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In Silico Evaluation of *Ocimum tenuiflorum* Phytochemicals Against SARS-CoV-2 Main Protease: ADME, PASS, and Docking Studies

Thesingu Rajan Arun

School of Sciences, Division of Chemistry, SRM Institute of Science and Technology, Tiruchirappalli 621105, Tamil Nadu, India.

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Abstract: Holy basil (*Ocimum tenuiflorum*) is a medicinal herb native to India and thrives in many parts of the country. Moreover, it is a significant part of Ayurveda, the traditional Indian medical system. This current research aims to assess previous studies that highlight the effectiveness of phytoconstituents from Ocimum tenuiflorum, including eugenol, methyl cinnamate, methyl eugenol and thymol, on the COVID-19 main protease protein. Using pkCSM Web tools, an in silico ADME analysis of these phytochemicals was conducted, providing insights into their Absorption, Distribution, Metabolism, and Excretion properties. Drug likeness was further assessed through PASS analysis. Additionally, molecular docking studies were performed to determine the preferred binding methods. The findings of this study could contribute to developing high-quality and safe medicinal products.

***Keywords**: Ocimum tenuiflorum, COVID-19 protein, Docking, ADME-Tox, PASS, Carcinogenicity.*

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I. INTRODUCTION

Tulsi, known as the 'holy basil' in Ayurveda, is a fragrant herb with medicinal properties [1]. In addition to being an excellent stress reliever [2], immune booster and aid for digestion [3], more recently, tulsi has been identified as a very potent insect repellant, and it also helps purify the air [4, 5]. This wonderful plant is sacred in India, where it holds an essential aspect of their culture. Many of these traditional benefits have been well-supported by modern science, revealing a wealth of bioactive compounds in tulsi, ranging from antibacterial and antifungal to analgesic and antioxidant agents that help balance blood sugar [6, 7]. The eugenol-rich essential oil of Ocimum tenuiflorum merits further exploration in this respect and development.

In line with the above observation, both computational and experimental approaches have been instrumental in solving various problems, with these two areas demonstrating significant synergy [8].

The structure of modern drugs and the concept of drug design have evolved from a purely stochastic process of natural product screening to a sophisticated combination of computational and structural chemistry [9]. Molecular docking has proven invaluable for *in silico* studies, enabling the rapid and cost-effective identification of energetically favorable modifiers from plant compounds that exhibit high affinity for the target protein (receptor) through scoring functions [10]. Furthermore, the paper highlights the utility of computational models in predicting the adsorption, distribution, metabolism, and excretion (ADME) properties of drug candidates at an early stage of development [11, 12].

The present study focuses on the in silico molecular docking of four constituents isolated from the Ocimum tenuiflorum plant, namely eugenol, methyl cinnamate, methyl eugenol, and thymol, to investigate their potential interaction with COVID-19 main protease protein. In silico PASS prediction of these compounds was conducted using an online web server, and their ADME/T properties were analysed to assess drug-like activity. Additionally, Carcino-Pred-EL was performed to classify the compounds as either carcinogens or non-carcinogens based solely on their two-dimensional structures.

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II. MATERIALS AND SOFTWARE TECHNIQUES

Compounds, namely Eugenol (CID: 3314), Methyl Cinnamate (CID: 637520), Methyl Eugenol (CID: 7127), and Thymol (CID: 6989), were retrieved from the PubChem database in SDF format.

❖ *Computational Evaluation*

Below are details of the software and methods used for molecular docking, in silico ADMET, PASS, and Carcino-Pred-EL analysis.

A. In silico Molecular Docking Investigation

In silico molecular docking studies of selected Ocimum tenuiflorum phytoconstituents were performed using HEX 8.0 software. This interactive molecular graphics system is specifically designed to analyze protein-ligand interactions [13], calculate docking free energies, and identify potential docked conformations of biomolecules. For this study, the X-ray crystal structure of the COVID-19 main protease (PDB ID: 5R7Y, resolution 1.65 Å) was obtained from the Protein Data Bank (Fearon et al., 2020) [14].

B. ADME Profiling and Toxicity Prediction

The online pkCSM platform was employed for computational analysis to assess the studied compounds' pharmacokinetic properties. Absorption parameters such as Lipinski's five laws, water solubility (log mol L−1), Caco-2 permeability (log Papp in 10^{-6} cms^{-1}), human intestinal absorption (human %), skin permeability (log Kp) and P-glycoprotein interaction were evaluated. Additional properties such as apparent volume of distribution (VDss), Fraction unbound (human) (Fu), blood-brain barrier penetration (Log BBB), and central nervous system permeability were considered. Furthermore, metabolic and excretion factors were analyzed [15]. The integrated PkCSM method assessed Max. Tolerated dose (human) (log mg kg^{-1} day^{-1}), skin sensitivity, cardiotoxicity, acute oral toxicity (LD50), hepatotoxicity, T. Pyriformis toxicity (log ug/L) and antibacterial activity. (http://biosig.unimelb.edu.au/pkcsm/).

C. Prediction of Activity Spectra for Substances

The biological activity spectrum of the selected component includes various biological effects resulting from interactions with biological systems. Biological activity is classified qualitatively as "present" or "absent." This means that the biological activity spectrum is intrinsically a property of a substance, determined primarily by its structural and physicochemical properties. This is essential as no single publication comprehensively covers all the diverse facets of the biological action of phyto-constituents [16] .(http://www.pharmaexpert.ru/PASSonline/predict.php).

D. Carcinogen Identification Using Ensemble Models

CarcinoPred-EL is a web-based platform designed to predict the carcinogenicity of compounds using ensemble learning methods. The server analyses solely the two-dimensional structures of chemicals. It categorizes them as carcinogenic or non-carcinogenic. Three novel cluster models were used. Ensemble XGBoost, Ensemble SVM, and Ensemble RF contributed to the accuracy and reliability of the forecast [17]. The platform is accessible at (http://112.126.70.33/toxicity/CarcinoPred-EL/index.html#).

III. RESULTS AND DISCUSSION

Computational evaluation of the compounds isolated from Ocimum Tenuiflorum revealed the following results.

➢ *Molecular Docking*

Molecular docking is a powerful computational tool for predicting protein-drug interactions [18], including eugenol, methyl cinnamate, methyl eugenol and thymol. Understanding these interactions is essential for drug development and efficacy. It is well-established that lower binding free energy scores correlate with stronger interactions between protein receptors and drug molecules. To investigate these molecular interactions more thoroughly, we developed computational models of the drug molecules and their corresponding target proteins [19].

In this study, the receptor was a portion of the COVID-19 protein containing one or more identifiable active sites. A docking process was conducted to assess ligand binding interactions and determine the preferred binding orientation [20]. The docked poses are depicted in Figure 1. From the seven generated docking poses, the lowest-energy conformation was selected for detailed analysis to identify potential interaction types that could induce a biological response. The results indicate that the drug molecules can successfully access the protein's active site, suggesting their potential as inhibitors against COVID-19. These molecules are stabilized within the site combination of van der Waals and hydrophobic interactions with functional groups of the protein [21]. The calculated docking free energy scores for eugenol, methyl cinnamate, methyl eugenol, and thymol were -159.06 kcal/mol, -170.34 kcal/mol, -171.05 kcal/mol, and -163.39 kcal/mol, respectively. The findings of the molecular docking showed that all selected phytoconstituents from Ocimum tenuiflorum significantly interacted with the COVID-19 protein. Due to their superior binding affinities to the target protein, methyl cinnamate and methyl eugenol emerged as the most promising drug candidates. These scores were much lower than those recorded for some previously known phytochemicals [22].

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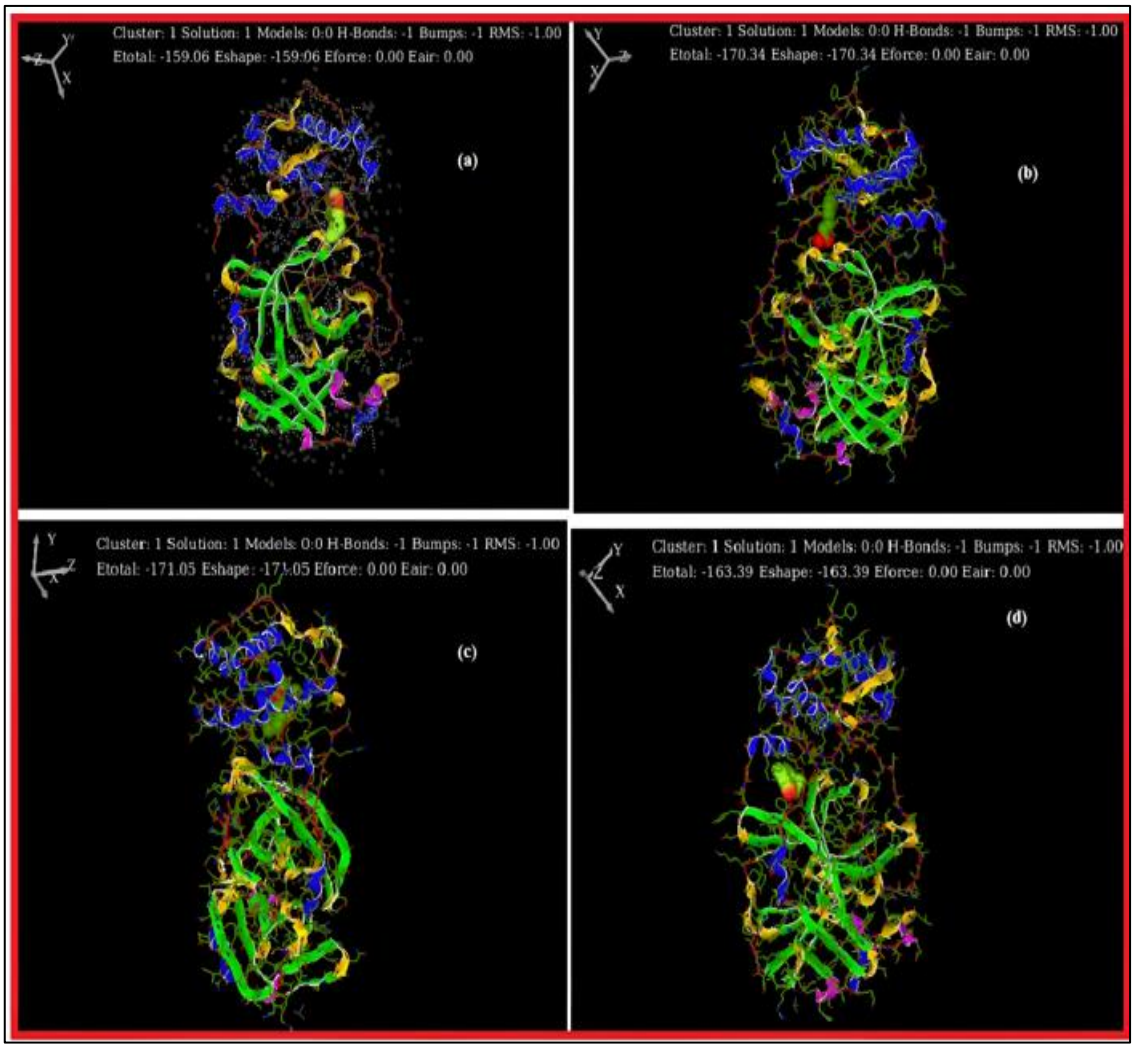

Fig. 1. Molecular Docked Model of Eugenol, Methyl Cinnamate, Methyl Eugenol, and Thymol with COVID-19 Protein

➢ *ADME Profiling and Toxicity Prediction*

Computationally, Ocimum tenuiflorum phyto-constituents can be studied for their basic pharmacological properties using in silico approaches as an alternative to early-stage animal trials. Table 1 presents the SMILES files for eugenol, methyl cinnamate, methyl eugenol, and thymol. The Swiss ADME/pkCSM web tool was employed to analyze the ADMET properties of the screened phytochemicals. The results are summarized in Table 2. The present study found that the screened phytochemicals exhibit excellent water solubility, significantly better than most drug molecules. Generally, if a phyto-constituent violates no more than one of Lipinski's five rules, it is considered orally active. The selected phytochemicals adhere to Lipinski's[23] rule of five, as shown in Table 1, indicating their potential for oral bioavailability. The BOILED-Egg model was used to predict Blood-Brain Barrier (BBB) penetration of the phyto-constituents of Ocimum tenuiflorum using Swiss ADME [24]. This is depicted in Fig. 2. All the screened phyto-constituents had the highest blood-brain barrier permeability (BBB) of 0.374, 0.238, 0.422, and 0.407 for eugenol, methyl cinnamate, methyl eugenol, and thymol, respectively. Additionally, owing to their lipophilic properties and toxicity on metabolism, they also show some activity as CYP1A2 inhibitors in a manner consistent with known mechanisms. The observed results may indicate that some of the phytochemicals screened in this study could interfere with or modify protein-drug interactions and potentially lead to oxidative stress [25].

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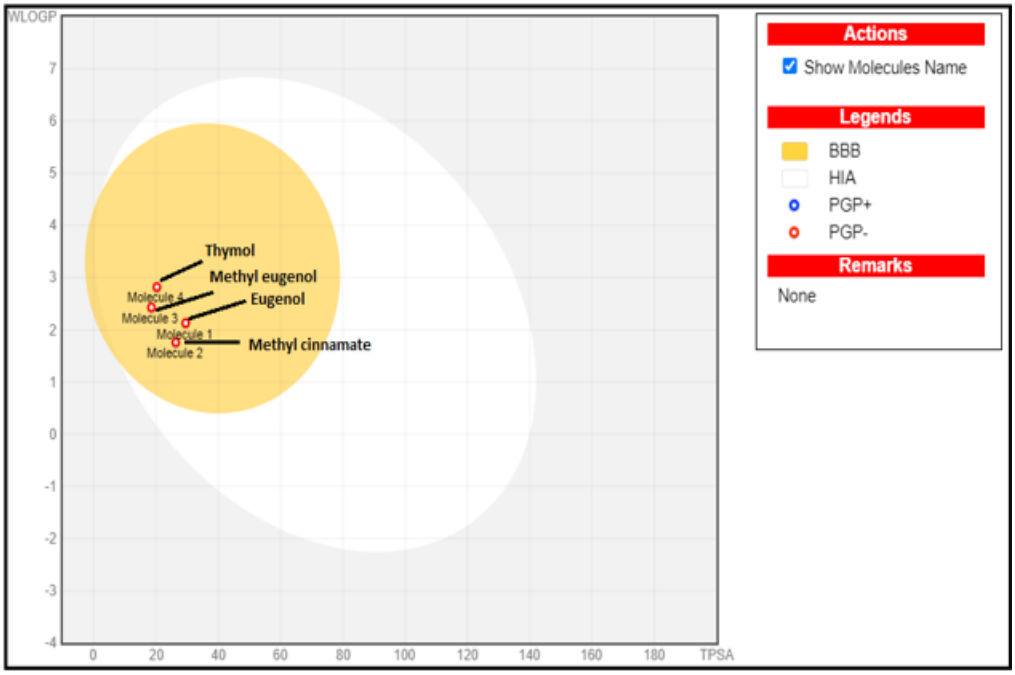

Fig 2. The BOILED-Egg model was used to predict Blood-Brain Barrier (BBB) penetration of the Phyto-constituents of *Ocimum tenuiflorum* using Swiss ADME

Table. 1. ADMET Properties of Eugenol, Methyl Cinnamate, Methyl Eugenol and Thymol.

Property		**Eugenol**	**Methyl cinnamate**	**Methyl Eugenol**	**Thymol**
Absorption	Water solubility (log mol L^{-1})	-2.25	-2.132	-2.671	-2.789
	Caco2 permeability (log Papp in 10^{-6} cm s^{-1})	1.559	1.442	1.528	1.606
	Intestinal absorption (human %)	92.041	97.453	94.532	90.843
	Skin Permeability (log K_p)	-2.207	-2.102	-1.916	-1.62
	P-glycoprotein substrate	No	No	No	No
	P-glycoprotein I inhibitor	No	No	No	No
	P-glycoprotein II inhibitor	No	No	No	No
Distribution	VDss (human)	0.24	-0.001	0.265	0.512
	Fraction unbound (human) (Fu)	0.251	0.307	0.208	0.203
	BBB permeability (log BB)	0.374	0.238	0.422	0.407
	CNS permeability (log PS)	-2.007	-1.802	-1.922	-1.664
Metabolism	CYP2D6 substrate	No	No	No	No
	CYP3A4 substrate	No	No	No	No
	CYP1A2 inhibitor	Yes	Yes	Yes	Yes
	CYP2C19 inhibitor	No	No	No	No
	CYP2C9 inhibitor	No	No	No	No
	CYP2D6 inhibitor	No	No	No	No
	CYP3A4 inhibitor	No	No	No	No
Excretion	Total Clearance (log ml mim^{-1} kg^{-1})	0.282	0.814	0.338	0.211
	Renal OCT2 substrate	Yes	No	Yes	No
Toxicity	AMES Toxicity	Yes	No	Yes	No
	Max. tolerated dose (human) (log mg kg^{-1} day^{-1})	1.024	1.102	0.959	1.007
	hERG I inhibitor	No	No	No	No
	hERG II inhibitor	No	No	No	No
	Oral Rat Acute Toxicity (LD50) (mol kg^{-1})	2.118	1.909	1.973	2.074
	Oral Rat Chronic Toxicity (LOAEL) (mol kg^{-1} bw day^{-1})	2.049	2.28	2.119	2.212
	Hepatotoxicity	No	No	No	Yes
	Skin Sensitization	Yes	Yes	Yes	Yes

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	T.Pyriformis toxicity (log ug/L)	0.3	0.724	0.742	0.387
	Minnow toxicity (log mM)	1.702	0.776	1.449	1.213
Drug Likeness	**Lipinski**	**Yes;0Violation**	**Yes;0 Violation**	**Yes;0 Violation**	**Yes;0 Violation**

➢ *Prediction of Activity Spectra for Substances (PASS)*

PASS (Prediction of Activity Spectra for Substances) is a computer program that helps predict the biological activity profile of compounds. Access to this information is crucial when identifying potential drug candidates. PASS provides two key values: Pa (probability of activity) and Pi (probability of inactivity). Pa indicates the likelihood of a compound being active for a specific biological process, while Pi suggests the chances of it being inactive.The structures of the phyto-constituents were analyzed using SMILES strings on the online PASS software[26]. The results indicated that these phyto-constituents possess significant biological activities beyond their established roles as anti-carcinogenic, antimutagenic, antiseptic, and antidyskinetic agents. They also show promise as for fungal disorders and in alleviating allergic responses. Tables 2(a), 2(b), 2(c) and 2(d) present the predicted biological activities of these phyto-constituents.

Tables 2(a) Predicted Biological Activities of Eugenol.

0,878	0,003	Antimutagenic
0,868	0,008	Antieczematic
0,722	0,005	Antiseptic
0,623	0,004	Pediculicide
0,611	0,008	Skin irritation, inactive
0,624	0,033	Antidyskinetic
0,562	0,005	Antiprotozoal
0,576	0,028	Peroxidase inhibitor
0,557	0,014	Antinociceptive
0,540	0,024	Antisecretoric
0,514	0,012	Antipyretic
0,516	0,020	Antiulcerative
0,539	0,065	Antiseborrheic
0,463	0,008	Antioxidant
0,449	0,004	Skin whitener
0,459	0,023	Anticarcinogenic
0,459	0,024	Antimyopathies
0,878	0,003	Antimutagenic
0,460	0,037	Antifungal
0,450	0,039	Antiallergic

Tables 2(b) Predicted biological activities of methyl cinnamate

0,732	0,005	Antihypoxic
0,715	0,004	Antihelmintic (Nematodes)
0,680	0,003	Antiinflammatory, intestinal
0,606	0,010	Antipsoriatic
0,641	0,048	Antiseborrheic
0,593	0,012	Antiulcerative
0,587	0,014	Antipruritic, allergic
0,636	0,070	Antieczematic
0,574	0,037	Antiinflammatory
0,546	0,019	Antiprotozoal (Leishmania)
0,549	0,023	Antisecretoric
0,527	0,029	Antipruritic
0,531	0,062	Antineoplastic
0,470	0,004	Antinephritic
0,503	0,049	Antiviral (Picornavirus)
0,481	0,033	Antithrombotic
0,449	0,009	Antioxidant
0,480	0,048	Antinociceptive
0,426	0,008	Anti-Helicobacter pylori
0,438	0,023	Antiparasitic

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Tables 2(c) Predicted Biological Activities of Methyl Eugenol

0,893	0,005	Antieczematic
0,807	0,004	Antimutagenic
0,554	0,010	Antiseptic
0,554	0,022	Antisecretoric
0,532	0,008	Antiprotozoal (Amoeba)
0,560	0,048	Antidyskinetic
0,531	0,021	Antinociceptive
0,503	0,028	Antiallergic
0,497	0,024	Antiulcerative
0,456	0,026	Antimyopathies
0,434	0,022	Antipyretic
0,464	0,055	Antipruritic, allergic
0,395	0,005	Antiviral (CMV)
0,459	0,070	Antiinflammatory
0,418	0,046	Antithrombotic
0,382	0,014	Antioxidant
0,414	0,047	Antifungal
0,391	0,042	Antiprotozoal
0,428	0,087	Antiseborrheic
0,367	0,038	Antiparasitic

Tables 2(d) Predicted Biological Activities of Thymol

0,913	0,003	Antiseptic
0,846	0,011	Antiseborrheic
0,829	0,005	Antiinfective
0,788	0,021	Antieczematic
0,718	0,014	Antidyskinetic
0,584	0,009	Antinociceptive
0,585	0,020	Antihypoxic
0,571	0,010	Antiparasitic
0,569	0,008	Antihelmintic
0,567	0,021	Antipruritic
0,533	0,005	Antihelmintic
0,550	0,022	Antipruritic, allergic
0,524	0,011	Antipyretic
0,549	0,044	Antiinflammatory
0,501	0,005	Antiuremic
0,486	0,015	Antiamyloidogenic
0,481	0,027	Antiulcerative
0,473	0,023	Antimycobacterial
0,464	0,037	Antifungal
0,451	0,048	Antiviral (Rhinovirus)

➢ *Prediction of Chemical Carcinogenicity Using Ensemble Learning Methods.*

CarcinoPred-EL is an online free web server for carcinogenicity prediction of phyto-constituents, and it is designed for only two-dimensional structural readouts of compounds and labels them either Carcinogens or Non-Carcinogens. Currently, this online web server includes three ensemble learning models for carcinogenicity prediction, which are Ensemble XGBoost, Ensemble SVM and Ensemble RF.

The ensemble models classify phyto-constituents as carcinogenic or non-carcinogenic. The "Average" column in the output table shows the probability values, while the "Class" column shows the predicted distribution. The probability values from each base model are also given in Table 3. These values range from 0 to 1. If the probability is greater than 0.5, the chemical is classified as a carcinogen. Otherwise, it is considered to be non-carcinogenic substances. These results show that the *Ocimum tenuiflorum* phyto-constituents is not carcinogenic in nature.

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Table.3 Carcinogenic or Non-Carcinogenic Nature of Eugenol, Methyl Cinnamate, Methyl Eugenol and Thymol.

Carcino Pred-EL of Compound **Eugenol**									
Method	**CDK**	**CDKExt**	**CDKGraph**	**KR**	**KRC**	**MACCS**	**Pubchem**	**Average**	**Class**
RF	0.32	0.32	0.22	0.47	0.45	0.35	0.31	0.35	Non-Carcinogen
SVM	0.60	0.62	0.29	0.67	0.54	0.55	0.37	0.47	Non-Carcinogen
XGBoost	0.07	0.19	0.47	0.45	0.89	0.63	0.76	0.49	Non-Carcinogen

Carcino Pred-EL of Compound **Methyl Eugenol**									
Method	**CDK**	**CDKExt**	**CDKGraph**	**KR**	**KRC**	**MACCS**	**Pubchem**	**Average**	**Class**
RF	0.82	0.81	0.20	0.24	0.46	0.23	0.36	0.27	Non-Carcinogen
SVM	0.79	0.78	0.47	0.52	0.44	0.62	0.55	0.48	Non-Carcinogen
XGBoost	0.07	0.19	0.47	0.45	0.91	0.63	0.76	0.50	Non-Carcinogen

Carcino Pred-EL of Compound **Thymol**									
Method	**CDK**	**CDKExt**	**CDKGraph**	**KR**	**KRC**	**MACCS**	**Pubchem**	**Average**	**Class**
RF	0.21	0.22	0.20	0.24	0.46	0.23	0.36	0.27	Non-Carcinogen
SVM	0.32	0.22	0.28	0.35	0.46	0.29	0.32	0.32	Non-Carcinogen
XGBoost	0.07	0.19	0.47	0.45	0.85	0.63	0.76	0.49	Non-Carcinogen

Carcino Pred-EL of Compound **Methyl Cinnamate**									
Method	**CDK**	**CDKExt**	**CDKGraph**	**KR**	**KRC**	**MACCS**	**Pubchem**	**Average**	**Class**
RF	0.43	0.46	0.24	0.48	0.54	0.39	0.27	0.40	Non-Carcinogen
SVM	0.34	0.33	0.50	0.46	0.36	0.33	0.23	0.37	Non-Carcinogen
XGBoost	0.07	0.19	0.47	0.45	0.89	0.63	0.76	0.49	Non-Carcinogen

IV. CONCLUSION

This computational evaluation aims to determine the pharmacological effectiveness of phytoconstituents from *Ocimum tenuiflorum*, including eugenol, methyl cinnamate, methyl eugenol, and thymol, on the COVID-19 main protease protein. The in silico evaluation revealed that all selected phytoconstituents from Tulsi (Ocimum tenuiflorum) significantly interacted with the COVID-19 protein. Among these, methyl cinnamate and methyl eugenol emerged as the most promising drug candidates due to their superior binding affinities to the target protein. Additionally, we analyzed the in silico ADME-Tox profile. The ADME-Tox properties pointed out that a good pharmacokinetic profile characterizes these phytoconstituents. PASS analysis revealed additional biological activities for these phytoconstituents, including anticarcinogenic, antimutagenic, antiseptic, and antidyskinetic properties. According to the XG Boost method, carcinoPred-EL analysis indicated that all phytoconstituents were non-carcinogenic. The results of our study provide grounds for creating more powerful and safer medicinal drugs.

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