No | -7.16 | Yes | Yes | Yes | 0.55 |
| 21 | Silibinin | Low | No | No | No | No | Yes | No | Yes | -7.40 | Yes | No | No | 0.55 |
| 22 | Genistein | High | No | No | Yes | No | No | Yes | Yes | -5.80 | Yes | Yes | Yes | 0.55 |

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 23 | Morin | Low | No | No | Yes | No | No | No | Yes | -7.40 | Yes | No | No | 0.55 |
| 24 | D-Lombricine | High | No | No | No | No | No | No | No | -9.84 | No | Yes | No | 0.56 |
| 25 | 6-Hydroxypentadecanedioic acid | High | No | No | No | No | No | No | No | -5.99 | Yes | Yes | Yes | 0.56 |
| 26 | 3-(2-Furanyl)-2-propenal | High | Yes | No | No | No | No | No | No | -6.23 | No | Yes | No | 0.55 |
| 27 | Quercitrin | Low | No | No | No | No | No | No | No | -8.42 | Yes | No | No | 0.17 |
| 28 | Cucurbic acid | High | No | Yes | No | Yes | Yes | No | No | -4.98 | Yes | Yes | Yes | 0.56 |
| 29 | 1,4-Ipomeadiol | High | Yes | No | No | No | No | No | No | -5.39 | Yes | Yes | Yes | 0.55 |
| 30 | 3-oxo-dodecanoic acid | High | Yes | No | No | No | No | No | No | -4.97 | Yes | Yes | Yes | 0.85 |
| 31 | trans-4-Hydroxycyclohexanecarboxylate | High | No | No | No | No | No | No | No | -6.94 | No | Yes | No | 0.85 |
| 32 | Suberic acid | High | No | No | No | No | No | No | No | -6.63 | Yes | Yes | No | 0.85 |
| 33 | Vitexin | Low | No | No | No | No | No | No | No | -9.42 | No | No | No | 0.55 |
| 34 | Sebacic acid | High | Yes | No | No | No | No | No | No | -6.04 | Yes | Yes | Yes | 0.85 |
| 35 | Imiquimod | High | Yes | No | Yes | No | No | No | No | -6.58 | Yes | Yes | Yes | 0.55 |
| 36 | Dodecanedioic acid | High | Yes | No | No | No | No | No | No | -5.44 | Yes | Yes | Yes | 0.85 |
| 37 | 9,10-Dihydroxy-12,13-epoxyoctadecanoate | High | No | Yes | No | No | No | Yes | No | -5.89 | Yes | Yes | Yes | 0.56 |
| 38 | (±)-1,4-Nonanediol diacetate | High | Yes | No | No | No | No | No | No | -5.19 | Yes | Yes | Yes | 0.55 |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 39 | Ethyl(E,Z)-decadienoate | High | Yes | No | Yes | No | No | No | No | -4.05 | Yes | Yes | No | 0.55 |
| 40 | Hexadecanedioic acid | High | No | No | No | No | Yes | No | No | -4.24 | Yes | Yes | No | 0.85 |

The visualization of the four best-ranked flavonoid compounds through the molecular docking technique gives essential information about the manner of action of the compounds in binding to the 2-adrenergic receptor (Figure 3). Luteolin (A, B) exhibited the best receptor complementarity with the 3D pose of deep penetration into the binding pocket and the formation of 6 hydrogen bonds with the key residues such as VAL114, PHE193, PHE289, and PHE290 and extensive 0 -0 interactions with aromatic residues stabilized the complex. Apigenin (C, D) showed the same binding orientation with 3 essential hydrogen bonds and numerous hydrophobic interactions, which was the reason of its high binding affinity (-9.5 kcal/mol). Chrysin (E, F) exhibited a specific binding affinity, with its planar conformation allowing successful 9 interaction with 9 -alkyl moieties and the formation of hydrogen bonds with the peptide on the VAL114 and PHE290 site, which is in line with its binding energy of -9.6 kcal/mol. Naringenin (G, H) exhibited strong receptive interactions of 5 hydrogen bonds and an extensive hydrophobic interaction network by its VAL114, VAL117, and several phenylalanine residues. The stable presence of VAL114 and aromatic phenylalanine in all four compounds shows that these two amino acids are the binding sites in the 2-adrenergic receptor binding site and hence its binding affinities are similar and thus these flavonoids can serve as the therapeutic agent in respiratory and cardiovascular disorders.

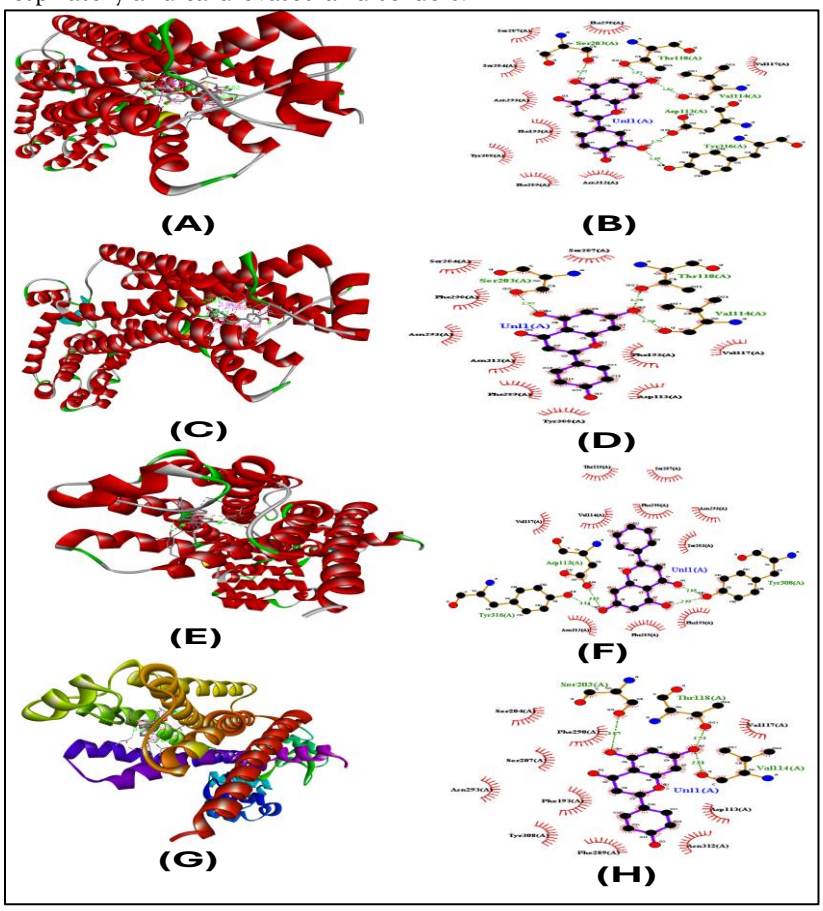


**Figure 3: (A) 3D docking pose of Luteolin showing binding pocket interactions; (B) 2D interaction diagram of Luteolin depicting hydrogen bonds and hydrophobic contacts with key residues; (C) 3D docking pose of Apigenin within the receptor binding site; (D) 2D interaction map of Apigenin showing hydrogen bonding network; (E) 3D docking conformation of Chrysin; (F) 2D ligand-receptor interaction**

**profile of Chrysin; (G) 3D docking pose of Naringenin in the β2-adrenergic receptor binding pocket; (H) 2D interaction diagram of Naringenin highlighting amino acid residues involved in binding stabilization. Green dashed lines represent hydrogen bonds, pink arcs indicate hydrophobic interactions, and purple spheres denote the ligand atoms forming interactions with the receptor.**

## DISCUSSION

The current study is a detailed phytochemical and computational study of *Ficus religiosa* bark extracts, which combines both the sophisticated analytical techniques and molecular modeling to understand the molecular genesis of its conventional therapeutic uses in respiratory and cardiovascular diseases. The experiment was able to determine 40 bioactive compounds by using the HRLCMS technique and assess their interactions with the β2-adrenergic receptor, one of the most important therapeutic targets of bronchodilation and vascular regulation [27]. Phytochemical screening of preliminary samples showed a variety of secondary metabolites such as flavonoids, tannin, phenolic compounds, alkaloids, glycosides, saponins, steroids, and terpenoids (Table 1). of particular importance is the high content of flavonoids and phenolic compounds, which have strong antioxidant, anti-inflammatory, bronchodilator, and cardioprotective properties, which can be scientifically explained by the various therapeutic uses of the plant traditionally [28]. It provided simultaneous solvent extraction, which allowed separation based on the differences in polarity, and obtained the different phytochemical profiles [29]. The ethanolic fraction had 23 compounds with hydroxylated flavonoids, such as quercetin, luteolin, apigenin, kaempferol and myricetin (Table 2, Figure 1) being predominant, and the chloroform fraction had 17 compounds, with dominance of aliphatic dicarboxylic acids, hydroxylated fatty acids, and flavonoid glycosides (Table 3, Figure 2), showing a wide range of phytochemical diversity [30].

Molecular docking analysis revealed binding energies ranging from -5.1 to -11.7 kcal/mol (Table 4). Silibinin exhibited the strongest binding affinity (-11.7 kcal/mol) through 6 hydrogen bonds and extensive hydrophobic interactions with VAL114, TYR199, TYR308, and multiple phenylalanine residues, followed by ellagic acid (-10.5 kcal/mol) and quercitrin (-10.3 kcal/mol). Among flavonoids, luteolin and beta-sitosterol demonstrated excellent binding (-9.9 kcal/mol), while quercetin, apigenin, chrysin, baicalein, and eriodictyol showed strong affinities (-9.2 to -9.7 kcal/mol) [31]. The consistent engagement of VAL114, PHE193, PHE289, PHE290, and VAL117 across multiple high-affinity compounds indicates these residues constitute critical pharmacophoric anchoring points within the β2-adrenergic receptor binding site. Chloroform fraction compounds displayed moderate binding energies (-5.1 to -7.4 kcal/mol), with aliphatic dicarboxylic acids showing progressive affinity improvement with increasing chain length, though primarily relying on hydrophobic rather than hydrogen bonding interactions [32]. Molecular docking visualization of top-ranked compounds (Figure 3) confirmed optimal receptor complementarity for luteolin, apigenin, chrysin, and naringenin, revealing deep binding pocket penetration with simultaneous hydrogen bonding and π-π stacking interactions [33]. The planar flavonoid structures enabled precise positioning of hydroxyl groups for hydrogen bonding while aromatic rings participated in extensive hydrophobic contacts, explaining their strong binding affinities and validating their potential as β2-adrenergic receptor modulators [34].

An evaluation of drug-likeness showed that 35 compounds had zero Lipinski violations (Table 5) with most flavonoids having an excellent oral bioavailability profile where the molecular weights ranged between 500 and 250 Da, moderate lipophilicity, and suitable hydrogen bond parameters. Beta-sitosterol had one violation because it was highly lipophilic and hesperidin had three violations because it was a glycosidic molecule [35]. By the usage of Veber criteria, the compounds having TPSA less than 140 WL and rotatable bonds were found to have higher potential of membrane permeability. Pharmacokinetic profiling showed that there were 32 compounds that have a high gastrointestinal absorption capacity (Table 6), which is an indication of good oral bioavailability. Chrysin, resveratrol, and some of the aliphatic compounds were found to exhibit blood-brain barrier permeability [36]. The analysis of cytochrome P450 inhibition revealed that quercetin, kaempferol, apigenin, and baicalein may be considered as potential CYP1A2 inhibitors, indicating the potential drug-drug interaction. Pharmaceutical potential was confirmed by the fact that most compounds met Ghose, Egan, and Muegge filters. After a thorough estimation of binding affinity, drug-likeness, and pharmacokinetic profile, luteolin, apigenin, chrysin, naringenin, and genistein were put up as lead candidates

with the best balance of all parameters, requiring further in vitro and in vivo confirmation as respiratory and cardiovascular therapies.

## CONCLUSION

This thorough research was able to determine 40 bioactive compounds of the *Ficus religiosa* bark extract via the HRLCMS examination and determine the molecular interactions of the previously established β2-adrenergic receptor with the 40 bioactive compounds. Silibinin, ellagic acid and quercitrin among others showed superior binding affinities (-11.7 to -10.3 kcal/mol), and flavonoids such as luteolin, apigenin, chrysin, naringenin and genistein showed the best balance between binding affinity, drug-likeness and pharmacokinetic properties and were selected as lead compounds. The persistent involvement of view critical residues VAL114, PHE193, PHE289, and PHE290 explained the molecular explanation of the conventional therapeutic effect of the plant in cardiovascular and respiratory diseases. These compounds show great clinical development potential as novel 2- adrenergic receptor modulators that have bronchodilatory and cardioprotective effects and good safety profiles. The results would justify the next step in in vitro receptor binding experiments, in isolated tissue preparations, followed by in vivo efficacy testing in animal models of both asthma and cardiovascular disease to confirm potential therapeutic and improve formulation options in clinical applications.

## ABBREVIATIONS

HRLCMS: High-Resolution Liquid Chromatography-Mass Spectrometry; CVD: Cardiovascular Disease; PDB: Protein Data Bank; ADME: Absorption, Distribution, Metabolism, and Excretion; HBA: Hydrogen Bond Acceptors; HBD: Hydrogen Bond Donors; TPSA: Topological Polar Surface Area; GI: Gastrointestinal; BBB: Blood-Brain Barrier; P-gp: P-glycoprotein; CYP: Cytochrome P450; MLogP: Moriguchi octanol-water partition coefficient; MW: Molecular Weight; TLC: Thin Layer Chromatography; ESI: Electrospray Ionization; Da: Dalton; ppm: Parts Per Million; 2D: Two-Dimensional; 3D: Three-Dimensional; BSI: Botanical Survey of India; °C: Degree Celsius; mL: Milliliter; g: Gram; mg: Milligram; µL: Microliter; µm: Micrometer; m/z: Mass-to-charge ratio; kcal/mol: Kilocalories per mole; Å: Angstrom; cm/s: Centimeter per second; VAL: Valine; PHE: Phenylalanine; TYR: Tyrosine; ALA: Alanine; LEU: Leucine; SER: Serine; THR: Threonine; ASN: Asparagine; ASP: Aspartate; TRP: Tryptophan; ILE: Isoleucine; LYS: Lysine; GLU: Glutamate; CYS: Cysteine; ARG: Arginine; PRO: Proline; HIS: Histidine; CNS: Central Nervous System.

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