OPEN ACCESS

**Scholars International Journal of Traditional and Complementary Medicine**

Abbreviated Key Title: Sch Int J Tradit Complement Med
ISSN 2616-8634 (Print) |ISSN 2617-3891 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

**Original Research Article**

# Exploring Antifungal Potential of Coleus Aromaticus Leaves Bioactive: In-Silico Validation

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**DOI:** https://doi.org10.36348/sijtcm.2025.v08i06.001 | **Received:** 30.04.2025 | **Accepted:** 04.06.2025 | **Published:** 11.06.2025

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## Abstract

***Background*:** Numerous secondary metabolites present in plants, such as tannins, terpenoids, alkaloids, flavonoids, and glycosides, have demonstrated antibacterial properties in vitro. Increasing data on the antibacterial properties of medicinal plants are emerging globally. These plants generate secondary metabolites with antibacterial properties, providing an alternative for developing chemical fungicides that are both relatively safe and cost-effective. *Coleus aromaticus*, a member of the Lamiaceae family, possesses bitter, aromatic, digestive-stimulating, stomachic, anathematic, deodorising, diuretic, and hepatoprotective properties. ***Aim*:** The aim of current investigation is to reveal the mechanisms of *C.aromaticus* leaf bioactive in treating fungal infection. ***Methodology*:** Scientific validation of the current investigation was done by computational based molecular docking study of selected lead molecules against *1,3β-Glycan synthase* enzyme. ***Result*:** The molecular docking results indicating binding energies of -4.02, -6.81,-4.24 and -5.18 kcal/mol for chlorogenic acid, quercetin, rosmarinic acid and rutin respectively. ***Conclusion*:** The findings indicated that each selected lead chemical for additional investigation shown significant inhibitory activity against *1,3β-Glycan synthase*, hence revealing its anti-fungal potential.

**Keywords:** *Coleus Aromaticus*, Antifungal Activity, Molecular Docking & *1,3β-Glycan Synthase*.



## INTRODUCTION

Contemporary natural medicines are predominantly sourced from flora. To identify the chemical components in medicinal plants that cure human ailments, 74 percent of the 119 pharmaceuticals derived from plants and now utilised globally were discovered [1]. Various applications, including pharmaceuticals, alternative medicine, and natural remedies, have been established based on the antibacterial capabilities of plant extracts [2]. Plant pathogens, such as fungus, bacteria, nematodes, and viruses, can damage plants or induce a range of illnesses. Fungi are the principal pathogens that harm plants, which is of greater significance. Globally, fungal infections markedly diminish crop yields in the agricultural industry. Fungi such as Fusarium spp. that proliferate on plants has the ability to generate mycotoxins that can be highly detrimental to consumers. P. digitatum and P. expansum are the causative agents of orange decay in the citrus sector [3]. Mycotoxins comprise fumitoxins produced by A. flavus and A. fumigatus, together with aflatoxin B1 and B2. Antimycotics are employed in agriculture to suppress fungal growth on plants and fruits, serving as one of their primary roles [4]. Secondly, they can be employed to mitigate or prevent the problem of post-harvest decay in plants and fruits [5]. The proliferation and prevalence of this fungus in food and animal feed jeopardise the health of both humans and animals.

### Predominant of Microbial Infection

Emerging infectious illnesses in humans have lately increased in prevalence or are anticipated to do so in the near future. Over the past thirty years, more than thirty new infectious agents have been identified globally, with 60% classified as zoonotic. Due to the convergence of contemporary environmental, social, and demographic conditions, emerging nations such as India disproportionately endure the burden of infectious illnesses [6]. Antibiotic resistance poses a significant danger to the efficacy of the current medical system. The emergence of multidrug-resistant bacteria has rendered the effectiveness of antibiotics uncertain, hence raising the associated risks. Antimicrobial resistance is readily generated yet challenging to overlook. The introduction of any new agent generates significant concerns regarding resistance, which will only escalate with the

development of new pharmacological classes. Due to their unparalleled chemical variety, natural products, whether in the form of pure chemicals or standardised extracts, provide limitless opportunities for novel therapeutic discoveries in pharmaceutical research. Consequently, natural products require a robust and comprehensive evaluation of their antibacterial properties in this extraordinary circumstance [7].

The herb *Coleus aromaticus* (CA), which is utilised for a number of purposes in many parts of the world, has several potential uses. The botanical genus Coleus, currently known as Plectranthus, and the herb *Coleus aromaticus/amboinicus* are both members of the Lamiaceae (Labiatae) family [8].

***Coleus Aromaticus***

It is a substantial, succulent, aromatic perennial herb with robust, fleshy stems and leaves, measuring 30-90 cm in height. Pubescent plant characterised by many branches and notably aromatic leaves. The plant is extensively distributed across India and cultivated in gardens. This traditional medicine is employed to treat several disorders, including helminthiasis, colic, convulsions, epilepsy, renal and vesicular calculi, cough, chronic asthma, hiccough, bronchitis, and malarial fever [9]. The plant has allelopathic potential, antibacterial and antimicrobial activity, insecticidal properties, components that scavenge free radicals, and give radioprotection, along with its newer culinary use. The herb's taste is mostly attributed to carvacrol and thymol, while the phenolic constituents encompass chlorogenic acid, rosmarinic acid, among others. The plant has been documented for both medicinal and pharmacological applications, as well as culinary usage [10].

**Experimental Work**

**Molecular Docking Studies**

***Ligand Preparation:***

2D Structure of chlorogenic acid was drawn using ChemSketch [11], the two-dimensional structure of the prepared ligand was converted into their 3-D structures optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligand were given below:

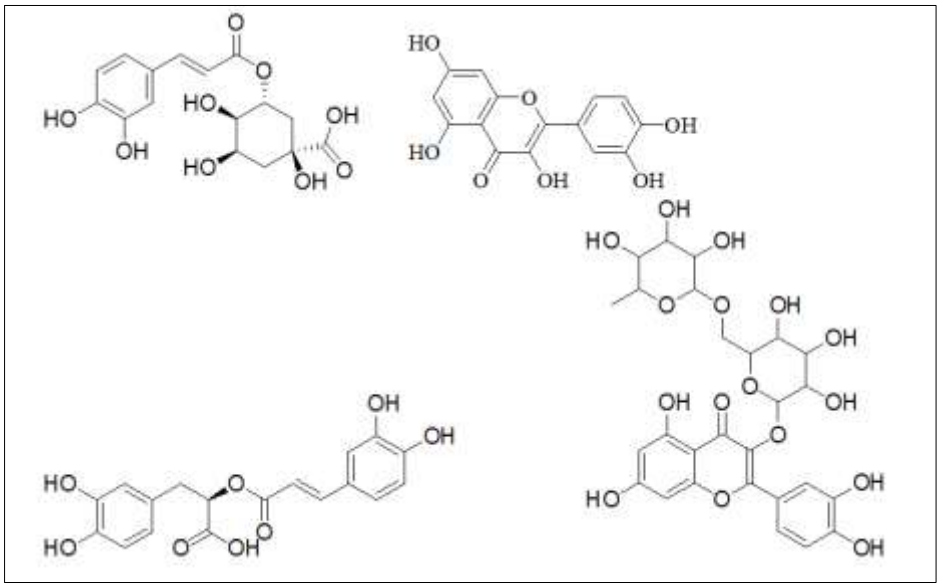


**Figure 1: 2D structure of chlorogenic acid, quercetin, rosmarinic acid and rutin**

***Preparation of the Grid File***

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing and grid points for the considered receptor in the current study are given in table 1 [12-13].

**Table 1: Grid parameters used in current docking analysis of 1,3β-Glycan synthase receptor**

| S. No. | Receptor | x-axis | y-axis | z-axis | Spacing | x center | y center | z center |
|---|---|---|---|---|---|---|---|---|
| 1 | 1,3β-Glycan synthase | 40 | 40 | 40 | 0.431 | 182.215 | 152.132 | 200.022 |

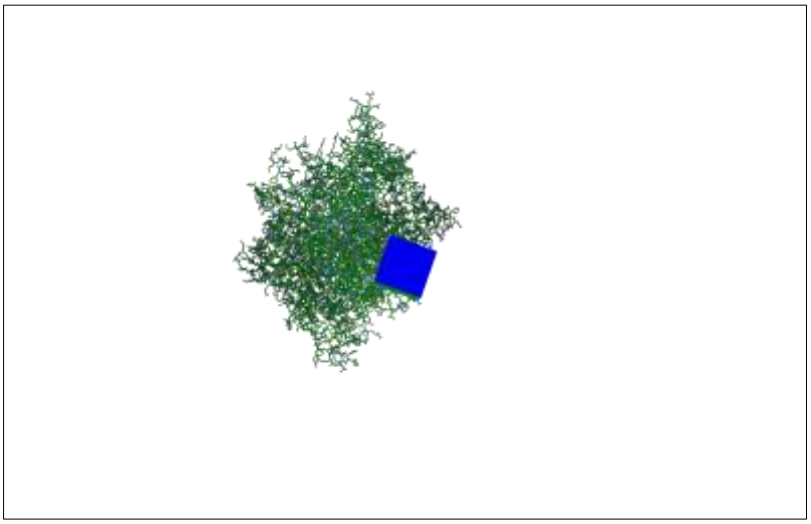


**Figure 2: Grid box covering all active sites in 1,3β-Glycan synthase receptor**

***Preparation of the Docking File***

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [14-16].

**Docking Study**

***Crystal Structure***

The crystal structure of the protein consisting of 1,3β-Glycan synthase receptor is downloaded from the Protein Data Bank portal. All the primary information regarding all the receptor's structure was registered in the Protein data bank [17-19]. The complex ligand was separated by using Chimera software for all the target receptors.

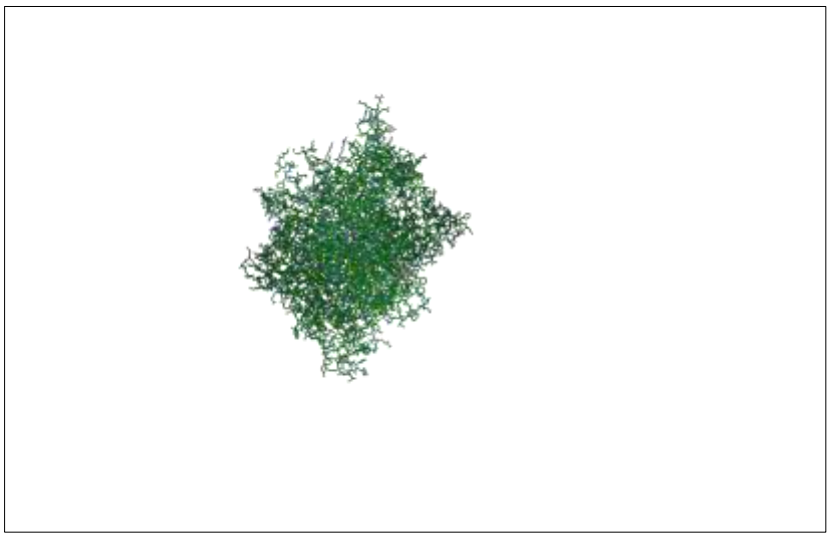


**Figure 3: Crystal structure of 1,3β-Glycan synthase receptor (PDB ID-8jzn)**

***Processing of Protein***

All the downloaded receptor proteins are having only one chains, i.e. chain A, which has been selected for experimental purpose and complex ligand was removed from it. The bound ligand was separated from the macromolecular complex by using software Chimera [20].

**Molecular Docking Simulation Studies**

Docking of ligand chlorogenic acid, quercetin, rosmarinic acid and rutin against 1,3β-Glycan synthase receptor was performed by Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [21].

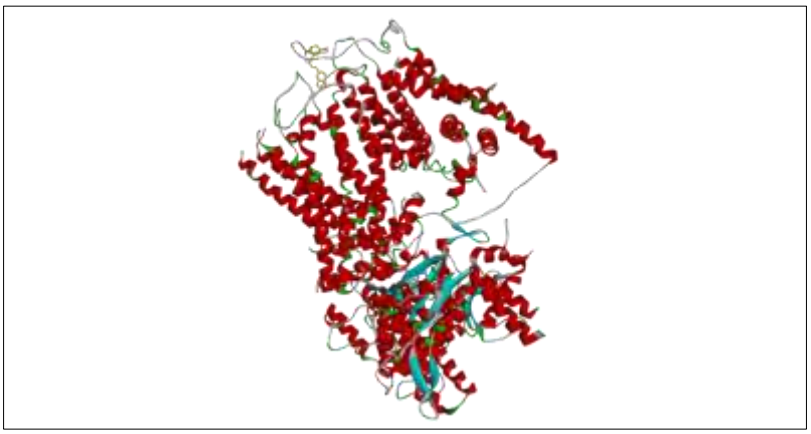


**Figure 4: Binding mode of chlorogenic acid within the active site of 1,3β-Glycan synthase receptor**

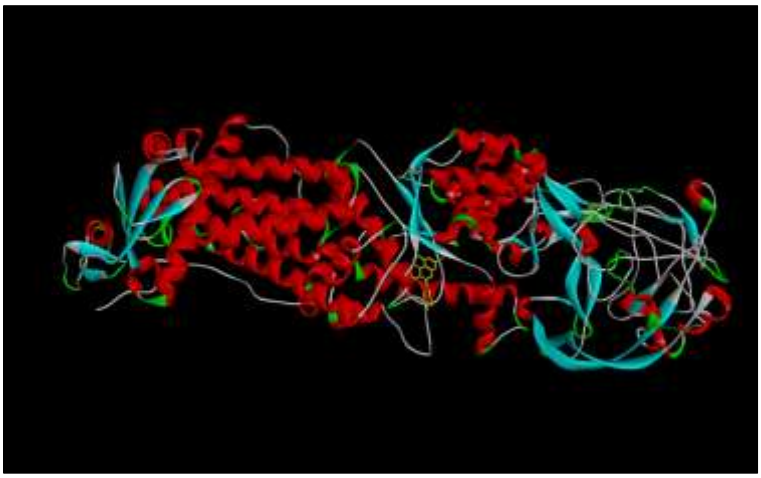


**Figure 5: Binding mode of quercetin within the active site of active site of 1,3β-Glycan synthase receptor**

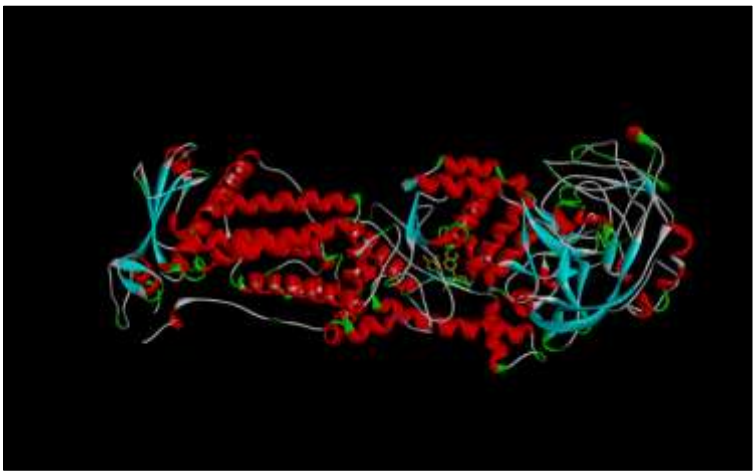


**Figure 6: Binding mode of rosmarinic acid within the active site of 1,3β-Glycan synthase receptor**

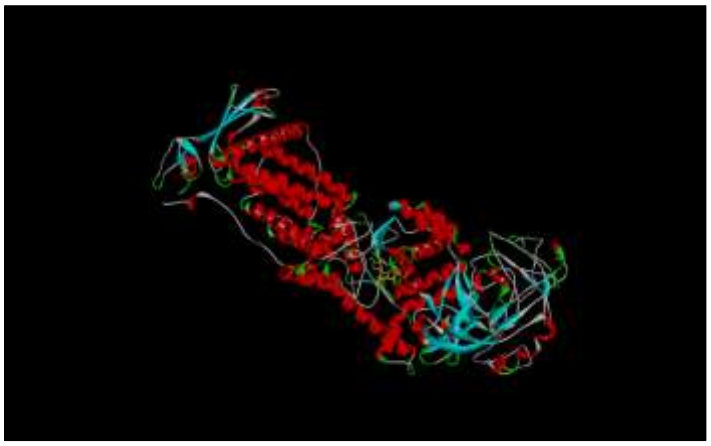


**Figure 7: Binding mode of rutin within the active site of 1,3β-Glycan synthase receptor**

**Toxicity & ADME-T Studies**

The ligand molecules viz. chlorogenic acid, quercetin, rosmarinic acid and rutin was studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [22].

## RESULT AND DISCUSSION

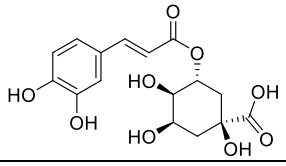
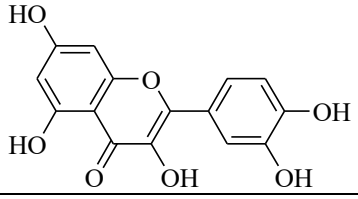
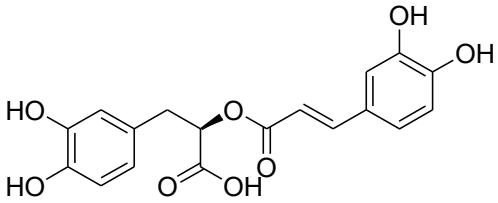
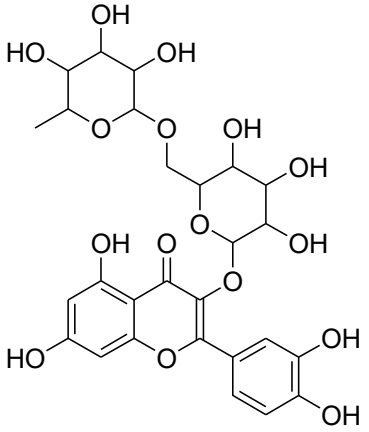
Plants have historically offered hope for fictional therapeutic molecules since plant herbal mixes have greatly benefited humans and its well-being. The popularity of using plant-based antimicrobial compounds as treatments for a variety of infectious illnesses has led to a high volume of searches for these compounds in plants. The anti-fungal activity of *C. aromaticus* leaf extract was assessed by in-silico molecular docking. The molecular docking results indicating binding energies of -4.02, -6.81,-4.24 and -5.18 kcal/mol for chlorogenic acid, quercetin, rosmarinic acid and rutin respectively. The result was tabulated in table 2. The binding mode of selected lead molecules showed in fig. 4-7. The 2D interaction of selected compounds displayed in fig.8-11. The interaction of chlorogenic acid, quercetin, rosmarinic acid and rutin with active site at *1,3β-Glycan synthase* showed as follows:

**Table 1:**

| Compound | Conventional Hydrogen bounding | π-alkyl | π - π | Week Vander's interaction | Pi-sulfur | Covalent | Unfavourable |
|---|---|---|---|---|---|---|---|
| **Chlorogenic acid** | Met 1327, Glu1854, Thr1851, Asn 1849 | Pro1342 | Ile1326 | Cys1328 Ile 1329 Ser1853 Gly1852 Thr 1847 | -- | --- | ---- |
| **Quercetin** | His585, Asp557, Met 596, Phe588 | ---- | ---- | Asn70, Leu69, Gly586, Phe588, Met65, Gly555, Ser597, Val603 | His64 | Gly66 | GLn558 |
| **Rosmarinic acid** | Ser531, Glu554, Gly555, Asp557, His67 | ---- | ---- | Trp562, Gly55, His585, Trp528, Asp95, Asn70, Tyr58, Phe587, His64 | ---- | Trp562, Pro56 | ------- |
| **Rutin** | GLn558, Tyr58, Asp95, Asp557 | Pro57, Pro56 | ------ | AsN70, Gly66, His585, His64, Gly561, Ser537 | Glu554 | ------ | ------ |

The pharmacokinetic profile reveals that it is having good pharmacokinetic profile but with the presence of any major toxic effects including mutagenicity, tumorogenicity and reproductive effects. The pharmacokinetic and toxicity profiling results of chlorogenic acid, quercetin, rosmarinic acid and rutin shown in figure12-15 & table 3-5. Theoretically, all the ligand molecules have shown encouraging docking score.

**Table 2: Results of docking of ligands against 1,3β-Glycan synthase receptor**

| S. No | Lead molecules | Structure | Binding energy |
|---|---|---|---|
| 1 | Chlorogenic acid |  | -4.04 |
| 2. | Quercetin |  | -6.81 |
| 3. | Rosmarinic acid |  | -4.24 |
| 4. | Rutin |  | -5.18 |

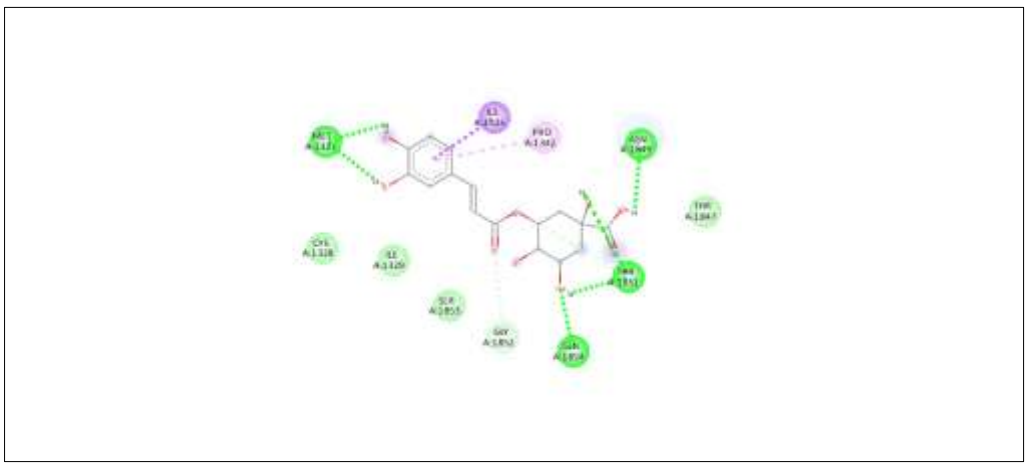


**Figure 8: Two-dimensional binding mode of chlorogenic acid within the active site of 1,3β-Glycan synthase receptor**

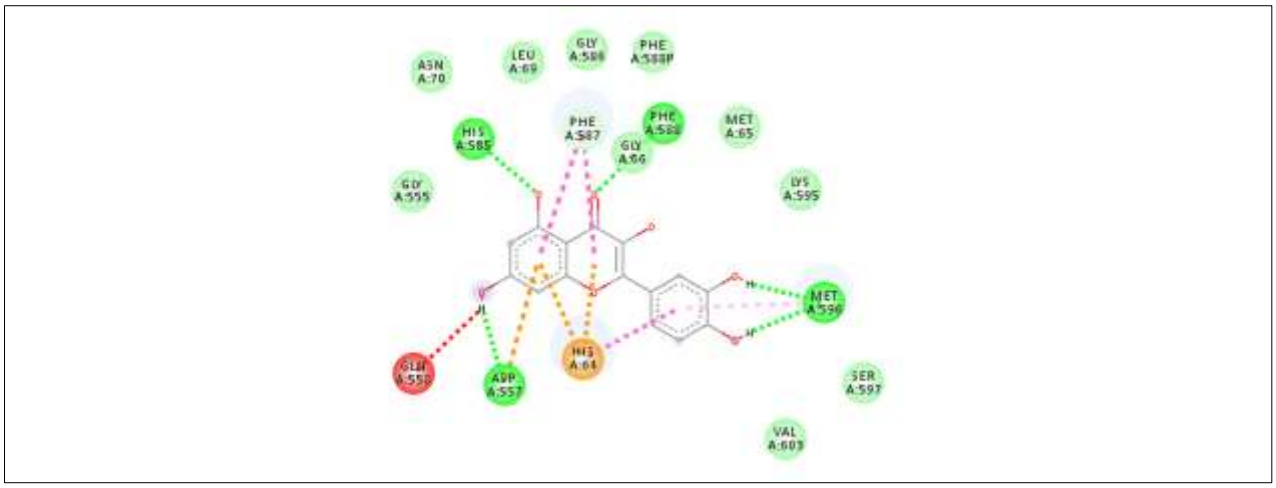



**Figure 9: Binding interaction of quercetin within the active site of 1,3β-Glycan synthase receptor**

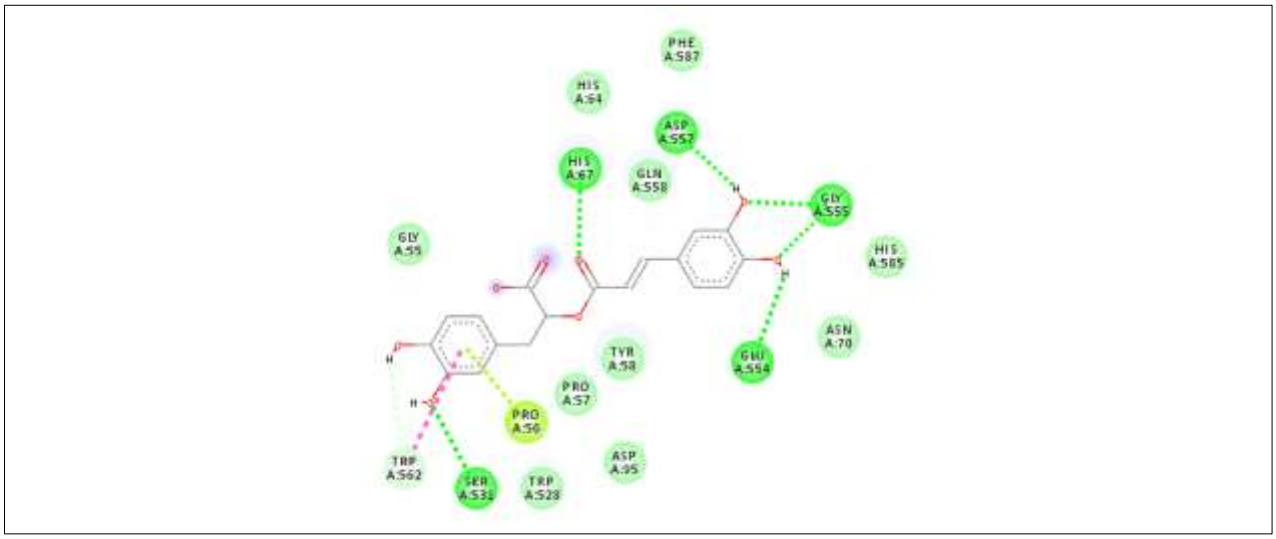



**Figure 10: Binding interaction of rosmarinic acid with active site of 1,3β-Glycan synthase receptor**

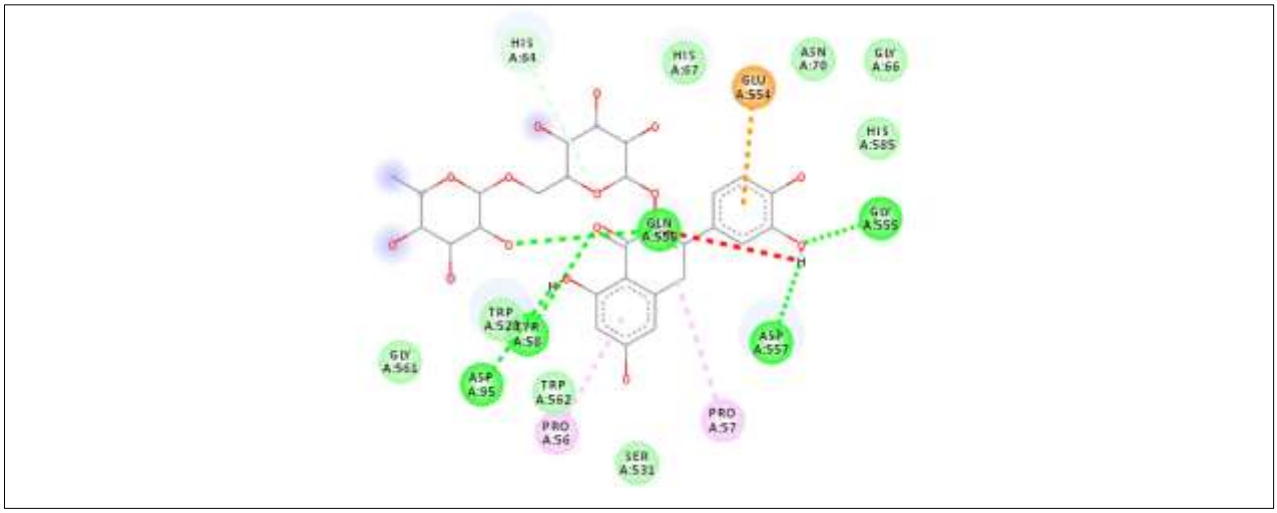



**Figure 11: Binding interaction of rutin with active site of 1,3β-Glycan synthase receptor**

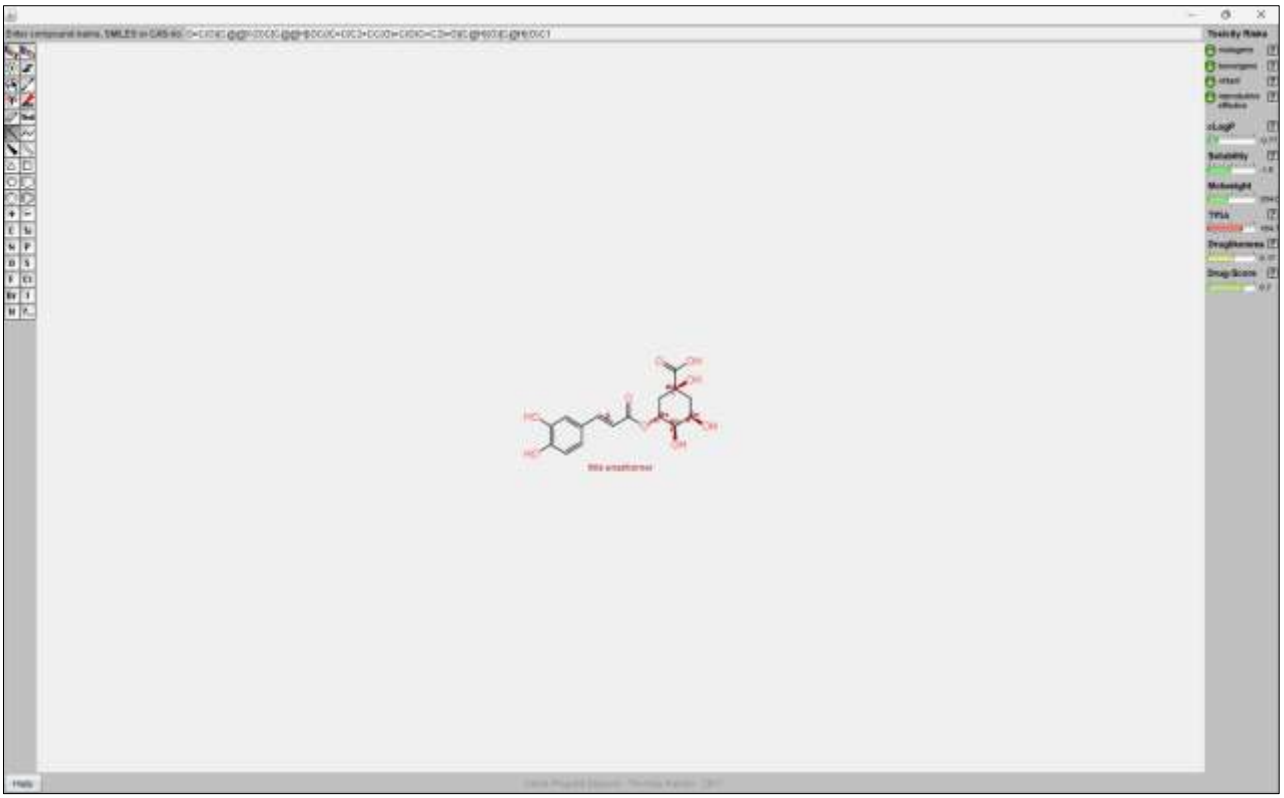


**Figure 12: Pharmacokinetic and toxicity profiling of chlorogenic acid**

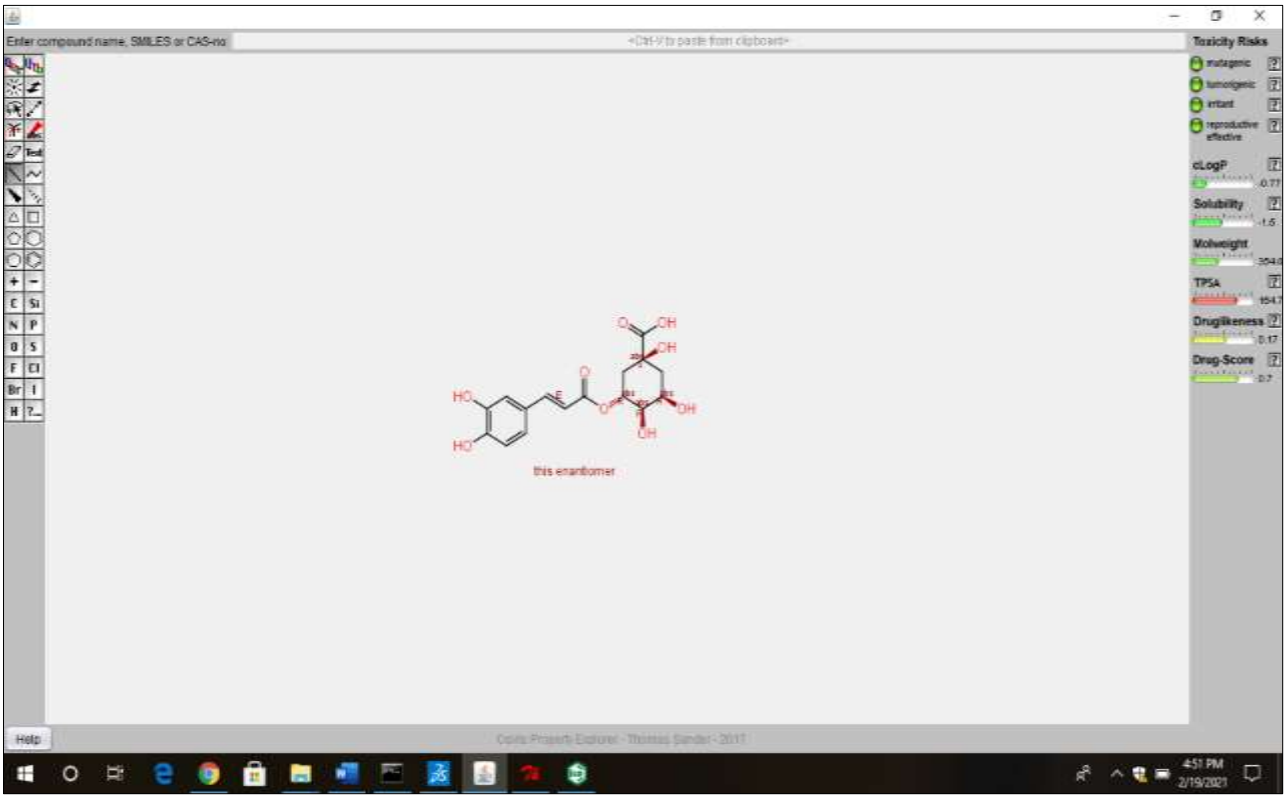



**Figure 13: Pharmacokinetic and toxicity profiling of quercetin**

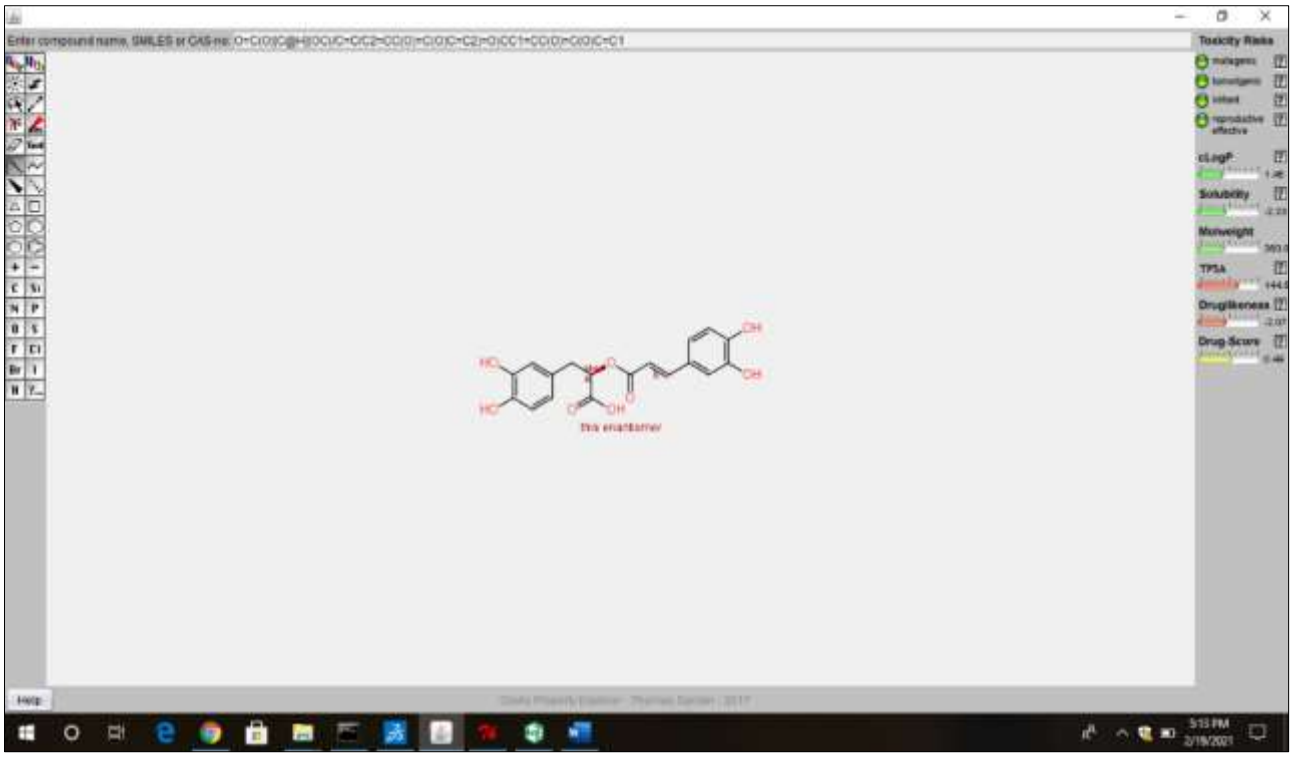


**Figure 14: Pharmacokinetic and toxicity profiling of rosmarinic acid**

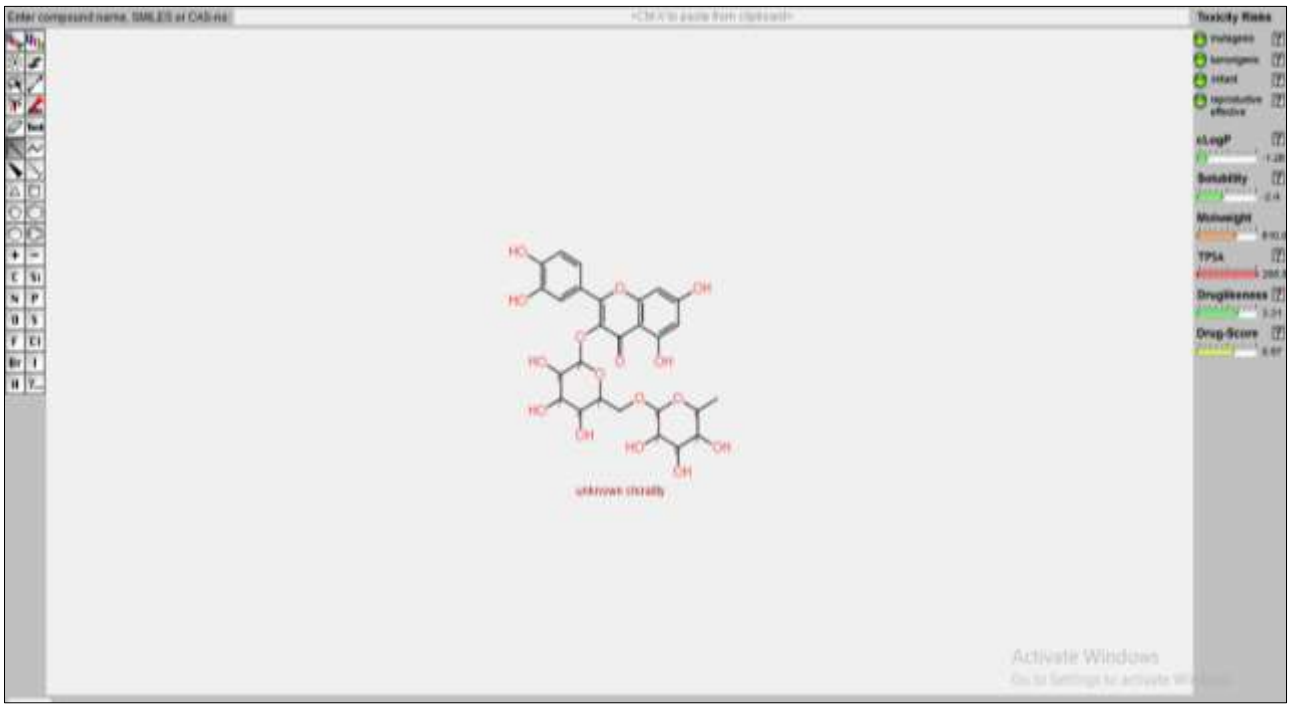


**Figure 15: Pharmacokinetic and toxicity profiling of rutin**

**Table 3: Pharmacokinetic Profiling of lead molecules**

| Compound | ADMET | | | |
|---|---|---|---|---|
| | Mutagenic | Tumorigenic | Irritant | Reproductive effectivity |
| Rosmarinic acid | NO | NO | Yes | NO |
| Chlorogenic acid | NO | NO | NO | No |
| Quercetin | NO | NO | NO | No |
| Rutin | NO | NO | NO | No |

**Table 4: Lipinski Properties of lead molecules**

| Compound | *cLogP* | Solubility | Mol.wt. | TPSA | Drug likeness | Drug score |
|---|---|---|---|---|---|---|
| Rosmarinic acid | 1.45 | 2.23 | 360 | 144.5 | -2.07 | 0.42 |
| Chlorogenic acid | 0.77 | 1.5 | 354 | 164.7 | -0.17 | 0.7 |
| Quercetin | 6.77 | 1.5 | 302 | 104 | -0.57 | 0.3 |
| Rutin | 1.28 | 0.8 | 610 | 344 | -3.34 | 0.08 |

**Table 5: Drug likeness of lead molecules**

| Compound | Lipinski rule of five | H bond donar | H bond acceptor |
|---|---|---|---|
| Rosmarinic acid | Yes | 5 | 8 |
| Chlorogenic acid | Yes | 6 | 9 |
| Quercetin | Yes | 5 | 7 |
| Rutin | Yes | 10 | 16 |

## CONCLUSION

The incidence of fungal infections is escalating rapidly, and the mechanisms of pathogenesis remain little comprehended. The prevalence of these fungal diseases is often attributed to their evolutionary evasion of antifungal resistance. The creation of effective novel antimicrobial medicines for fungal infections remains a significant challenge in contemporary clinical practice. Therefore, it is imperative to create surrogate agents that surpass the efficacy of already existing medications. Flavonoids are a category of plant-derived compounds identified in previous studies on natural medicines, known for their ability to confer many beneficial effects on humans. The discovery of flavonoids with potential antifungal properties at low concentrations or in synergistic combinations may assist in addressing this issue. The molecular docking analysis revealed that the chosen lead compounds inhibited *1,3β-Glycan synthase*, hence impeding the production of 1,3-β-Glucan, the primary constituent of the fungal cell wall, and subsequently exhibiting antifungal action.

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