
ADMET analysis and molecular docking of phytocompounds of *Magnolia champaca* leaf essential oil as potential inhibitors of α -Glucosidase, Estrogen Receptor- α , TNF- α , and Xanthine Oxidase

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Abstract: *Magnolia champaca* extracts have various pharmacological properties like antifertility, antibacterial, anti-inflammatory, and antioxidant activities. However, the pharmacological activities of *Magnolia champaca* leaf essential oils are still unknown. This study aimed to examine the antidiabetic, antifertility, anti-inflammatory, and antioxidant properties of the phytoconstituents of MCLEO using computational biological approaches. After analysing 65 compounds, 28 satisfied ADMET properties and were selected for molecular docking to provide mechanistic insights into α -Glucosidase, Estrogen Receptor- α , Tumour Necrosis Factor- α , and Xanthine Oxidase inhibition. Crystallographic structures with PDB ID: 8D43, 1R5K, 5MU8, and 2CKJ of α -G, ER- α , TNF- α , and XO, respectively were used as models for molecular docking. The result showed that cis-Muuroloa-3,5-diene and Selin-11-en-4- α -ol showed docking scores of -8.489 and -9.146 against α -G and ER- α , respectively. δ -Cadinene showed docking scores of -7.951 and -8.268 against TNF- α and XO. This is the first *in silico* study to discover prospective bioactive compounds from MCLEO which could be useful in developing novel and effective medications.

Keywords: *Magnolia champaca*; *Michelia champaca*; antidiabetic; antifertility; anti-inflammatory; antioxidant; ADMET analysis; molecular docking.

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Biographical notes: Chiranjibi Sahoo (PhD Scholar) investigates aromatic and medicinal plants in order to extract their volatile content and determine their relationship through chemometric studies. His area of research includes transcriptome analysis using next-generation sequencing.

Ananya Nayak (PhD Scholar) works on drug design, *in silico*, *in vitro* and chemical profiling using volatile compounds of medicinal plants. She has expertise in the area of bioinformatics and proteomics work.

Ayushman Gadnayak (PhD scholar) is conducting research on the essential oil of *Curcuma* rhizomes. His research aims to extract the volatile compounds present in these botanicals and establish their interrelationships through the application of bioinformatics methodologies. His research domain encompasses various aspects of genomics and proteomics techniques.

Sudipta Jena (Assistant Professor) has expertise in medicinal plants utilised in traditional folk medicine. She investigates the bioactivities of essential oils and extracts *in vitro* and *in vivo*. She is a plant biotechnologist with a desire to pursue research for bioprospecting and improvement of commercially important medicinal plants for the benefit of human health.

Asit Ray (Assistant Professor) works on several medicinal plants and has extensive expertise in analytical instruments. His area of research lies in the exploration, extraction and screening of new chemical entities from unexplored plants to develop useful leads for potentially new drugs.

Pratap Chandra Panda (Professor) is a plant taxonomist, who has been continuing his research work on bioprospecting of different medicinal and aromatic plants for 38 years. He is working on bioprospecting of wild plants with the intent to make the wild plant resources of interest to human welfare. He has worked on the conservation biology of medicinal and essential oil-bearing plants and the commercial application of wild economic plants. Presently, he is involved in phytochemical screening of essential oil-bearing plants and their biological activities.

Sanghamitra Nayak (Professor) has been continuing her research on different medicinal plants and their phytochemical evaluation for 38 years. She is a plant biotechnologist with a desire to pursue research by integrating the concepts of genomics and metabolomics for bioprospecting and improvement of commercially important medicinal plants for the benefit of human health.

Ambika Sahoo (Assistant Professor) has been continuing her research on different medicinal plants and their phytochemical evaluation for 10 years. She is a plant biotechnologist with a desire to pursue research by integrating the concepts of genomics, transcriptomics and metabolomics for bioprospecting and improvement of commercially important medicinal plants for the benefit of human health.

1 Introduction

Magnolia champaca (L.) Baill. ex Pierre, commonly known as Swarna Champa of family Magnoliaceae is native to South India to South Central China, primarily in the wet tropical biome (POWO, 2023). It is well recognised for its tranquilising and lovely fragrant flowers, which promote relaxation. Geographically, the *Magnolia champaca* is found in India, China, Nepal, Sri Lanka, Malaysia, Vietnam, Myanmar, Indonesia, and Thailand, as well as other tropical and subtropical parts of Asia (Sinha and Varma, 2016; Sahoo et al., 2022). In India, wild populations of Swarna Champa are mainly found in the sub-Himalayan zone, Assam, Western Ghat, and south India. Traditionally the plant parts are used to treat various diseases like colic, fever, cephalalgia, gout, cough, leprosy, eye disorders, inflammation, antifertility, and antidote for snake and scorpion venoms etc. (Taprial et al., 2013; Sinha and Varma, 2016; Sahoo et al., 2022). The plant has various pharmacological activities, i.e., memory-improving, antidiabetic, antiinflammatory, antioxidant, anticancer, antimicrobial, and wound-healing properties (Sahoo et al., 2022). The *M. champaca* leaf extract contains helminthic, antifertility, antibacterial, antiinflammatory, antioxidant, analgesic, cytotoxic, antihyperglycemic effect and antiulcerogenic effects (Dama et al., 2011; Taprial et al., 2013; Khan et al., 2002; Gupta et al., 2011; Hossain et al., 2009; Gupta et al., 2010; Mullaicharam, 2011). Further, a mixture of Champak leaf juice and coconut oil is utilised to clean hair and remove dandruff and lice (Mandal et al., 2020). Several *in silico* molecular docking studies have been conducted to explore the bioactivity such as antiinflammatory, anti-plasmodial activity etc. of phytoconstituents found in *M. champaca* (Maghfiroh et al., 2021; Patil et al., 2023). These studies underscore the importance of these phytoconstituents in potential therapeutic applications.

Research in *M. champaca* essential oil (EO) is slowly gaining importance. *M. champaca* leaf essential oil (MCLEO) is rich in terpenoids, i.e., sesquiterpenoids such as β -elemene, γ -muurolene and β -caryophyllene, etc. (Sahoo et al., 2022). Since the beginning of human existence, EOs have been used in traditional systems of medicine. Numerous biological characteristics of EOs, including their antibacterial, antimutagenic, antiviral, anticancer, antiinflammatory, antioxidant, antiprotozoal, and immunomodulatory actions, are being characterised by researchers from across the world (Raut and Karuppayil, 2014; Bakkali et al., 2008). Although the chemical makeup of MCLEO has been studied, a thorough investigation of the mechanisms underlying its pharmacological activities has not yet been done. Further, the phytoconstituents responsible for several pharmacological properties, including their inhibition potential against enzymes/proteins related to various clinical conditions like diabetes, antifertility, inflammation, oxidative stress, etc., have not been studied yet.

As several volatile constituents are reported in MCLEO, separating individual phytocompounds and screening them utilising *in vitro* and *in vivo* assays is challenging. Due to the increased cost-effectiveness, computer-assisted *in silico* techniques have gained importance in the early stages of drug development (Marrero-Ponce et al., 2011; Lionta et al., 2014). With this approach, fewer animals are killed, and fewer attempts at the final stage fail (Lionta et al., 2014). Moreover, Molecular docking plays a vital role in rational drug design. Through molecular docking, computer-generated 3D structures of

small ligands are positioned into receptor structures in different conformations, orientations, and locations to form a stable complex (Rolta et al., 2022). This technique provides insights into molecular recognition and is helpful in medicinal chemistry and drug discovery. Docking is nowadays crucial to computer-aided drug discovery and design (CADD). Dynamic docking thoroughly analyses drug-receptor binding and recognition from both a mechanistic and energetic point of view and solvation and entropic consequences (Jakhar et al., 2020). Using molecular modelling to screen phytocompounds may strengthen the pipeline for *in vitro* and *in vivo* testing and lower the risk of clinical trial failure (Rolta et al., 2022). Furthermore, *in silico* approach may help to understand the mechanism of action and targets of phytocompounds.

The present study focused on drug-likeness property analysis and molecular docking to identify the bioactive volatile compounds from the leaf essential oil of *Magnolia champaca*, that can effectively inhibit multiple enzymes i.e., α -Glucosidase, Estrogen Receptor- α , TNF- α , and Xanthine Oxidase and thus provide a way to treat disorders such as diabetes, antifertility, several inflammatory diseases and oxidative stress, respectively.

2 Materials and methods

2.1 Prediction of drug-likeness properties

The phytoconstituents of MCLEO were considered for the present study (Sahoo et al., 2022). The selected 65 phytocompounds' drug-like characteristics were predicted using the **SwissADME** database (<http://www.swissadme.ch/>). The canonical **SMILES** for the selected volatiles were collected from the **PubChem** database (<https://pubchem.ncbi.nlm.nih.gov/>) and considered as the input for **SwissADME** to calculate different molecular properties, including molecular weight, the number of hydrogen-bond donors, and acceptors, and the number of rotatable bonds etc. (Daina et al., 2017; Nayak et al., 2022). Those key parameters were further checked in **admetSAR** (version 2.0) (<http://lmmd.ecust.edu.cn/admetSar2/>) to validate the findings (Yang et al., 2019; Cheng et al., 2012). The phytoconstituents were further filtered based on Veber's rule (Veber et al., 2002) and the Lipinski rule of five (Lipinski et al., 1997).

2.2 Bio-activity score prediction

Molinspiration (<https://www.molinspiration.com/cgi-bin/properties>) tool was used to predict bioactivity scores of selected phytoconstituents, using canonical **SMILES** as input (Molinspiration, 2011). The **Molinspiration** tool predicts a bioactivity score that takes into account a variety of characteristic outputs for different parameters like enzyme inhibitors, nuclear receptors, kinase inhibitors, GPCR ligands, protease inhibitors, and ion channel modulators. Further analysis was performed using the phytochemicals with positive enzyme inhibitor scores (Nayak et al., 2022).

To check the hydrophilicity, the **CLogP** value of the phytocompounds was calculated using **OSIRIS** Property Explorer software (Sander, 2009). The phytocompound's hydrophilicity is increased when the **CLogP** value is decreased.

2.3 Prediction of toxicity

Since it is crucial to know if a molecule is toxic or not when used as a medicine, the toxicity analysis is incorporated into the pharmacokinetic property of phytocompounds. Toxic compounds must be avoided during the drug discovery and development process. This requires a toxicity risk assessment (Balakrishnan et al., 2015). Using the **ProTox-II** webserver ([https://tox-new.charite.de/protox_II/index.php?site = compound_input](https://tox-new.charite.de/protox_II/index.php?site=compound_input)), the toxicity class of the screened phytoconstituents was evaluated (Banerjee et al., 2018). The **LD50** value was determined in mg/kg. The **LD50** toxicity class was used to sort the data further.

2.4 In-silico analysis

2.4.1 Ligand preparation

All the selected 28 phytocompounds of *Magnolia champaca* leaf sample were then processed for further analysis. The 3D structures of the 28 compounds were downloaded from **PubChem** database (<https://pubchem.ncbi.nlm.nih.gov/>).

2.4.2 Protein pre-processing

For antidiabetic, antifertility, antiinflammatory, and antioxidant activity, GANAB_HUMAN protein (UniProtKB: Q14697), ESR1_HUMAN protein (UniProtKB: P03372), TNFA_HUMAN protein (UniProtKB: P01375), and XDH_HUMAN protein (UniProtKB: P47989) were selected respectively. **FASTA** files of these proteins were downloaded from the **UniProt** database (<https://www.uniprot.org/>) (UniProt Consortium, 2019). All the **FASTA** files were then exported for a local alignment into **BLASTp** ([https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE = Proteins](https://blast.ncbi.nlm.nih.gov/Blast.cgi?PAGE=Proteins)). The **PDB IDs** were then selected on the basis of per identity score and E-value. The crystal structures of all the selected **PDB IDs** i.e., 8D43, 1R5K, 5MU8, and 2CKJ with resolution 2.88 Å, 2.70 Å, 3.00 Å and 3.59 Å respectively were downloaded from **RCSB PDB** (<https://www.rcsb.org/>). All the structures were then processed for protein homology modelling and refinement by using **PHYRE2** ([http://www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id = index](http://www.sbg.bio.ic.ac.uk/~phyre2/html/page.cgi?id=index)) Protein Fold Recognition Server (Protein Homology/analogy Recognition Engine V 2.0) (Kelley et al., 2015). The process was followed for removing ligand and water molecules attached to the protein structures to avoid interference in the docking study.

2.4.3 Validation of protein structures

The protein structures were further validated by using **Ramachandran plot** that enable the protein visualisation of highly preferred, preferred and disallowed angles of each amino acid in the protein. The Ramachandran plot was generated by using **SAVES** Version 6.0 server (<https://saves.mbi.ucla.edu/>) for all the protein structures.

2.5 Molecular docking

The receptor-ligand docking was performed using **DockThor** (<https://dockthor.lncc.br/v2/>) using the MMFF94S force field (Guedes et al., 2021). The following settings are made in the web server's parameters for this Virtual Screening: 12 docking runs, 500,000

evaluations per docking run, 750 people in the population, and a maximum of 29 cluster leaders per docking run. During the docking process, the ligands were flexible while the target protein was fixed.

Further, a post-docking analysis was done to check hydrophobic and hydrogen bond interactions between protein-ligand complexes. To visualise the protein-ligand complexes, **PyMol** (<https://pymol.org/2/>) and **LigPlot+** (<https://www.ebi.ac.uk/thornton-srv/software/LigPlus/>) were used (Lill and Danielson, 2011; Laskowski and Swindells, 2011).

3 Results and discussion

3.1 Prediction of drug-likeness properties

Using **SwissADME**, the drug-likeness characteristics of 65 phytocompounds from MCLEO were predicted, and the phytocompounds with insignificant drug-like qualities were removed. These were further crosschecked with **admetSAR**.

For the drug-likeness prediction, the following factors were taken into account: the Lipinski Rule of 5, the Veber Rule, the molecular weight < 500, the number of hydrogen acceptors ≤ 5 , and the number of hydrogen donors ≤ 10 (Lipinski et al., 1997; Veber et al., 2002). The aforesaid criteria were considered for the elimination of unqualified phytoconstituents. Fifty-six of the 65 phytoconstituents examined were qualified for the drug-like characteristics (Table 1).

3.2 Prediction of bioactivity scores

The chosen phytoconstituents' bioactivity score was calculated using the online tool **Molinspiration**. When the bioactivity score is larger than 0, between -0.5 and 0, or less than -0.5 , it is classified as active, moderately active, or inactive, respectively (Gadnayak et al., 2022). For further investigation, 39 phytocompounds with bioactivity scores (for the class of enzyme inhibitors) larger than zero were chosen (Table 2).

The **CLogP** value of the targeted chemicals was predicted using the **Osiris** software. The compound's water permeability increases with decreasing **CLogP** values. Thus 30 compounds were chosen for additional study since their **CLogP** values were less than 5 (Table 1).

3.3 Toxicity prediction

The toxicity was predicted using the **ProTox-II** website and a total of 28 compounds that followed the LD50 (lethal dose) class-IV/V/VI were chosen as potential compounds for further research (Table 1) (Figures 7 and 8).

None of the selected phytoconstituents was expected to be immunotoxic, mutagenic, hepatotoxic or carcinogenic. These phytochemicals are safe for biological delivery and might be thought of as possible therapeutic targets. Finally, a total of 28 phytoconstituents (out of 65) that satisfied all the guidelines were chosen for molecular docking analysis.

Table 1 Drug-likeness properties of selected phytoconstituents using SwissADME

S. no.	Phytoconstituents	Canonical SMILES	Molecular weight	Hydrogen bond donor count	Hydrogen bond acceptor count	Rotatable bond count	Lipinski's rule	Veber rule	cLogP	Toxicity
1	Linalool	<chem>CC(=CCCC(C)C=O)C</chem>	154.25	1	1	4	Yes	Yes	3.23	5
2	Linalool formate	<chem>CC(=CCCC(C)C=O)C=O</chem>	182.26	0	2	6	Yes	Yes	3.34	5
3	δ-Elemene	<chem>CC(C)C1=CC(C(C)C)C=C(C)C</chem>	204.35	0	0	3	Yes	Yes	4.9	5
4	α-Copaene	<chem>CC1=CCC2C3C1C2(CCC3C(C)C)C</chem>	204.35	0	0	1	Yes	Yes	3.98	5
5	cis-Muurola-3,5-diene	<chem>CC1CCC(C2=CC(=CCC12)O)C(C)C</chem>	204.35	0	0	1	Yes	Yes	4.25	4
6	γ-Gurjunene	<chem>CC1CCC(C=C2C1CCC2C)C(=O)C</chem>	204.35	0	0	1	Yes	Yes	4.56	5
7	γ-Muurolene	<chem>CC1=CC2C(C(C)C)C(=C)CCC2C(C)C</chem>	204.35	0	0	1	Yes	Yes	4.33	5
8	β-Selinene	<chem>CC(=C)C1CCC2(CCCC(=C)C2C1)C</chem>	204.35	0	0	1	Yes	Yes	4.7	5
9	γ-Amorphene	<chem>CC1=CC2C(C(C)C)C(=C)CCC2C(C)C</chem>	204.35	0	0	1	Yes	Yes	4.33	5
10	γ-Cadinene	<chem>CC1=CC2C(C(C)C)C(=C)CCC2C(C)C</chem>	204.35	0	0	1	Yes	Yes	4.33	5
11	δ-Cadinene	<chem>CC1=CC2C(CCC(=C2CC1)C)C(C)C</chem>	204.35	0	0	1	Yes	Yes	4.42	5
12	trans-Cadina-1,4-diene	<chem>CC1CCC(C2C1=CCC(=C2)C)C(C)C</chem>	204.35	0	0	1	Yes	Yes	4.25	5
13	α-Cadinene	<chem>CC1=CC2C(C(C)C)C(=CCC2C(C)C)C</chem>	204.35	0	0	1	Yes	Yes	4.25	5
14	cis-Sesquisabinene hydrate (IPP vs. OH)	<chem>CC(CCC=C(C)C)C12CCC(C1C2)C(O)</chem>	222.37	1	1	4	Yes	Yes	4.24	5
15	β-Copaen-4-ol	<chem>CC(C)C1(C2CC(=C)CCC2C3(C1C3)C)O</chem>	220.35	1	1	1	Yes	Yes	3.24	5
16	Spathulenol	<chem>CC1(C2C1C3C(CCC3(C)O)C(=C)CC2)C</chem>	220.35	1	1	0	Yes	Yes	3.17	5

Table 1 Drug-likeness properties of selected phytoconstituents using SwissADME (continued)

S. no.	Phytoconstituents	Canonical SMILES	Molecular weight	Hydrogen bond			Rotatable bond		Lipinski's rule	Veber rule	cLogP	Toxicity
				donor count	acceptor count	bond count						
17	Guaiol	CC1CCC(CC2 = C1CCC2C)C(C)O	222.37	1	1	1	Yes	Yes	Yes	3.67	5	
18	10- <i>epi</i> - γ -Eudesmol	CC1 = C2CC(CCCC2(CCC1)C)C(C)O	222.37	1	1	1	Yes	Yes	Yes	3.73	5	
19	Murola-4,10(14)-dien-1- β -ol	CC1 = CC2C(CCC(=C)C2(CCC1)O)C(C)C	220.35	1	1	1	Yes	Yes	Yes	3.51	4	
20	γ -Eudesmol	CC1 = C2CC(CCCC2(CCC1)C)C(C)O	222.37	1	1	1	Yes	Yes	Yes	3.73	5	
21	<i>cis</i> -Cadin-4-en-7-ol	CC1CCC(C2C1CCC(=C2)C)C(C)O	222.37	1	1	1	Yes	Yes	Yes	3.53	4	
22	<i>epi</i> - α -Cadinol	CC1 = CC2C(CCC(C2CC1)C)O)C(C)C	222.37	1	1	1	Yes	Yes	Yes	3.53	5	
23	α -Murolol (=Torreyol)	CC1 = CC2C(CCC(C2CC1)C)O)C(C)C	222.37	1	1	1	Yes	Yes	Yes	3.53	5	
24	α -Cadinol	CC1 = CC2C(CCC(C2CC1)C)O)C(C)C	222.37	1	1	1	Yes	Yes	Yes	3.53	5	
25	Selin-11-en-4- α -ol	CC(=C)C1CCC2(CCCC(C2C1)C)O)C	222.37	1	1	1	Yes	Yes	Yes	3.9	4	
26	Eudesm-7(11)-en-4-ol	CC(=C1CCC2(CCCC(C2C1)C)O)C)C	222.37	1	1	0	Yes	Yes	Yes	4	5	
27	γ -Costol	CC1 = C2CC(CCCC2(CCC1)C)C(=C)CO	220.35	1	1	2	Yes	Yes	Yes	3.87	5	
28	Manool oxide	CC1(CCCCC2(C1CCC3(C2CCC(O3)C)C = C)C)C	290.48	0	1	1	Yes	Yes	Yes	4.92	5	

Table 2 Bioactivity scores of selected phytoconstituents using Molinspiration

S. no.	Phytoconstituents	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Linalool	-0.731	0.065	-1.256	-0.061	-0.942	0.074
2	Linalool formate	-0.681	-0.044	-1.077	-0.314	-0.827	0.462
3	δ -Elemene	-0.360	0.248	-0.693	0.626	-0.601	0.456
4	α -Copaene	-0.327	0.167	-0.788	0.024	-0.489	0.095
5	cis-Muurolo-3.5-diene	-0.448	-0.075	-0.769	0.106	-0.702	0.125
6	γ -Gurjunene	-0.485	-0.044	-1.072	-0.084	-0.623	0.103
7	γ -Muurolole	-0.210	0.113	-0.798	0.273	-0.729	0.271
8	β -Selinene	-0.263	0.176	-0.936	0.355	-0.476	0.292
9	γ -Amorphene	-0.210	0.113	-0.798	0.273	-0.729	0.271
10	γ -Cadinene	-0.210	0.113	-0.798	0.273	-0.729	0.271
11	δ -Cadinene	-0.580	-0.019	-0.751	0.003	-0.677	0.189
12	trans-Cadina-1.4-diene	-0.326	-0.148	-0.847	-0.088	-0.774	0.190
13	α -Cadinene	-0.151	0.031	-0.841	0.220	-0.738	0.280
14	cis-Sesquisabinene hydrate (IPP vs. OH)	-0.120	0.117	-0.630	0.311	-0.035	0.222

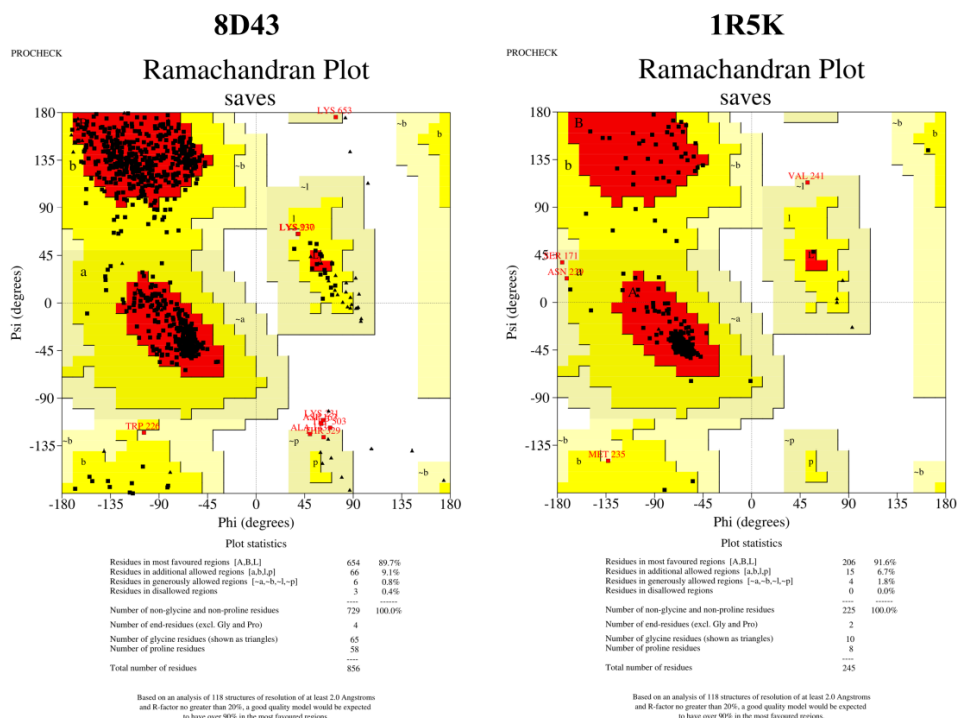
Table 2 Bioactivity scores of selected phytoconstituents using Molinspiration (continued)

S. no.	Phytoconstituents	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
15	β -Copaen-4- α -ol	0.008	0.175	-0.767	0.294	0.027	0.189
16	Spathulenol	-0.418	-0.277	-0.676	0.276	-0.357	0.055
17	Guaiol	-0.208	-0.130	-0.885	0.174	-0.168	0.071
18	10-epi- γ -Eudesmol	-0.287	0.199	-0.812	0.531	-0.321	0.397
19	Murola-4,10(14)-dien-1- β -ol	-0.127	0.431	-0.598	0.343	-0.364	0.356
20	γ -Eudesmol	-0.287	0.199	-0.812	0.531	-0.321	0.397
21	cis-Cadin-4-en-7-ol	-0.052	0.360	-0.853	0.326	-0.357	0.322
22	epi- α -Cadinol	-0.090	0.049	-0.874	0.386	-0.628	0.399
23	α -Murolol (=Torreyol)	-0.090	0.049	-0.874	0.386	-0.628	0.399
24	α -Cadinol	-0.090	0.049	-0.874	0.386	-0.628	0.399
25	Selin-11-en-4- α -ol	-0.118	0.368	-1.013	0.591	-0.415	0.344
26	Eudesm-7(11)-en-4-ol	-0.194	0.180	-0.833	0.511	-0.703	0.286
27	γ -Costol	-0.388	-0.074	-0.764	0.447	-0.530	0.375
28	Manool oxide	-0.050	0.228	-0.488	0.397	-0.303	0.593

3.4 Validation of protein structures

The obtained Ramachandran plot analysis represented that the majority of the amino acid residues of all four proteins were found within the most favoured regions. The scores for all the proteins are above 80% confirming that the models of the proteins used are of high quality for molecular docking (Figures 1 and 2).

Figure 1 Ramachandran plot for the model of the structure of α -Glucosidase (PDB: 8D43) and Estrogen Receptor- α (PDB: 1R5K) proteins generated by PROCHECK. The red colour shows the residues of the protein present in the most favoured regions; the brown colour shows the presence of the residues in the additional allowed regions and the yellow indicates residues in the generously allowed regions (see online version for colours)



3.5 Molecular docking analysis

3.5.1 Molecular docking against α -Glucosidase

The enzyme α -Glucosidase is mainly found in the small intestine at the brush boundary. It is also known as maltase, α -D-glucosidase, glucosidosucrase, maltase-glucoamylase, glucoinvertase, α -glucopyranosidase, α -1,4-glucosidase, glucosidoinvertase, α -glucoside hydrolase, α -D-glucoside glucohydrolase. Its primary function is to improve glucose absorption by catalysing the hydrolysis of polysaccharides (Starch) to glucose (acts on α (1 $\rightarrow$ 4) bonds). This increases blood glucose levels (Mechchate et al., 2021).

Molecular docking was used to examine the molecular interactions between the enzymes and their ligands. All 28 compounds that were selected based on ADMET screening were docked against α -Glucosidase and showed binding affinity ranging between -6.680 to -8.489 . Amongst the docked compounds, cis-Muurolo-3,5-diene, Manool oxide, γ -Gurjunene, cis-Sesquisabinene hydrate and δ -Elemene were the top 5 phytoconstituents, well-suited to the α -Glucosidase's binding site and produced a variety of interactions with the embedded amino acid residues that were both polar and non-polar. The most significant interaction was the ionic connection between the carboxylate moiety and the protonated secondary cyclic amine group of Arg501 and/or Asp498 of the ligand. Compounds cis-Muurolo-3,5-diene and Manool oxide showed the lowest binding energies, as evidenced by docking scores of -8.489 kcal/mol and -8.446 kcal/mol, respectively. Next, compounds γ -Gurjunene followed with a docking score of -8.114 kcal/mol. δ -Elemene and cis-Sesquisabinene hydrate had binding energies that were nearly identical, at -8.081 kcal/mol and -8.084 kcal/mol (Table 3).

Figure 2 Ramachandran plot for the model of the structure of Tumour Necrosis Factor- α (PDB: 5MU8) and Xanthine Oxidase (PDB: 2CKJ) proteins generated by PROCHECK. The red colour region denotes residues of the protein in the most favoured regions; the brown colour denotes residues in the additional allowed regions and the yellow indicates residues in the generously allowed regions (see online version for colours)

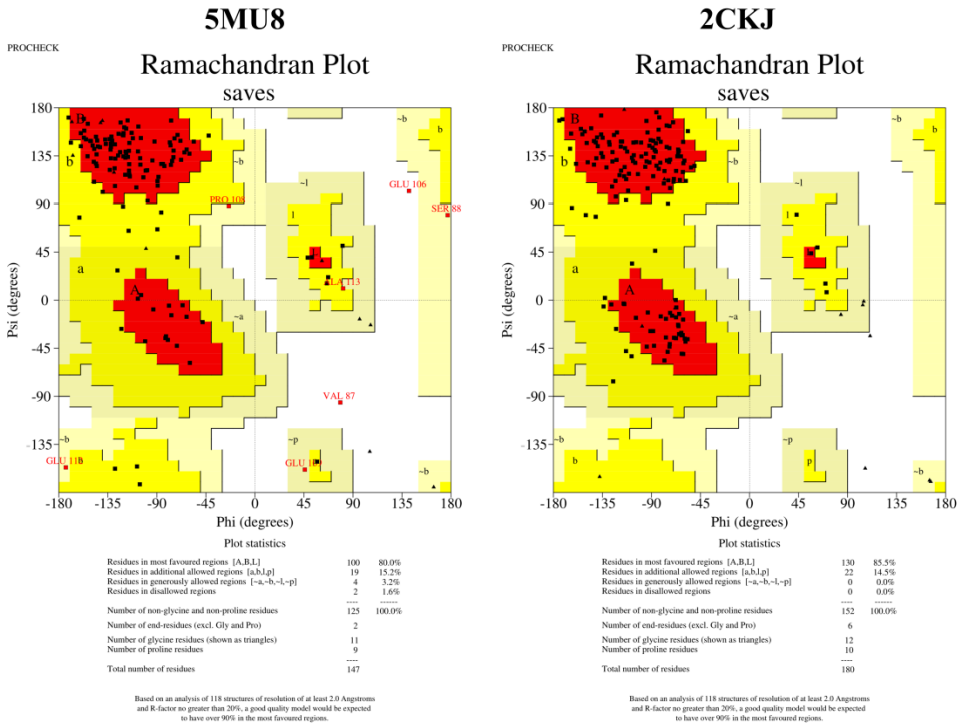


Table 3 DockThor docking score of selected phytoconstituents against α -Glucosidase, Estrogen Receptor- α , Tumor Necrosis Factor- α and Xanthine Oxidase

S. no.	Phytoconstituents	Molecular docking scores			
		α -Glucosidase (8D43)	Estrogen receptor- α (1R5K)	Tumor Necrosis Factor- α (5MU8)	Xanthine oxidase (2CKJ)
1	Linalool	-6.680	-6.633	-6.726	-6.355
2	Linalool formate	-7.074	-7.427	-6.869	-6.933
3	δ -Elemene	-8.081	-7.803	-7.548	-7.893
4	α -Copaene	-7.556	-8.517	-7.497	-8.120
5	cis-Muurolo-3,5-diene	-8.489	-8.066	-7.721	-8.002
6	γ -Gurjunene	-8.114	-7.867	-7.705	-8.090
7	γ -Muuroloene	-8.015	-8.057	-7.799	-8.128
8	β -Selinene	-7.596	-7.984	-7.725	-7.937
9	γ -Amorphene	-8.032	-7.946	-7.609	-8.014
10	γ -Cadinene	-7.950	-8.996	-7.761	-8.012
11	δ -Cadinene	-7.942	-7.934	-7.951	-8.268
12	trans-Cadina-1,4-diene	-8.014	-8.682	-7.711	-7.996
13	α -Cadinene	-7.945	-8.500	-7.811	-8.236
14	cis-Sesquisabinene hydrate (IPP vs. OH)	-8.084	-7.367	-7.557	-7.062

Table 3 DockThor docking score of selected phytoconstituents against α -Glucosidase, Estrogen Receptor- α , Tumor Necrosis Factor- α and Xanthine Oxidase (continued)

S. no.	Phytoconstituents	Molecular docking scores			
		<i>Alpha-Glucosidase</i> (8D43)	<i>Estrogen receptor-α</i> (1R5K)	<i>Tumor Necrosis Factor-α</i> (5MU8)	<i>Xanthine oxidase</i> (2CKJ)
15	β -Copaen-4- α -ol	-7.278	-7.127	-7.609	-7.274
16	Spathulenol	-7.066	-9.108	-7.626	-7.011
17	Guaiol	-7.595	-7.052	-7.471	-6.634
18	10- <i>epi</i> - γ -Eudesmol	-7.082	-7.141	-7.515	-7.364
19	Murola-4,10(14)-dien-1- β -ol	-7.455	-7.033	-7.730	-6.244
20	γ -Eudesmol	-7.281	-7.021	-7.441	-7.063
21	<i>cis</i> -Cadin-4-en-7-ol	-7.326	-6.902	-7.370	-7.071
22	<i>epi</i> - α -Cadinol	-7.714	-7.018	-7.589	-7.259
23	α -Murolol (=Torreyol)	-7.945	-6.912	-7.227	-6.884
24	α -Cadinol	-7.903	-7.186	-7.575	-6.630
25	Selin-11-en-4- α -ol	-7.643	-9.146	-7.332	-6.859
26	Eudesm-7(11)-en-4-ol	-7.334	-8.943	-7.602	-7.210
27	γ -Costol	-7.844	-7.077	-7.407	-6.980
28	Manool oxide	-8.446	-7.528	-7.839	-7.986

Multiple interactions between compounds (cis-Muurolo-3,5-diene, Manool oxide, γ -Gurjunene, cis-Sesquisabinene hydrate and δ -Elemene) and the binding site residues were discovered by molecular docking analysis (Figure 3). As seen on 2D docking results, cis-Muurolo-3,5-diene docked to the active site of α -Glucosidase specifically with the residues Ala300, Arg501, Arg523, Asp498, Leu301, Phe765, and Pro510. Similarly, γ -Gurjunene interacted with the residues Ala300, Arg523, Pro510 and Thr298, and δ -Elemene with the residues Ala300, Ala497, Arg501, Arg523, His632, Phe524, Pro510 and Thr298. In the case of Manool oxide, the ligand creates active interaction with the residues Ala300, Ala497, Arg501, and Arg523, where the ligand initiates hydrogen bonds towards two amino acids i.e., Ala300 and Arg501. Similarly cis-Sesquisabinene hydrate interacts with the residues Ala300, Ala497, Arg501, Arg523, Asp498, His632, Phe524, Phe765 and Pro510, where Pro510, Asp498 and Arg501 interacted by hydrogen bonds.

Sampath et al. (2024) showed Cynaroside, Rutin, Biorobin, Quercetin and Kaempferol found in *Annona species* have good α -Glucosidase enzyme inhibition, with binding affinity values of -9.2 kcal/mol, -9 kcal/mol, -8.5 kcal/mol, -8.2 kcal/mol and -8 kcal/mol respectively. Similarly, Zakaria et al. (2023) showed that hesperidin, pomiferin, osajin, and cosmosiin from aloe vera have promising α -Glucosidase enzyme inhibition, with binding affinity values of -8.8 kcal/mol, -8.1 kcal/mol, -7.8 kcal/mol, and -7.7 kcal/mol respectively, which is also higher than acarbose with -7.3 kcal/mol. The above-mentioned compounds share interactions with α -Glucosidase at specific amino acid residues i.e., Trp377, Ser379, Glu380, Ser381, Gly382, Ile383, Ile384, Asp385, Val386, Arg591, Asp592, Ile593, His594, Asn595, Phe627. Whereas in the present study the ligands interacted with α -Glucosidase in a different active site which might be more useful in reducing activity of the enzyme.

3.5.2 Molecular docking against Estrogen Receptor- α

An individual's ovulation, fertilisation, or uterine receptivity can all be modified by the Estrogen Receptor- α (ER- α). The estrogen receptor is crucial for the menstrual cycle, fertilisation, and pregnancy. Since estrogen can affect the ovulation process, the estrogen receptor is a key target for substances that affect the ovulation process. The estrogen receptors are one of the targets that all combination oral contraceptives now on the market contain. Oral contraceptives can have minor to severe side effects, including changes to the metabolic process and an increased risk of cancer. Finding and evaluating safer alternatives to contraception is crucial (Priya et al., 2021).

Molecular docking was used to examine the molecular interactions between the enzymes and their ligands. The docked compounds Selin-11-en-4- α -ol, Spathulenol, γ -Cadinene, Eudesm-7(11)-en-4-ol and trans-Cadina-1,4-diene were five major phytoconstituents, well-suited to the Estrogen Receptor- α 's binding site and produced a variety of polar and non-polar interactions with the embedded amino acid residues. Selin-11-en-4- α -ol and Spathulenol displayed the lowest binding energies, as evidenced by docking scores of -9.146 and -9.108 kcal/mol, respectively. Next, compounds γ -Cadinene and Eudesm-7(11)-en-4-ol displayed binding energies that were at -8.996 and -8.943 kcal/mol, and compound trans-Cadina-1,4-diene followed with a docking score of -8.682 kcal/mol (Table 3).

Figure 3 The top five ligands ((A) cis-Muurolo-3,5-diene, (B) Manool oxide, (C) γ -Gurjunene, (D) cis-Sesquisabinene hydrate and (E) δ -Elemene) for α -Glucosidase were analysed in 2-D diagrams of intermolecular interactions using DockThor docking. The image was created using LigPlot+ and PyMol. The red dots represent hydrogen bonding (see online version for colours)

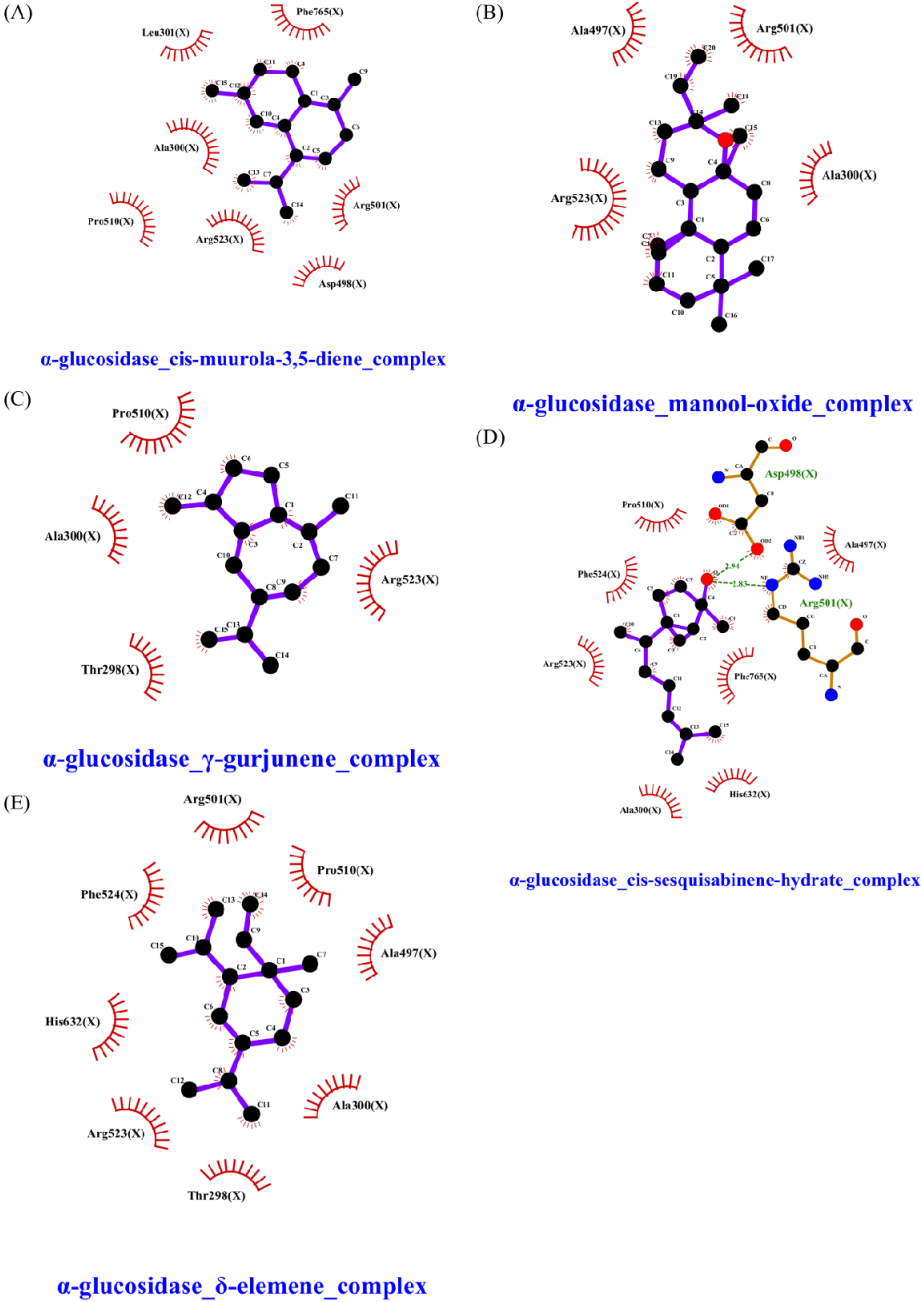
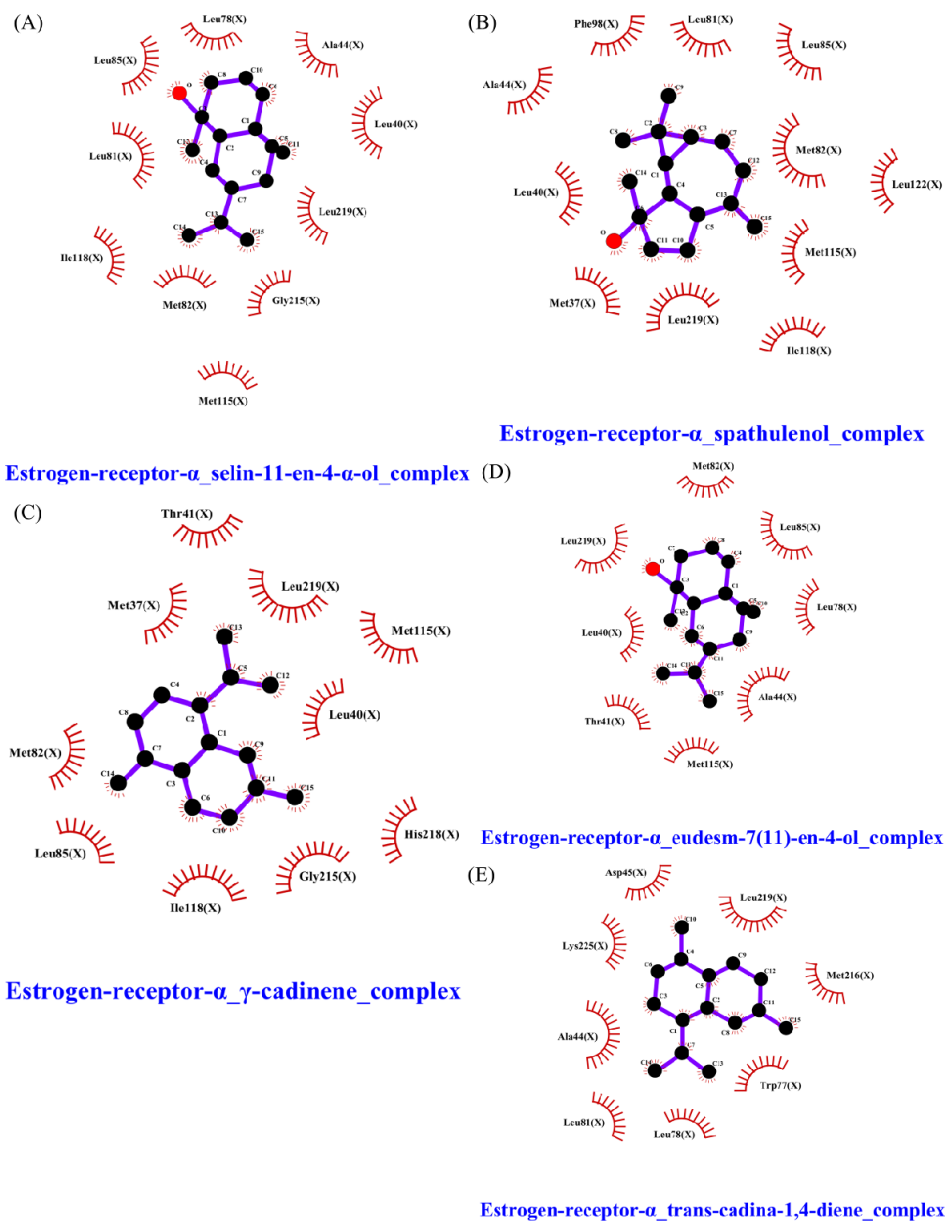


Figure 4 The top five ligands ((A) Selin-11-en-4- α -ol, (B) Spathulenol, (C) γ -Cadinene, (D) Eudesm-7(11)-en-4-ol and (E) trans-Cadina-1,4-diene) for Estrogen Receptor- α were analysed in 2-D diagrams of intermolecular interactions using DockThor docking. The image was created using LigPlot+ and PyMol. The red dots represent hydrogen bonding (see online version for colours)



Multiple interactions between compounds (Selin-11-en-4- α -ol, Spathulenol, γ -Cadinene, Eudesm-7(11)-en-4-ol and trans-Cadina-1,4-diene) and the binding site residues were discovered by molecular docking analysis. As seen in 2D docking results (Figure 4) Selin-11-en-4- α -ol docked to the active site of Estrogen Receptor- α specifically with the residues Ala44, Gly215, Ile118, Leu40, Leu78, Leu81, Leu85, Leu219, Met82 and Met115 where Leu85 showed to interact with hydrogen bonding from the ligand site. Similarly, Spathulenol interacted with the residues Ala44, Ile118, Leu40, Leu81, Leu85, Leu122, Leu219, Met37, Met82, Met115 and Phe98 and Met37 is seen to be interacted with hydrogen bonds. Eudesm-7(11)-en-4-ol interacted with the residues Ala44, Leu40, Leu78, Leu85, Leu219, Met82, Met115 and Thr41 and the ligand-initiated hydrogen bond towards Leu219. γ -Cadinene interacted with the residues Gly215, His218, Ile118, Leu40, Leu85, Leu219, Met37, Met82, Met115 and Thr41, and trans-Cadina-1,4-diene with the residues Ala44, Asp45, Leu78, Leu81, Leu219, Lys225, Met216 and Trp77.

Mohaideen et al. (2023) showed that Ethanone, 1-phenyl-2-(4,5-diphenyl-2-imidazolylthio)-; Thiazolo [3,2-a]benzimidazol-3(2H)-one, 2-(4-acetoxybenzylideno and Phenanthro [1,2-b]furan-10,11-dione, 6,7,8,9-tetrahydro-1,6,6-trimethyl- from *Borassus flabellifer* haustorium has a greater binding affinity of -9.3 kcal/mol, -8.7 kcal/mol and -8.1 kcal/mol to ER- α . Similarly, Akbari et al. (2022) reported that the phytochemicals of *Astragalus microcephalus* Willd. i.e., kaempferol-based structures, formononetin, calycosin-7-O-beta-D-glucoside, and quercetin-3-O-neohesperidoside had a high affinity (<-6.3) to ER- α . Kaempferol showed interactions with ER- α at the amino acid residue positions Glu330, Met342, Met343, Leu345, Glu353, Arg394, and His524. Whereas in the present study, the top five phytoconstituents resulted in a docking score ranging from -8.682 to -9.146 kcal/mol. Further, the ligands interacted with other active sites of the ER- α in comparison to the reported one.

3.5.3 Molecular docking against Tumour Necrosis Factor- α

One of the most active areas of drug research for treating inflammatory illnesses over the past decade has been the development of inhibitors for Tumour Necrosis Factor- α (TNF- α) (Baugh and Bucala, 2001). TNF- α , or cachectin, is a potent pro-inflammatory cytokine crucial for the immune system's function during inflammation, cell division, proliferation, and apoptosis (Baud and Karin, 2001). Inflammation eliminates the irritant and hastens tissue repair (Zelová and Hošek, 2013).

Molecular docking was used to study the molecular interactions between the enzymes and their ligands. Amongst the docked compounds δ -Cadinene, Manool oxide, α -Cadinene, γ -Muurolene and γ -Cadinene were five major phytoconstituents, well-suited to the Tumour Necrosis Factor- α 's binding site and produced a variety of polar and non-polar interactions with the embedded amino acid residues. Compounds δ -Cadinene and Manool oxide displayed the lowest binding energies, as evidenced by docking scores of -7.951 kcal/mol and -7.839 kcal/mol, respectively. Next, compounds α -Cadinene and γ -Muurolene showed binding energies that were at -7.811 and -7.799 kcal/mol, and compound γ -Cadinene followed with a docking score of -7.761 kcal/mol (Table 3).

Multiple interactions between compounds (δ -Cadinene, Manool oxide, α -Cadinene, γ -Muurolene, and γ -Cadinene) and the binding site residues were discovered by molecular docking analysis (Figure 5). As seen in 2D docking results, δ -Cadinene docked to the active site of Tumour Necrosis Factor- α specifically with the residues Ala13, Ala136, Asn10, Gln16, Gly15, Leu133, Pro11 and Pro130, Manool oxide with the

residues Ala13, Asp131, Leu133, Lys56, and Pro11, α -Cadinene with the residues Ala13, Asn10, Asp131, Gly15, Leu133, Pro11 and Pro130, γ -Muurolene with the residues Ala13, Asn10, Glu14, Gly15, Leu133, Pro11 and Pro130 and γ -Cadinene with the residues Ala13, Asn10, Asp131, Glu14, Gln16, Leu133, Phe135, Pro11 and Pro130. Manool oxide is seen to initiate hydrogen bonds towards the amino acid residue Lys56 of the protein TNF- α .

Gupta et al., 2021 reported rhamnetin has a higher binding affinity than the other two compounds at -6.9 kcal/mol. They also showed the binding sites in the enzymes i.e., Pro139, Leu142, and Phe144. Prathap et al. (2021) reported that the inhibitor with a binding affinity of -6.8 kcal/mol with TNF- α has shown hydrogen bonding with Tyr378, Arg332, Arg372 and Val373. Whereas in the present study, the top five phytoconstituents resulted a docking score ranging from -7.761 kcal/mol to -7.951 kcal/mol which is higher than the previous reports. Further the ligands interacted with TNF- α in different active sites which might be more useful in inhibiting the activity of TNF- α .

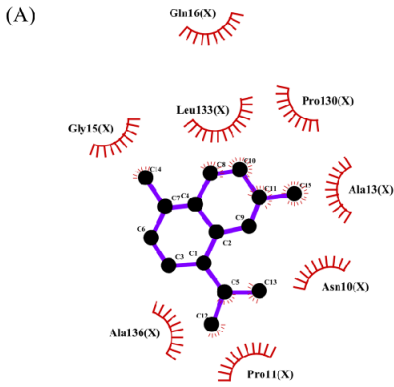
3.5.4 Molecular docking against Xanthine Oxidase

The major enzymes that result in the production of uric acid from adenine nucleotides are xanthine dehydrogenase (XDH) and Xanthine Oxidase (XO), which are single-gene products that occur in a variety of forms but are interchangeable (Borges et al., 2002). Oxidative stress is more likely to happen when XO is too active since it produces superoxide anion and hydrogen peroxide. When this route is inhibited, uric acid production and loading into joints decreases. In healthy tissues, XDH predominates, whereas, in sick ones, it is transformed into XO. Due to the availability of many XO inhibitors in the market, XO is a proven target for the therapeutic management of gout and other hyperuricemia-related disorders (Lü et al., 2013; Šmelcerović et al., 2017).

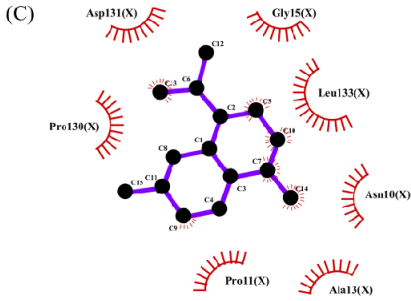
Molecular docking was used to examine the molecular interactions between the enzymes and their ligands. The docked compounds δ -Cadinene, α -Cadinene, γ -Muurolene, α -Copaene, and γ -Gurjunene were 5 major phytoconstituents, well-suited to the Xanthine Oxidase's binding site and produced a variety of polar and non-polar interactions with the embedded amino acid residues. Compounds δ -Cadinene and α -Cadinene displayed the lowest binding energies, as evidenced by docking scores of -8.268 kcal/mol and -8.236 kcal/mol, respectively. Next, compounds γ -Muurolene and α -Copaene showed binding energies that were at -8.128 kcal/mol and -8.120 kcal/mol, and compound γ -Gurjunene followed with a docking score of -8.090 kcal/mol (Table 3).

Multiple interactions between compounds δ -Cadinene, α -Cadinene, γ -Muurolene, α -Copaene and γ -Gurjunene and the binding site residues were discovered by molecular docking analysis. As seen in 2D docking results δ -Cadinene interacted with the active site of Xanthine Oxidase, specifically with the residues Ala162, Asp107, Leu164, Phe109, Pro159 and Val152, α -Cadinene with the residues Ala162, Asp107, Leu163, Leu164, Lys98, Phe109 and Pro159, γ -Muurolene with the residues Ala162, Leu163, Leu164, Lys98, Phe109, Pro159 and Val152, α -Copaene with the residues Ala162, Asp107, Leu163, Leu164, Lys98, Lys157, Phe109, Pro159 and Val152 and γ -Gurjunene with the residues Ala162, Asp107, Leu163, Leu164, Lys157 and Phe109 (Figure 6).

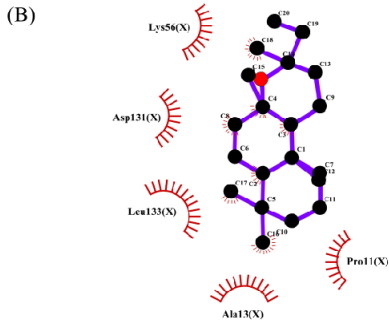
Figure 5 The top five ligands ((A) δ -Cadinene, (B) Manool oxide, (C) α -Cadinene, (D) γ -Muurolene and (E) γ -Cadinene) for Tumour Necrosis Factor- α were analysed in 2-D diagrams of intermolecular interactions using DockThor docking. The image was created using LigPlot+ and PyMol. The red dots represent hydrogen bonding (see online version for colours)



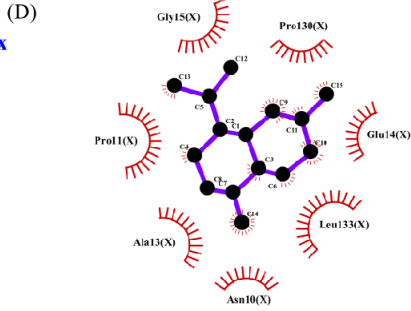
Tumor-necrosis-factor- α δ -cadinene_complex



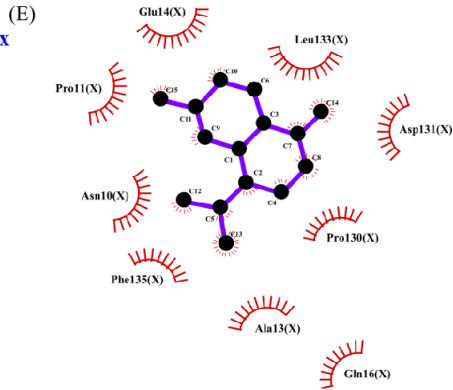
Tumor-necrosis-factor- α α -cadinene_complex



Tumor-necrosis-factor- α manool-oxide_complex



Tumor-necrosis-factor- α γ -muurolene_complex



Tumor-necrosis-factor- α γ -cadinene_complex

Figure 6 The top five ligands ((A) δ -Cadinene, (B) α -Cadinene, (C) γ -Muurolene, (D) α -Copaene and (E) γ -Gurjunene) for Xanthine Oxidase were analysed in 2-D diagrams of intermolecular interactions using DockThor docking. The image was created using LigPlot+ and PyMol. The red dots represent hydrogen bonding (see online version for colours)

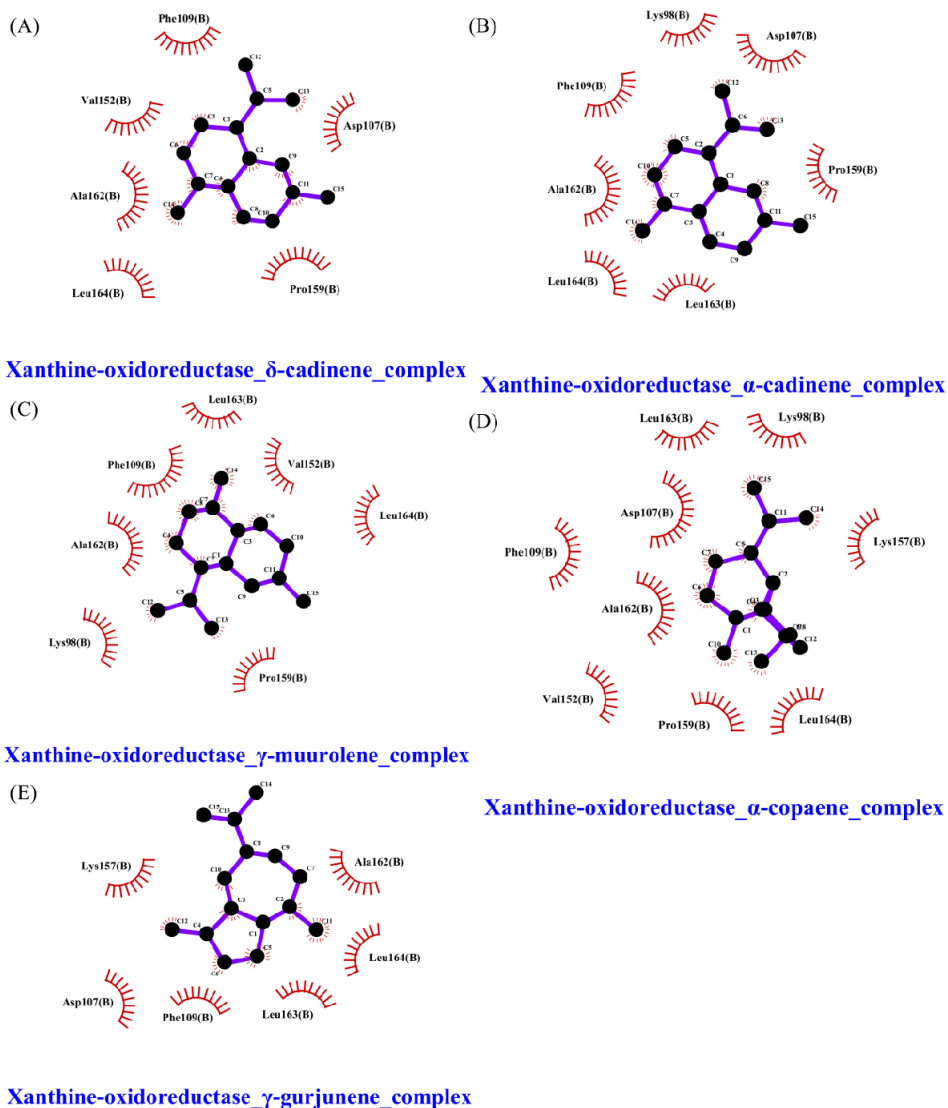


Figure 7 2D structure of 14 phytoconstituents i.e., Linalool, Linalool formate, δ -Elemene, α -Copaene, cis-Muurolo-3,5-diene, γ -Gurjunene, γ -Muuroloene, β -Selinene, γ -Amorphene, γ -Cadinene, δ -Cadinene, trans-Cadina-1,4-diene, α -Cadinene, cis-Sesquisabinene hydrate (IPP vs. OH) used for molecular docking (see online version for colours)

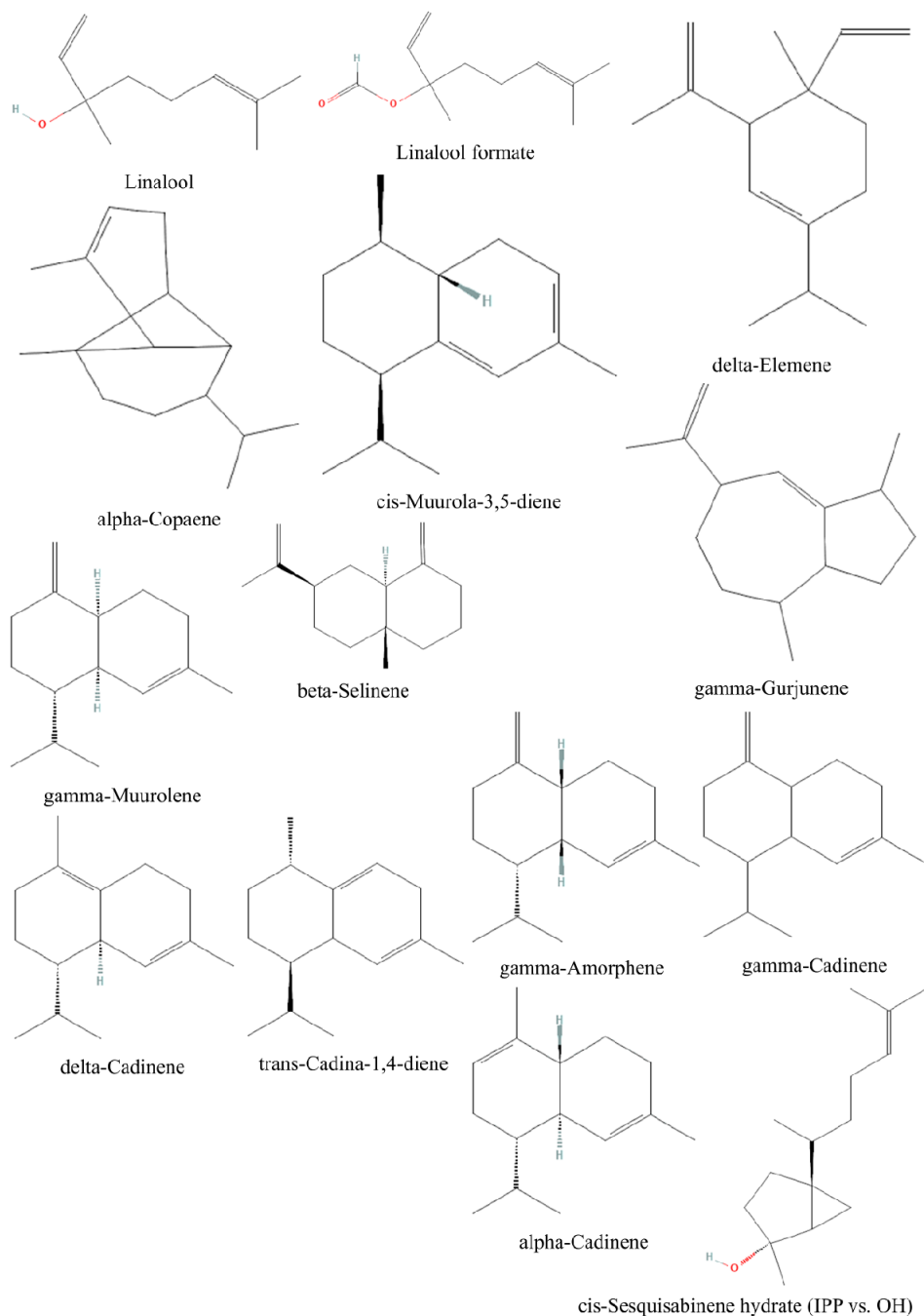
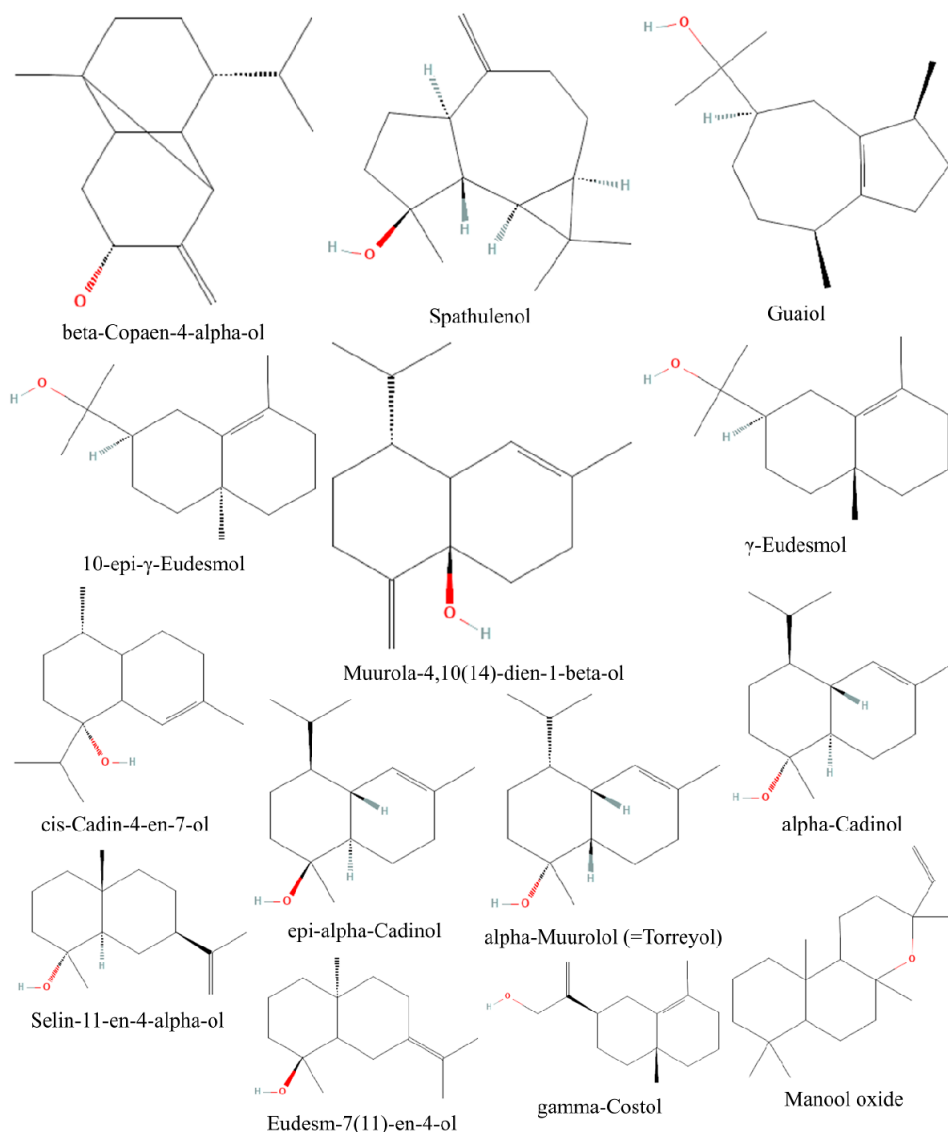


Figure 8 2D structure of other 14 phytoconstituents i.e., β -Copaen-4- α -ol, Spathulenol, Guaiol, 10-epi- γ -Eudesmol, Muurola-4,10(14)-dien-1- β -ol, γ -Eudesmol, cis-Cadin-4-en-7-ol, epi- α -Cadinol, α -Muurolol (=Torreyol), α -Cadinol, Selin-11-en-4- α -ol, Eudesm-7(11)-en-4-ol, γ -Costol, Manool oxide used for molecular docking (see online version for colours)



Nurjannah et al., 2024 reported 9,12,15-Octadecatrienoic acid, methyl ester, (Z, Z, Z); 1s1,14,17-Eicosatrienoic acid, methyl ester; Methyl eicosa-5,8,11,14,17-pentaenoate and Hexadecanoic acid, 15-methyl-, methyl ester have higher binding affinity towards XO with -5.7 kcal/mol (Leu257, Val259, Ile353, Thr354, Leu398, Leu404), -5.2 kcal/mol (Glu23, Thr25, Leu27, Glu677, Gln680), -4.7 kcal/mol (Asn19, Asp21, Thr24, Tyr29, Arg32, Lys33, Glu677) and -4.6 kcal/mol (Asp59, Val66, Phe680, Ala302, Pro304, Val345) respectively. Ali et al., 2021 have proved that 4-Terpineol (-6.457 kcal/mol) and

T-cadinol (−6.882 kcal/mol) obtained from *Homalomena aromatica* (Spreng.) Schott, showed better docking scores than ascorbic acid (−6.407 kcal/mol). Whereas in the present study, the top five phytoconstituents resulted a docking score ranging from −8.090 to −8.268 kcal/mol which is higher than the previous reports. Thus, the selected phytoconstituents of *M. champaca* leaf essential oil could be used as potential inhibitors of Xanthine Oxidase.

4 Conclusions

The results of the current study demonstrate that the phytochemicals of *M. champaca* leaf essential oil have a powerful inhibitory effect on α -Glucosidase, Estrogen Receptor- α , Xanthine Oxidase, Tumour Necrosis Factor- α , proteins through integrative computational approaches. The findings suggest that cis-Muurolo-3,5-diene and Selin-11-en-4- α -ol have the potential to inhibit the activity of α -G and ER- α respectively. Similarly, δ -Cadinene possesses the capacity to inhibit TNF- α and XO. This is the first *in silico* study to discover prospective bioactive compounds from *Magnolia champaca* leaf essential oil with greater binding affinity against target proteins. By harnessing the potential of *M. champaca*, this research paves the way for the development of more effective treatments for diabetes, infertility, inflammatory diseases, and oxidative stress. However, further *in vitro* and *in vivo* study is necessary before developing innovative antidiabetic, antifertility, antiinflammatory, and antioxidant medications for treating respective illnesses.

Acknowledgement

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Conflicts of interest

The authors declare no conflict of interest.

Data availability

Data are available upon request from the authors.

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