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In Silico Study of Hops Plant (*Humulus lupulus* L.) Compounds as Phytoestrogens for Insulin Resistance

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Abstract

Postmenopausal women often experience insulin resistance, a condition linked to declining estrogen levels. Structurally similar to endogenous estrogen, phytoestrogens derived from *Humulus lupulus* L. (hops) hold potential as natural agents in hormone replacement strategies. This research utilized a comprehensive in silico methodology to assess 20 bioactive hop-derived compounds for their ability to act as agonists of estrogen receptor alpha (ERα). The evaluation involved Lipinski's Rule of Five, ADME-Tox profiling, pharmacophore-based screening, and molecular docking analyses. Seven compounds satisfied the pharmacophore model criteria. Among them, isoxanthohumol and 8-prenylnaringenin displayed the most favorable binding affinities, while desmethylxanthohumol and naringenin showed interaction patterns closely aligned with those of the native ligand. Although the majority demonstrated favorable pharmacokinetic properties, a few compounds presented potential mutagenic or carcinogenic effects. Considering binding performance, interaction resemblance, and predicted safety, these four compounds emerge as strong phytoestrogen candidates for ERα modulation in insulin resistance. Experimental validation through biological studies is necessary to substantiate these computational findings.

Keywords: *Humulus lupulus*, phytoestrogen, insulin resistance, ERα agonist, molecular docking

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Introduction

A reduction in estrogen levels during menopause is closely associated with various metabolic disturbances, including increased body weight, the buildup of visceral fat, and a heightened risk of metabolic syndrome, particularly insulin resistance (IR) (Mauvais-Jarvis et al., 2017). Insulin resistance arises when peripheral tissues such as adipose tissue, skeletal muscles, and the liver exhibit a diminished response to insulin, leading to decreased glucose uptake. Under normal physiological conditions, elevated blood glucose levels prompt insulin release from pancreatic β-cells and simultaneously inhibit hepatic glucose production. However, in the context of insulin resistance, this regulatory mechanism becomes impaired. Consequently, the liver continues to produce excess glucose while insulin secretion remains elevated, exacerbating hyperglycemia and increasing the likelihood of progression toward diabetes (De Paoli et al., 2021).

Estrogen plays a crucial role in maintaining insulin sensitivity and glucose homeostasis through multiple mechanisms. Estrogen maintains insulin sensitivity by enhancing insulin signaling in muscle and adipose tissues through upregulation of IRS-1 and promotion of GLUT4 translocation. It also regulates hepatic glucose metabolism by inhibiting gluconeogenesis and lipid accumulation while activating ERα to suppress inflammation and oxidative stress, which are key factors in insulin resistance. Consequently,

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estrogen deficiency during menopause disrupts these pathways, leading to impaired insulin signaling and increased visceral fat deposition (Ribas et al., 2016; Barros & Gustafsson, 2011).

The prevalence of insulin resistance globally ranges from 15.5% to 46.5%, with Indonesia reporting a prevalence as high as 42.2% (Goh et al., 2022). This significant prevalence highlights the urgent need for effective and safe strategies to manage insulin resistance, especially in postmenopausal women who experience a decline in estrogen levels.

A study by Park et al. (2022) using a streptozotocin-induced diabetic mouse model reported that treatment with 50 mg/kg of naringenin and 8-prenylnaringenin (8-PN) protected pancreatic β-cells from oxidative damage and restored ERα expression in the pancreas and liver, leading to improved insulin signaling and glucose regulation. These findings highlight the critical role of phytoestrogens in modulating estrogen receptor activity and glucose metabolism (Park et al., 2022).

In this context, hop plants (*Humulus lupulus* L.) have attracted considerable attention as natural alternatives to hormone replacement therapy because they contain various bioactive compounds, particularly phytoestrogens. The lupulin glands of hops are rich in flavonoids such as kaempferol, quercetin, catechin, and 8-prenylnaringenin (8-PN), a potent phytoestrogen derived from xanthohumol (Steenackers et al., 2015). These compounds are known to bind to estrogen receptors, especially ERα, thereby mimicking estrogenic activity that may help restore impaired insulin signaling.

Building on this evidence, the present study aims to provide scientific support for the potential of major bioactive compounds from *Humulus lupulus* L. (hops) in improving insulin resistance through activation of estrogen receptor alpha (ERα). A total of twenty major phytochemicals commonly reported in hops were initially selected and evaluated for their drug-likeness and pharmacokinetic properties using Lipinski's Rule of Five and ADMETox screening. Compounds that met these criteria were further subjected to pharmacophore-based screening, which yielded eight hit compounds with favorable structural and pharmacophoric features. These eight compounds were then analyzed through molecular docking to assess their binding affinity and interacting amino acid residues with ERα. Given their phytoestrogenic potential, these compounds could serve as natural alternatives for hormone replacement therapy, particularly in managing metabolic syndrome associated with menopause.

Methods

The hardware utilized in this study consisted of a laptop with the following specifications: a 12th Gen Intel® Core™ i7-1255U processor running at 1.70 GHz, 8.00 GB of RAM, and Windows 11 Home Single Language, version 24H2. Various online databases and software tools were employed during the research process. PubChem (*https://pubchem.ncbi.nlm.nih.gov/*) was used to download the chemical structures of natural compounds and reference ligands. Chem3D Pro 12.0 was utilized to construct the ligand structures and perform energy minimization. The three-dimensional structures of the target proteins were obtained from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (*https://www.rcsb.org/*). The PreADMET web tool (*https://preadmet.webservice.bmdrc.org/*) was used to predict the ADME (Absorption, Distribution, Metabolism, and Excretion) profiles and toxicity of both test and reference compounds. To facilitate pharmacophore modeling, the DUD.E (Database of Useful Decoys: Enhanced) platform (*https://dude.docking.org*) was accessed to acquire active and decoy compounds. LigandScout software was employed to develop pharmacophore models for the test ligands. Molecular docking analysis was carried out using AutoDock software, while BIOVIA Discovery Studio 2025 was used for the preparation of ligands and receptors, as well as the visualization of docking results. Furthermore, the Mcule platform (*https://mcule.com/search/*) was utilized to determine the physicochemical properties of the test compounds.

Lipinski's Rule of Five Predictions

The prediction of Lipinski's Rule of Five was performed to assess the physicochemical properties and evaluate the drug-likeness profile of the test compounds in

order to determine their potential as oral drug candidates (Nhlapho et al., 2024). The compounds were downloaded from PubChem (*https://pubchem.ncbi.nlm.nih.gov/*) and analyzed using the Mcule website (*https://mcule.com/search/*). The analysis focused on Lipinski's parameters, which include molecular weight (<500 Da), LogP (<5), and the number of hydrogen bond donors (<5) and acceptors (<10).

ADMET Prediction

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicology) analysis was conducted to evaluate the physicochemical properties, drug-likeness, and toxicity profile of the tested compounds (Ghannay et al., 2020). The test compound molecular structures were taken from PubChem (*https://pubchem.ncbi.nlm.nih.gov/*), and the ADMET prediction was carried out using the PreADMET web server (*https://preadmet.webservice.bmdrc.org/*). The parameters assessed in this analysis included Human Intestinal Absorption (HIA %), Caco-2 permeability (Cancer coli-2), Blood–Brain Barrier (BBB) penetration, Plasma Protein Binding (PPB), and toxicity evaluation based on the Ames test and Rodent Carcinogenicity results.

Pharmacophore Screening

Pharmacophore screening was conducted by creating a database of active and decoy compounds targeting the ER-alpha receptor, sourced from the DUD-E database. The test compounds were formatted into a database by uploading each one in SDF format, which was downloaded from PubChem. Ten pharmacophore models were generated and analyzed using LigandScout software (Hariyanti et al., 2020). These models were subsequently validated using Receiver Operating Characteristic (ROC) curve plots to assess their discriminatory performance. After validation, the database of test compounds was screened using the Screening Perspective module in LigandScout, and the compounds identified as hits were presented as the final results of the screening process.

Molecular Docking Simulation

The molecular docking process began by downloading the 3D structure of the ER-alpha receptor (PDB ID: 1SJ0) from the RCSB Protein Data Bank and saving it in PDB format. The receptor structure was prepared using BIOVIA Discovery Studio 2025, which involved removing water molecules and native ligands, converting non-polar hydrogens to polar-only, and saving the structure in PDBQT format. The natural ligand was optimized using the MM2 method in Chem3D Pro X and saved as a PDB file. Next, further preparation steps were conducted in AutoDock, where the docking grid box was defined with dimensions of 40×40×40 and specific coordinates. Redocking was performed to validate the docking protocol, ensuring that the root mean square deviation (RMSD) value was less than 2 Å. The test compounds were also optimized and prepared using the same grid box parameters. Finally, docking was executed using AutoDock via the Command Prompt with the genetic algorithm set to run 100 times. All resulting ligand-receptor complexes were analyzed using BIOVIA to observe the interactions between the test compounds and the receptor (Hasan et al., 2023).

Results and Discussion

Lipinski's Rule of Five Predictions

An evaluation based on Lipinski’s Rule of Five (RO5) was conducted on the bioactive constituents derived from the Hops plant (Humulus lupulus L.). This assessment considered key physicochemical parameters, including molecular weight, Log P value, and the number of hydrogen bond donors and acceptors. According to the RO5 prediction summarized in Table 1, all 20 compounds analyzed fulfilled the Lipinski criteria. The Rule of Five serves as a guiding principle for estimating the likelihood of a compound’s oral bioavailability and its potential biological activity. To be considered suitable for oral drug development, a compound generally needs to adhere to RO5 guidelines, which stipulate that its molecular weight should be under 500 g/mol, Log P should be below 5, and it should have fewer than 5 hydrogen bond donors and fewer than 10 hydrogen bond acceptors (Chen et al., 2020). Log P, which stands for the logarithm of the partition coefficient, is a measure of lipophilicity and represents the compound’s preference for partitioning between octanol and

water. A higher Log P implies greater lipid solubility, while a lower value suggests better water solubility (Ivanovic et al., 2020). The prediction results displayed in Table 1 show that all tested compounds are within the acceptable range for RO5 compliance. More specifically, 17 out of the 20 bioactive compounds fully complied with all RO5 parameters. The remaining three compounds—lupulone, co-lupulone, and humulene—each exhibited a single deviation from the criteria, particularly in their Log P values. Nonetheless, these compounds are still considered RO5-compliant, as the rule allows for one permissible violation. A compound is regarded as non-compliant only when two or more of the four criteria are not met (Roskoski, 2023).

ADMET Predictions

A lead compound should possess a favorable ADME profile and demonstrate low toxicity (Table 2). The original definition of ADME encompasses descriptors that evaluate the extent to which a drug enters the body (absorption), circulates within the body (distribution), undergoes transformation in the body (metabolism), and is eliminated from the body (excretion) (Doogue & Polasek, 2025). By conducting PreADMET testing, the risk of failure during the drug development stage can be minimized. A drug that is both safe and effective combines optimal pharmacodynamics and pharmacokinetics, featuring high potency, affinity, and selectivity for its molecular target, along with a well-tolerated ADMET (absorption, distribution, metabolism, excretion, and toxicity) profile (Ferreira & Andricopulo, 2019). The pharmacokinetic profile of the drug candidate compound includes ADME, which includes absorption, distribution, metabolism, and excretion. Meanwhile, the safety aspect of the compound is assessed based on its toxicity profile.

The bioactive compounds tested showed HIA (Human Intestinal Absorption) values in the range of 63.485215% to 100%. Where an adequate HIA category is 20% to 70% and a good category is in the range of 70% to 100%. Most compounds exhibited high absorption (HIA >80%) and moderate intestinal permeability, with exceptions like Quercetin, Catechin, and Epicatechin showing low absorption and poor permeability. Caco-2 parameter, 17 compounds have medium permeability values (4-70 nm/sec), and the other 3 are in the low permeability range (<4 nm/sec). Furthermore, 13 compounds showed a good ability to bind to plasma proteins, with a PPB value of more than 90%. While 7 other compounds have a PBB value below 90% (Hasan & Herowati, 2024).

Additionally, 14 compounds demonstrate strong blood-brain barrier (BBB) penetration, with BBB values exceeding 2. In contrast, 6 other compounds exhibit BBB penetration values ranging from 0.1 to 2 (Lestari et al., 2023). Compounds with minimal BBB penetration, such as Quercetin, can be beneficial for targeting non-central nervous system (non-CNS) locations. When it comes to compounds aimed at modulating Estrogen Receptor Alpha to enhance insulin resistance, high BBB permeability is not essential, as their primary targets reside in adipose tissue, skeletal muscle, and the liver (Blüher, 2013; Hairi et al., 2024; Meda et al., 2024). Toxicity assessments show that while many compounds are mutagenic, some, such as desmethylxanthohumol and α-bisabolol, are categorized as non-mutagenic and non-carcinogenic in rats and mice, positioning them as safer candidates. Conversely, certain compounds with favorable ADME profiles, like xanthohumol and quercetin, still present mutagenic or carcinogenic risks and necessitate further toxicity investigations. Notably, desmethylxanthohumol and α-bisabolol stand out as the most promising candidates, thanks to their favorable ADME characteristics and low toxicity. On the other hand, compounds like Catechin and Epicatechin exhibit poor absorption, while others warrant caution due to potential genotoxicity.

Table 1. Lipinski's Rule of Five-based predictions of *H. lupulus* bioactive compounds

Compound	Molecular Weight (<500 Da)	Log P (<5)	Hydrogen Bond		Violation
			Donor (<5)	Acceptor (<10)	
Xanthohumol	354.3951	4.2168	3	5	0
Desmethylxanthohumol	340.3685	3.9138	4	5	0
Isoxanthohumol	354.3951	4.3216	2	5	0
8-prenylnaringenin	340.3685	4.0168	3	5	0
Naringenin	272.2517	2.5099	3	5	0
Quercetin	302.2346	1.9880	5	7	0
Catechin	290.2671	1.5461	5	6	0
Epicatechin	290.2671	1.5461	5	6	0
Humulone	362.4589	4.2522	3	5	0
Co-humulone	348.4323	3.8621	3	5	0
Lupulone	414.5762	6.8638	2	4	0
Co-lupulone	400.5497	6.4737	2	4	0
Myrcene	136.2336	3.4750	0	0	0
β-Caryophyllene	204.3504	4.7252	0	0	0
Humulene	204.3504	5.0354	0	0	0
β-Pinene	136.2336	2.9987	0	0	0
Linalool	154.2490	2.6698	1	1	0
Limonene	136.2336	3.3089	0	0	0
α-Bisabolol	222.3658	4.2302	1	1	0
β-elemene	204.3504	4.7472	0	0	0

Table 2. ADME-Tox predictions of *H. lupulus* bioactive compounds

Compound	Absorption		Distribution		Toxicity		
	HIA (%)	Caco-2 (nm/sec)	PPB (%)	BBB	Mutagen	Carcinogen	
						Mouse	Rat
Xanthohumol	91.108521	18.8503	96.756150	3.01913	Mutagen	-	+
Desmethylxanthohumol	86.057589	17.7514	100.000000	2.45823	Non-mutagen	-	-
Isoxanthohumol	93.833075	21.3547	98.064277	1.67241	Mutagen	-	+
8-prenylnaringenin	90.291240	13.0333	100.000000	1.93444	Mutagen	-	-
Naringenin	87.318069	10.5211	100.000000	0.59697	Mutagen	-	+
Quercetin	63.485215	3.4129	93.236103	0.172765	Mutagen	-	+
Catechin	66.707957	0.656962	100.000000	0.394913	Mutagen	-	-
Epicatechin	66.707957	0.656962	100.000000	0.394913	Mutagen	-	-
Humulone	89.088805	9.16678	99.517456	2.56336	Mutagen	+	+
Co-humulone	88.506355	10.7375	100.000000	2.19948	Non-Mutagen	+	+
Lupulone	94.282978	24.3192	100.000000	7.41047	Mutagen	+	+
Co-lupulone	94.114209	23.2294	100.000000	7.05847	Non-Mutagen	+	+
Myrcene	100.000000	23.6306	100.000000	9.1018	Mutagen	_	+
β-Caryophyllene	100.000000	23.6315	100.000000	13.3193	Mutagen	_	+
Humulene	100.000000	23.1636	100.000000	14.2219	Non-Mutagen	+	+
β-Pinene	100.000000	23.4924	100.000000	5.75623	Mutagen	-	+
Linalool	100.000000	29.355	100.000000	6.12506	Mutagen	-	-
Limonene	100.000000	23.6317	100.000000	8.27823	Mutagen	-	+

Table 2. Continued

α-Bisabolol	100.000 000	51.1062	90.290776	10.5531	Non-Mutagen	-	-
β-elemene	100.000 000	23.4917	100.000000	13.4359	Mutagen	-	+

Pharmacophore Screening

Pharmacophore screening is a method based on pharmacophore principles that is used for virtual screening to differentiate between active and inactive compounds. The outcomes of pharmacophore screening aim to eliminate compounds with a low likelihood of being active (Vuorinen & Schuster, 2015). The ROC (Receiver Operating Characteristic) curve is employed to evaluate the model's effectiveness in distinguishing active compounds from inactive ones. The ER alpha Receptor Active Database (PDB code: 1SJ0) was obtained from *http://dude.docking.org*, and from this database, 100 active compounds and 400 decoy compounds were selected. The decoy database consists of inactive compounds that do not possess pharmacological activity (Lestari et al., 2023).

In the ROC curve (Fig 1), the x-axis represents the percentage of accepted decoys, where lower values indicate higher accuracy. The y-axis, based on CO2 sensitivity, measures the model's ability to identify active compounds, with higher values reflecting better accuracy (Djamaluddin et al., 2024). In addition to the ROC curve, the Area Under the Curve (AUC) value is also calculated during pharmacophore screening. A higher AUC signifies a greater ability of the model to effectively filter out decoys. A model is deemed capable of distinguishing between active and inactive compounds if the AUC value of the ROC exceeds 0.7 (Sangande & Uneputty, 2021).

Based on the database, 10 pharmacophore models were generated and validated by plotting ROC curves. From the 10 pharmacophore models, model 2 was used because it showed excellent performance in distinguishing active compounds from inactive compounds (decoy). This is shown by the AUC value 0.94 out of 1 which is close to the maximum value. This model can also detect 91 active compounds out of a total of 100 compounds, indicating that the model can recognize almost all available active compounds. The initial screening yielded 7 compounds (Table 3) that met the pharmacophore feature criteria and will be further screened using molecular docking methods

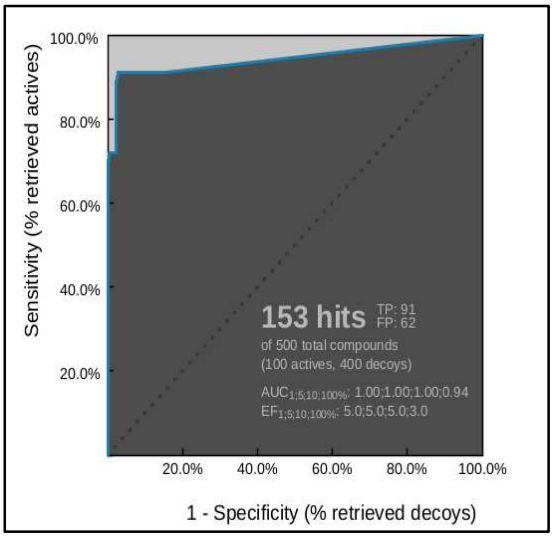


Figure 1. ROC curve model 2

Table 3. Visualization of hit compound chromophore

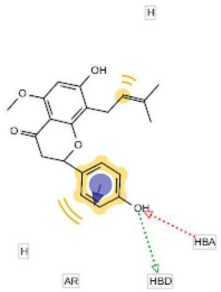
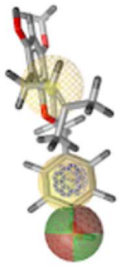
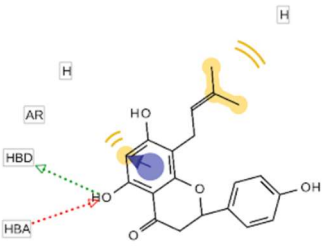
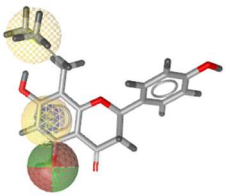
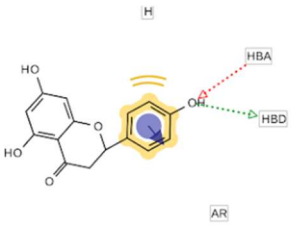
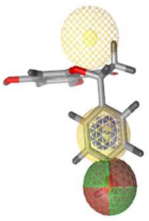
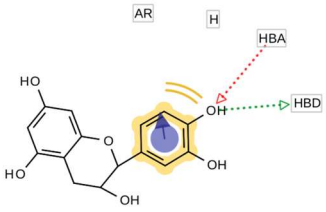
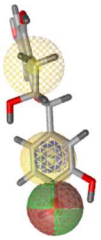
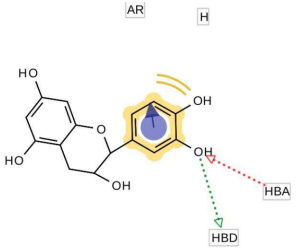
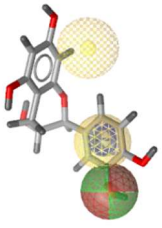
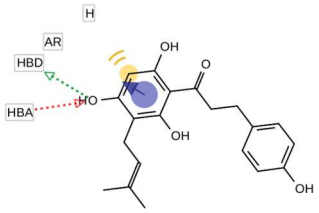
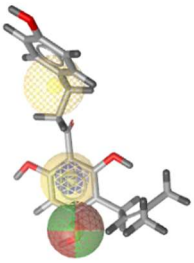
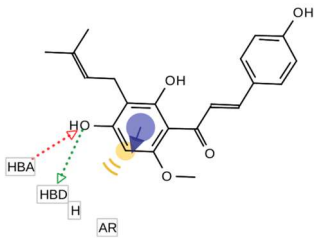
Compound	Pharmacophore Hit Score	2D Model	3D Model
Isoxanthohumol	54.47		
8-prenylnaringenin	53.76		
Naringenin	46.63		
Epicatechin	46.52		
Catechin	46.30		

Table 3. Continued

Desmethylxanthohumol	44.31		
Xanthohumol	44.25		

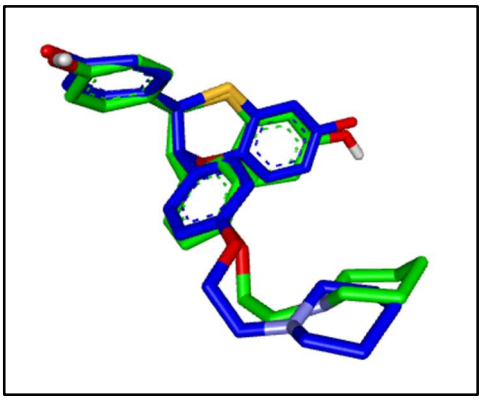


Figure 2. Overlay of native ligand (2S,3R)-2-(4-(2-(Piperidin-1-yl)ethoxy)phenyl)-2,3-dihydro-3-(4-hydroxyphenyl)benzo[b][1,4]oxathiin-6-ol before (blue) and after redocking (green).

Molecular Docking Simulation

Before conducting a molecular docking simulation, grid box validation is performed to confirm the precise location of the binding site within the target protein (Fig 2). The validity of the molecular docking parameters is assessed using the root mean square deviation (RMSD) metric. A docking method is deemed valid if the RMSD values are less than 2Å. The grid box employed measured 40 x 40 x 40Å, positioned at coordinates x (22.426), y (5.703), and z (21.988), with a spacing of 0.375Å to ensure the natural ligand is situated within the active pocket of estrogen alpha. The validation yielded an RMSD value of 0.86Å, indicating that the molecular docking method is valid as it meets the required threshold of less than 2Å. Among the hit compounds, Isoxanthohumol exhibited the strongest binding affinity to the receptor, as indicated by the lowest binding energy (-10.25 kcal/mol) and the smallest inhibition constant (0.03063 μM) (Table 4). However, binding affinity alone does not fully determine the similarity of a compound's activity to the natural ligand. If a compound exhibits low binding energy but does not interact with the same key residues as the natural ligand, its interaction pattern is considered suboptimal, and the compound cannot yet be regarded as having similar activity to the natural ligand (Amrulloh et al., 2023).

In this regard, the compounds that shared the most similar interaction profile with Estradiol and the native ligand were 8-

prenylnaringenin, Naringenin, and Desmethylxanthohumol (Table 5). These three compounds interacted with the key amino acid residues HIS A:524, GLU A:353, and ARG A:394 through hydrogen bonding (Mirza et al., 2021), which are also involved in the binding of estradiol and the native ligand. Among them, 8-prenylnaringenin demonstrated the highest receptor affinity, with a binding energy of -10.01 kcal/mol and an inhibition constant of 0.04634 μM. A lower binding energy suggests a stronger affinity between the compound and the receptor (Putri et al., 2024). Similarly, a lower Ki value signifies that a reduced concentration of the compound is necessary to inhibit the enzyme or receptor activity, indicative of a more pronounced interaction between the ligand and the receptor (Puspita et al., 2022).

Table 4. Molecular docking result of hit compounds

Compound	Binding Energy (kcal/mol)	Inhibition constant (μm)	Interaction with Amino Acid	
			Important Amino Acid Residues	Other Amino Acid Residues
Isoxanthohumol	-10.25	0.03063	HIS A:524	**Conventional Hydrogen Bond:** LEU A:384, LEU A:346 **van der Waals:** ARG A:394, MET A:388, LEU A:384, LEU A:349, THE A:347 **Carbon Hydrogen Bond:** GLU A:353 **Pi-Pi T-shaped:** PHE A:404 **Alkyl & Pi-Alkyl:** LEU A:387, ALA A:350, LEU A:391, LEU A:525, ILE A:424, MET A:343
8-prenylnaringenin	-10.01	0.04634	HIS A:524 GLU A:353 ARG A:394	**Conventional Hydrogen Bond:** LEU A:387, GLY A:521 **van der Waals:** LEU A:428, LEU A:384, THR A:347, LEU A:349 **Carbon Hydrogen Bond:** MET A:388 **Pi-Pi T-shaped:** PHE A:404 **Alkil & Pi-Alkyl:** ILE A:424, MET A:421, LEU A:525, MET A:343, LEU A:346, ALA A:350, LEU A:391

Table 4. Continued

Naringenin	-8.57	0.52643	HIS A:524 GLU A:353 ARG A:394	**Conventional Hydrogen Bond:** LEU A:387, GLY A:521 **van der Waals:** LEU A:428, MET A:343, LEU A:384, LEU A:346, PHE A:404, LEU A:349 **Pi-Sulfur:** MET A:421 **Pi-Alkyl:** ILE A:424, LEU A:525, ALA A:350, LEU A:391
Epicatechin	-7.91	1.60	HIS A:524 GLU A:353	**Conventional Hydrogen Bond:** GLY A:521 **van der Waals**: LEU A:349, ARG A:394, LEU A:428, MET A:522 **Pi-Pi T-shaped:** PHE A:404 **Alkyl & Pi-Alkyl:** ILE A:424, LEU A:384, LEU A:391, MET A:388, ALA A:350, LEU A:525
Catechin	-7.67	2.40	GLU A:353	**Conventional Hydrogen Bond:** THR A:347, ASP A:351 **van der Waals:** CYS A:530, MET A:343, LEU A:384, MET A:388, LEU A:391, ARG A:394, LEU A:346, TRP A:383, PHE A:404, LEU A:349 **Pi-Sigma:** ALA A:350 **Alkyl & Pi-Alkyl:** LEU A:525, LEU A:386
Desmethylxanthohumol	-9.45	0.11752	HIS A:524 GLU A:353 ARG A:394	**Conventional Hydrogen bond:** GLY A:521, LEU A:387 **van der Waals:** LEU A:408, ALA A:350, LEU A:384, MET A:343, MET A:388, LEU A:428, VAL A:392 **Pi-Sigma:** LEU A:387 **Pi-Sulfur:** MET A:421 **Alkyl & Pi-Alkyl:** LEU A:349, LEU A:346, PHE A:404, LEU A:391, LEU A:525, ILE A:424

Table 4. Continued

Xanthohumol	-8.33	0.77771	-	**Conventional Hydrogen bond:** LEU A:346, ASP A:351 **van der Waals:** MET A:388, LEU A:428, LEU A:391, GLU A:353, LEU A:387, ARG A:394 **Pi-Sigma:** THR A:347 **Pi-Pi T-shaped:** PHE A:404 **Alkyl & Pi-Alkyl:** LEU A:349, ALA A:350, CYS A:530, HIS A:524, MET A:343, LEU A:525, MET A:421

Table 5. Visualization of the interaction between the hit compounds and the receptor. The surrounding structures represent the interacting amino acid residues within the binding pocket.

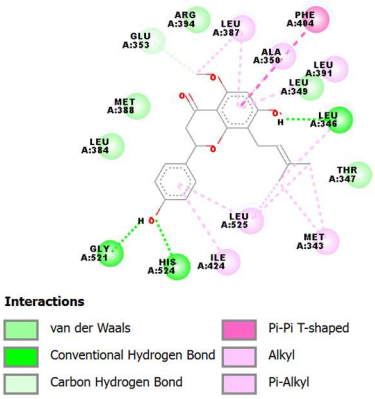
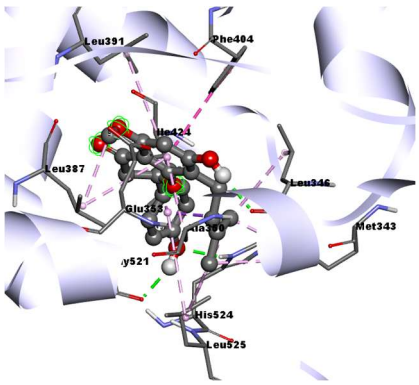
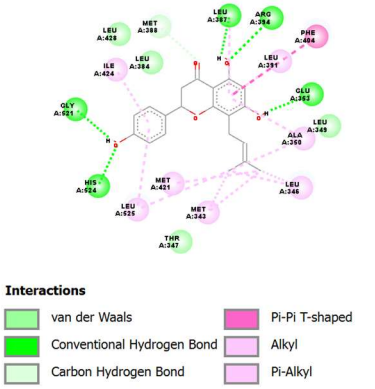
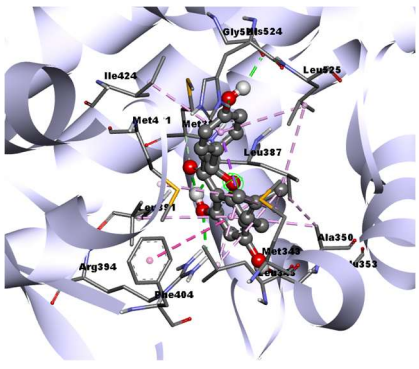
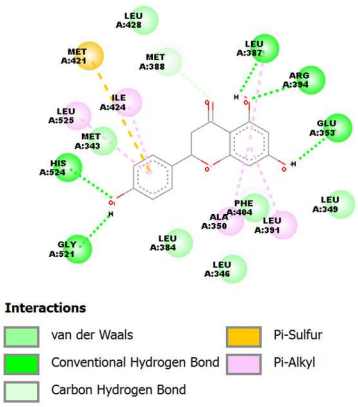
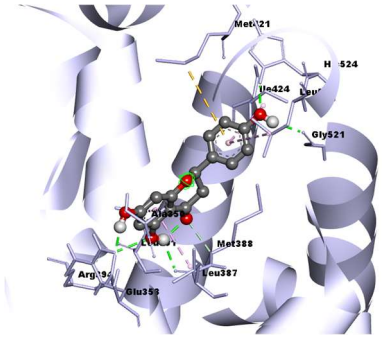
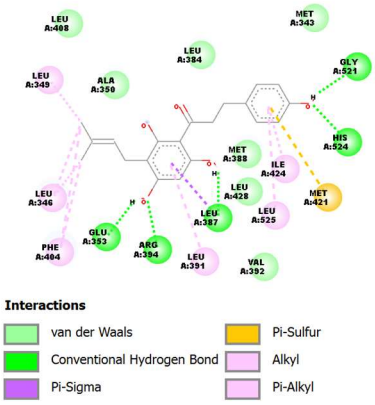
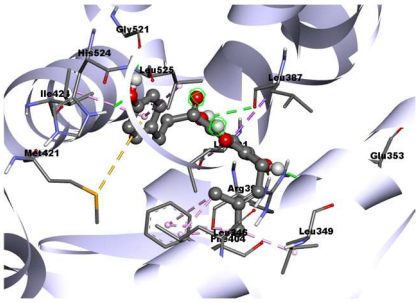
Compound	2D Visualization	3D Visualization
Isoxanthohumol		
8-prenylnaringenin		

Table 5. Continued

Naringenin		
Desmethylxanthohumol		

Based on a comprehensive analysis of binding affinity, interaction similarity with the native ligand, and ADME-Tox predictions, 8-prenylnaringenin emerges as a promising candidate. It demonstrates a strong binding affinity, closely mirroring the primary interactions of the native ligand and estradiol, and exhibits a favorable ADME-Tox profile, including the absence of predicted carcinogenicity. Furthermore, 8-prenylnaringenin has been thoroughly investigated for its estrogenic properties, enhancing its potential as a phytoestrogenic agent. The binding of estrogen to the ERα receptor can bolster insulin activity, promoting glucose uptake (Gupte et al., 2015).

In a previous in silico study, phytoconstituents of *Anastatica hierochuntica* L. (commonly known as "Rumput Fatimah") were evaluated for their estrogenic potential. isopimaric acid, one of the major compounds, was shown to bind to estrogen receptor alpha (ERα) with a binding affinity of –9.7 kcal/mol and interact with key amino acid residues such as His524 (Astutik et al., 2019). The strong binding affinity of hop-derived compounds to ERα observed in this study is consistent with previous experimental findings showing that 8-prenylnaringenin (8-PN), one of the main phytoestrogens in *Humulus lupulus* L., possesses the highest estrogenic activity among plant-derived compounds and exhibits strong affinity toward ERα. In both *in vitro* and *in vivo* models, 8-PN has been demonstrated to modulate estrogen receptor signaling, enhance insulin sensitivity, and improve lipid metabolism. These findings support the results of the present molecular docking analysis, suggesting that the interaction between hop-derived phytoestrogens and ERα may contribute to the restoration of insulin signaling and metabolic regulation under estrogen-deficient conditions (Pohjanvirta & Nasri, 2022).

Consequently, compounds like 8-prenylnaringenin, which can activate ERα, may help improve insulin sensitivity and mitigate metabolic disorders linked to estrogen deficiency. Desmethylxanthohumol also presents promising attributes, particularly regarding safety, as it is non-mutagenic and non-carcinogenic while maintaining

comparable interaction characteristics. Although isoxanthohumol exhibits the strongest binding affinity among the compounds tested, its lower similarity in interaction with the native ligand, along with potential mutagenic and carcinogenic effects, may limit its appeal. Naringenin shows good interaction similarity and moderate binding energy but is associated with less favorable ADME-Tox properties. It is essential to note that all findings are derived from computational predictions. Therefore, further *in vitro* and *in vivo* studies are warranted to validate the biological activity, efficacy, and safety profiles of these compounds before considering them as potential therapeutic agents.

Conclusion

The utilization of cabbage waste and fish meal for local catfish (*Clarias batrachus*) farming in Way Dadi Urban Village, Bandar Lampung City, has a significant impact on research parameters such as length growth, weight gain, and feed conversion ratio (FCR). The most effective treatment in enhancing catfish growth was obtained with a feed protein content of 32.14%, corresponding to Treatment 3 with a 12% feeding dosage, which resulted in an average length growth of 14.22 cm, weight gain of 20.59 g, and an FCR value of 1.73. These findings indicate a statistically significant improvement compared to other treatments. Future research development can focus on using cabbage waste and fish meal for the farming of other fish species such as tilapia, pangasius, gourami, and others. Additionally, the use of environmentally friendly alternative protein sources should be considered, such as maggots, salted fish waste, meat meal, and other similar materials.

References

Anis, M. Y., Hariani, D., Biologi, J., Matematika, F., Ilmu, D., Alam, P., & Surabaya, U. N. (2019). Pemberian pakan komersial dengan penambahan EM4 (effective microorganisme 4) untuk meningkatkan laju pertumbuhan lele (*Clarias* sp.). *Jurnal Riset Biologi Dan Aplikasinya* 1(1): 1–8. https://journal.unesa.ac.id/index.php/risetbiologi.

Bouk, G., Dewi, Y. L., Dapawole, R. R., Kamlasi, Y., & Bere, E. K. (2022). Fermentasi dedak padi dan ampas tahu sebagai pakan alternatif ternak. *Jurnal Pengabdian Masyarakat* 5(1): 5.

Iswandiary, M. B. P., Khikmiyah, F., Rahim, A. R., Fauziyah, N., & Sukaris, S. (2021). Pemanfaatan limbah rumah tangga (usus ikan) dikelurahan lumpur sebagai pakan ikan (pelet ikan). *DedikasiMU (Journal of Community Service)* 3(2): 869–876. http://journal.umg.ac.id/index.php/dedikasimu/article/view/2674.

Khalil, M., Salamah, S., & Azdami, C. (2022). The effect of addition of fish oil in commercial feed on growth of carp (*Cyprinus carpio*). *Acta Aquatica: Aquatic Sciences Journal* 9(3): 178. https://doi.org/10.29103/aa.v9i3.7037.

Listiana, I., Ayuni, T., Saputri, A.D., Amelia, I. (2024). *Pemanfaatan eco-enzyme pada tanaman kangkung darat (Ipomoea reptans poir.) dengan sistem hidroponik desain wick (sumbu)* (Bachelor's thesis). UIN Raden Intan Lampung.

Manik, R. R. D. S., & Arleston, J. (2021). Nutrisi Dan Pakan Ikan. In *Widina Bhakti Persada Bandung (Group CV. Widina Media Utama)*. Widana Bhakti Persada Bandung: Bandung.

Manik, R. R. D. S., Handoco, E., Tambunan, L. O., Tambunan, J., & Sitompul, S. (2022). Socialization of catfish (*Clarias* sp.) using semi-artificial spawning in Aras Village, Batu Bara Regency. *Mattawang: Jurnal Pengabdian Masyarakat* 3(1): 47–51. https://doi.org/10.35877/454ri.mattawang822.

Masriah, A., & Alpiani. (2019). Pertumbuhan dan sintasan ikan bandeng (*Chanos chanos forsskal*) yang diberi pakan dengan dua jenis sumber bahan baku karbohidrat pakan yang terhidrolisis limbah cairan rumen sapi. *Gorontalo Fisheries Journal* 2(2): 78–87.

Muntafiah, I. (2020). Analisis pakan pada budidaya ikan lele (*Clarias* sp.) di Mranggen. *JRST (Jurnal Riset Sains Dan Teknologi)* 4(1): 35. https://doi.org/10.30595/jrst.v4i1.6129.

Nugraha, eulis hendra. (2020). Pengaruh pakan buatan terhadap pertumbuhan benih clarias gariepinus dikelompok budidaya ikan Manunggal Jaya. *Jurnal Pendidikan Fisika dan Sains (JPFS)* 5(1): 2022–2045.

Nurilmala M, Safithri M, Pradita FT, & Pertiwi RM. (2020). Profil protein ikan gabus (*Channa*

striata), Toman (*Channa micropeltes*) dan betutu (*Oxyeleotris marmorata*). *Jphpi* 23(3): 548–557.

Pradhana, S., Fitriyah, H., & Ichsan, M. H. H. (2021). Sistem kendali kualitas air kolam ikan nila dengan metode jaringan syaraf tiruan berdasarkan pH dan turbidity berbasis arduino uno. *Jurnal Pengembangan Teknologi Informasi Dan Ilmu Komputer* 5(10): 4197–4204.

Praptiwi, I. I., & Wahida, W. (2021). Kualitas tepung ikan di pesisir pantai Kabupaten Merauke sebagai bahan pakan. *Jurnal Ilmu Peternakan Dan Veteriner Tropis (Journal of Tropical Animal and Veterinary Science)* 11(2): 156. https://doi.org/10.46549/jipvet.v11i2.146.

Puteri, B. J., Subandiyono, ., & Hastuti, S. (2020). Peran kromium (Cr) dalam pakan buatan terhadap tingkat efesiensi pemanfaatan pakan dan pertumbuhan lele (*Clarias* sp.). *Sains Akuakultur Tropis* 4(2): 161–170. https://doi.org/10.14710/sat.v4i2.6053.

Rahayu, D. R. U. S., Piranti, A. S., & Sihwaningrum, I. (2019). Diversifikasi hasil olahan ikan lele di desa Kaliwangi Kecamatan Purwojati Kabupaten Banyumas. *Dinamika Journal : Pengabdian Masyarakat* 1(1). https://doi.org/10.20884/1.dj.2019.1.1.602.

Rusad, R. E., Santosa, S., & Hasyim, Z. (2016). Pemanfaatan limbah sayur kubis (*Brassica oleracea*) dan buah pepaya (*Carica papaya*) sebagai pakan cacing tanah *Lumbricus rubellus*. *Jurnal Biologi Makassar* 1(1): 8–15. https://journal.unhas.ac.id/index.php/bioma/article/view/990.

Sajid, M., Naseer, Muhammad Nihal, & Benjakul, S. (2024). *Fish waste to valuable products*. Springer: Singapore.

Santika, L., Diniarti, N., & Lestari, D. P. (2021). Pengaruh penambahan ekstrak kunyit pada pakan buatan terhadap pertumbuhan dan efisiensi pemanfaatan pakan ikan kakap putih (*Lates calcarifer*). *Jurnal Kelautan: Indonesian Journal of Marine Science and Technology* 14(1): 48–57. https://doi.org/10.21107/jk.v14i1.8988.

Sonavel, N. ., Sapto, & Diantari, R. (2020). Pengaruh tingkat pemberian pakan buatan terhadap performa ikan jelawat (*Leptobarbus hoeveni*). *Jurnal Sains Teknologi Akuakultur* 3(1): 52–65.

Suek, H. (2023). *Analisis Usaha Ternak Babi Peranakan Landrace Fase Starter Yang Diberi Tepung Limbah Kubis (Brassica oleraceae) Terfermentasi Dalam Ransum* (Bachelor's thesis). Undana Kupang.

Sugara, A., . A., & Ryanto, I. (2020). Pengaruh penggunaan limbah kubis dalam silase ransum komplit berbasis limbah tebu terhadap kecernaan bahan kering, bahan organik dan VFA secara in-vitro. *Jurnal Ilmu Ternak Universitas Padjadjaran* 20(1): 10. https://doi.org/10.24198/jit.v20i1.27531.

Wulandari, F. A., & Astuti, S. (2022). Pengolahan limbah kubis menjadi tepung kubis dengan variasi blansing dan suhu pengeringan. *Prosiding SENIATI* 6(2): 267–272. https://doi.org/10.36040/seniati.v6i2.5030.