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# Catechin from Avocado Seed (*Persea Americana* Mill.) Potentially Targets Estrogen Receptor-Alpha: Computational-Based Analysis

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**Abstract**

**Avocado seeds (P*ersea americana* Mill.) are known to possess various pharmacological properties, including notable anticancer potential. While preliminary studies have reported the cytotoxic effects of avocado seed extracts on breast cancer cells, there is still a lack of comprehensive research exploring the underlying molecular mechanisms responsible for these effects. This study explores bioactive compounds found in avocado seeds as potential agents targeting estrogen receptor alpha (ERα), a key biomarker in breast and cervical cancers. The investigation employs a range of computational approaches, including the Lipinski Rule of Five, ADME/Tox predictions, pharmacophore screening, and molecular docking analysis. Of the ten tested compounds, seven passed the Lipinski Rule of Five. ADME/Tox analysis revealed that most compounds exhibited adequate human intestinal absorption (HIA), poor blood-brain barrier (BBB) penetration, moderate Caco-2 permeability, and good plasma protein binding (PPB), while some were predicted to be mutagenic or carcinogenic. Pharmacophore modeling yielded an AUC of 0.87, with procyanidin B scoring 45.09 as a hit compound. Molecular docking revealed catechin, hiosiamin, and atropine had the lowest Gibbs free energy (-5.15, -0.10, -0.07 kcal/mol). Among the compounds, catechin in avocado seed shows the highest potential for development as an ER-targeted anticancer agent.**

**Keywords: Anticancer, avocado seed, estrogen receptor-alpha, molecular docking, pharmacophore modelling**

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## Introduction

Cancer has become one of the most significant public health problems, requiring a comprehensive approach to its management. Recent data shows that by 2022, the incidence of breast cancer and cervical cancer will be among the top 3 cancer cases in Indonesia, covering all levels of society, regardless of gender (IARC, 2024). Estrogen receptor alpha (ERα) is frequently overexpressed in hormone-dependent breast cancer and plays a central role in promoting tumor growth and progression through estrogen signaling pathways (Furth et al., 2023). In addition to breast cancer, ERα expression has also been observed in cervical cancer, where it contributes to estrogen-mediated carcinogenesis (Chung et al., 2010). Therapeutic management of breast and cervical cancer includes surgical procedures, radiation therapy, and chemotherapy. Although chemotherapy is one of the most frequently used systemic approaches, its use is often associated with adverse side effects for patients. In addition, the choice of available



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chemotherapeutic agents is limited (Dange et al., 2017). The physical side effects of chemotherapy include symptoms of nausea and vomiting, constipation, changes in sensory perception of taste, unwanted weight loss, skin toxicity, hair loss (alopecia), decreased appetite, pain sensation, and peripheral neuropathy that can affect peripheral nerve function (Wardani, 2022). Therefore, efforts are needed to develop alternative therapies, including both synthetic drugs and herbal medicines, that are more effective and have a better safety profile, while still considering the quality of life aspects of patients.

The use of traditional plants as medicine is increasingly favored by the public today. This phenomenon is driven by various advantages of phytotherapy, such as high accessibility, affordable costs, and public perception of a more favorable safety profile compared to synthetic drug compounds (Suryati et al., 2016). One of the natural ingredients with potential to be developed as an anticancer drug is the avocado seed (*Persea americana* Mill.). Avocado seeds generally contain secondary metabolite compounds, including alkaloids, flavonoids, saponins, tannins, triterpenoids, and steroids (Kopon et al., 2020). Studies conducted by Bangar et al. (2022) revealed that avocado seeds contain many active compounds, such as epicatechin, catechin, atropine, hiosiamin, norhiosiamin, scopolamine, trans-5-O-caffeoyl-D-quinic acid, procyanidin A1, procyanidin A2, and procyanidin B2. Procyanidin compounds exhibit anticancer effects through several pathways, including inhibition of pro-inflammatory cytokines, suppression of PI3K/AKT/mTOR and MAPK/ERK pathways, and regulation of apoptosis-related proteins such as BAX, BCL-2, and caspases (Ademiluyi et al., 2025). Additionally, catechin compounds exhibit anticancer effects against breast, liver, prostate, and lung cancers (Tsouh Fokou et al., 2025) (Fokou et al., 2025). Avocado seed extracts have been examined for various bioactivities, including antihyperglycemic, anticancer, anti-inflammatory, anti-hypercholesterolemic, antioxidant, antimicrobial, and anti-neurodegenerative properties. Previous studies have reported that methanol extract of avocado seeds induces apoptosis and exhibits strong cytotoxic activity, with $IC_{50}$ values of 13.3 µg/mL and 3 µg/mL, respectively (Alkhalaf et al., 2019; Astuti et al., 2017). In line with these findings, our recent study demonstrated that both the extract and the n-hexane fraction of avocado seeds possess cytotoxic effects against MCF7 breast cancer cells, with the n-hexane fraction showing significantly greater potency and selectivity ($IC_{50}$= $47.87 \pm 1.5$ µg/mL; Selectivity Index = 4.73). This fraction also extended the cell doubling time and induced apoptosis, as evidenced by fluorescence staining (Rahwawati et al., 2022). Despite these promising cytotoxic effects, the specific molecular mechanisms of action remain unclear. Therefore, the current research aims to identify potential bioactive compounds from avocado seeds that may target ERα, using computational predictive methods. The findings are expected to contribute scientific evidence supporting the potential of avocado seed-derived compounds in the development of natural-based therapies for ERα-overexpressing cancer cells.

# Methods

### Physicochemical Properties Prediction

Lipinski's rule of five predictions determines a compound's physicochemical properties and permeability for passive diffusion (Lipinski, 2004). The test compound must fulfill Lipinski's five rules to be used. The molecular structure of the test compound was downloaded from the PubChem page: https://pubchem.ncbi.nlm.nih.gov/search/search.cgi. The test compound is then predicted online physicochemical properties on the mcule page (https://mcule.com/apps/property-calculator/) by uploading a 3-dimensional structure file saved in .mol format. The next stage is to analyze the results and determine which test compounds fall into the Lipinski rules of five: molecular weight, log P value, hydrogen bond donor, and hydrogen bond acceptor.

### Pharmacokinetic and Toxicity Prediction

ADME/Tox prediction includes absorption, distribution, metabolism, excretion, and toxicity profiles that can be done by drawing the structure of the compound that you want to predict its pharmacokinetic profile and calculating it on the website https://preadmet.webservice.bmdrc.org/., then

selecting the Drug-likeness prediction feature to predict drug-likeness properties. Viewed drug-likeness results are then downloaded to save the prediction results. In predicting ADME/Tox, the parameters observed were the values of human intestinal absorption (HIA), human colon adenocarcinoma (CaCo-2), plasma protein binding (PPB), blood-brain barrier (BBB), and the presence or absence of potentially mutagenic and carcinogenic properties that can be the toxicity of the compound.

**Pharmacophore Screening**

Pharmacophore screening was carried out on 10 test compounds selected based on the content of the most chemical compounds that had pharmacological activity in avocado seeds, including epicatechin, catechin, atropine, hiosiamin, norhiosiamin, scopolamine, trans-5-O-caffeoyl-D-quinic acid, procyanidin A1, procyanidin A2, and procyanidin B2 using the previously prepared pdb format. This process began with preparing a database downloaded from the page http://dude.docking.org, specifically estrogen alpha protein with PDB code 1SJ0 in SDF.gz format, which was then converted into LDB format. The next stage involved preparing the database for the test compounds, which entailed converting the format of 10 test compounds into a lab-friendly format. Next, pharmacophore models were created using the database of active compounds simplified into groups (clusters). The result of this process produced 10 different pharmacophore models. In pharmacophore modeling, compounds are grouped (clustered) based on pharmacophore features such as hydrogen donors and acceptors, hydrophobic points, and aromatic rings. Clustering also considers structural similarity, biological activity, binding energy, and feature distribution in three-dimensional space. The best model was determined from the 10 pharmacophore models based on the ROC curve plot. After obtaining the best model, pharmacophore screening of the test compound database was conducted using the best pharmacophore model and the decoy database. This process lasted until completion, resulting in the identification of suitable compounds (hits).

**Molecular Docking**

The target protein estrogen receptor-alpha (ESR1) with PDB ID: 3ERT was downloaded from the Protein Data Bank website (https://www.rcsb.org/). With AutoDockTools software, the receptor separated from its natural ligand is repaired by adding a polar hydrogen atom and giving a Kollman charge. Then, the compound is combined and given a Gasteiger charge on the ligand to become non-polar, which then inputs torque.

The validation stage was carried out by utilizing AutoDock, which involved placing the native ligand back into the receptor. The grid box size and position were set correctly so that when the running process gets a value of 10. If the RMSD value was less than 2 Å, the bond energy was negative, or the value was getting smaller, the validation results can be acceptable. The configuration used was as follows: grid box (x = 40; y = 40; z = 40) and grid coordinate (x = 30.282; y = -1.913; z = 24.207) with a distance of 0.375 Å. The next step is to perform molecular docking between the test ligand and the receptor or target protein (ESR-PDB ID: 3ERT). The procedure used in this stage is similar to the previous validation stage. The results of the molecular docking will be analyzed using AutoDock. The analysis results will be visualized through the BIOVIA Discovery Studio Visualizer®. Through this application, 2D and 3D images can be generated showing the position of the test ligand successfully docked to the receptor.

## Results and Discussion

This research was conducted based on the active substance content of avocado seeds, which was a candidate compound for breast and cervical anticancer drugs. In a study, it was stated that avocado seeds could reduce the survival of human breast (MCF-7), lung (H1299), colon (HT-29), and prostate (LNCaP) cancer cell lines. Half maximal inhibitory concentrations ($IC_{50}$) ranged from 19 to 132 μg/mL after treatment for 48 hours. Avocado seeds also downregulated the expression of cyclin D1 and E2 in LNCaP cells, which was associated with G0/G1 cell phase cycle arrest (Dabas et al., 2019). Another study reported that lipid extracts from avocado seeds were cytotoxic to Caco-2

cells. The extract had an $IC_{50}$ of 28 µg/mL and induced apoptosis by activating caspases 8 and 9. In another study, chloroform extract of dried avocado seed powder showed potent cytotoxic activity against the MCF-7 cell line, with an $IC_{50}$ value of 94.87 µg/mL (Zhao et al., 2022). There are several compounds responsible for the anticancer activity in avocado seeds, one of which is catechins. Currently, available research suggests that catechins have several health benefits. The benefits include anticancer, anti-inflammatory, antimicrobial, antiviral, antidiabetic, and cardiovascular (Bhuyan et al., 2019). The mechanisms underlying the anticarcinogenic effects of catechins involve inhibiting cancer cell proliferation and growth, counteracting free radicals, suppressing cancer cell metastasis, enhancing immunity, interacting with other anticancer drugs, and regulating signaling pathways (Li et al., 2022).

**Table 1.** Prediction of physicochemical properties based on Lipinski's rule

| Compound | Molecular Weight (<500 Da) | Log P (<5) | Hydrogen Bonds | | F/NF |
|---|---|---|---|---|---|
| | | | Donor (<5) | Acceptor (<10) | |
| *Epicatechin* | 290.2671 Da | 1.5461 | 5 | 6 | F |
| *Catechin* | 290.2671 Da | 1.5641 | 5 | 6 | F |
| *Prosianidin A1* | 576.5022 Da | 2.7935 | 9 | 12 | NF |
| *Prosianidin A2* | 576.5022 Da | 2.7935 | 9 | 12 | NF |
| *Prosianidin B1* | 578.5182 Da | 2.9950 | 10 | 15 | NF |
| *Atropine* | 289.3687 Da | 1.8688 | 1 | 5 | F |
| *Hiosiamine* | 289.3687 Da | 1.8688 | 1 | 4 | F |
| *Skopolamine* | 303.3521 Da | 0,8560 | 1 | 5 | F |
| *Trans-5-O-caffeoyl-D-quinate* | 370.3503 Da | -0.1523 | 6 | 9 | F |
| *Norhiosiamine* | 275.3421 Da | 1.9175 | 2 | 4 | F |

Note :
F: Fulfilled
NF: Not Fulfilled

**Table 2.** Prediction of Pharmacokinetic and Toxicity Properties

| Compound | Absorption | | Distribution | | Toxicity | |
|---|---|---|---|---|---|---|
| | HIA(%) | Caco-2 (nm/sec) | PPB(%) | BBB | Mutagen | Carcinogen |
| *Epicatechin* | 66.707957 | 0.656962 | 100.0000 | 0.394913 | + | Rat (-) Mouse (-) |
| *Catechin* | 66.707957 | 0.656962 | 100.0000 | 0.394913 | + | Rat (-) Mouse (-) |
| *Prosianidin A1* | 35.297711 | 9.23937 | 100.0000 | 0.0732707 | - | Rat (+) Mouse (-) |
| *Prosianidin A2* | 35.293711 | 9.23937 | 100.0000 | 0.0732707 | - | Rat (+) Mouse (-) |
| *Prosianidin B1* | 19.510403 | 13.6793 | 100.0000 | 0.0649419 | - | Rat (+) Mouse (-) |
| *Atropine* | 95.403877 | 28.2833 | 35.26454 | 0.0508703 | - | Rat (-) Mouse (+) |
| *Hiosiamine* | 95.403877 | 28.2833 | 35.26454 | 0.0508703 | - | Rat (-) Mouse (+) |
| *Scopolamine* | 95.828527 | 25.7179 | 24.86095 | 0.0207253 | + | Rat (-) Mouse (+) |
| *Trans-5-O-caffeoyl-D-quinate* | 20.427827 | 18.7168 | 41.96179 | 0.033661 | + | Rat (-) Mouse (-) |
| *Norhiosiamine* | 92.295567 | 21.8504 | 27.24940 | 0,120626 | + | Rat (-) Mouse (+) |

This research began with predicting chemical properties based on the Lipinski Rule of Five. Lipinski's Prediction is a set of rules that enable the prediction of physicochemical properties in compounds, which in turn affect their success in distributing in the circulatory system (Miebs et al., 2024). Lipinski's rule states that a compound has characteristics similar to drugs if the molecular weight (BM) of the compound is less than 500 Daltons, the log P partition coefficient is less than 5, the number of hydrogen bond donors (HBD) is less than 5, and the number of hydrogen bond acceptors (HBA) is less than 10 (Lipinski, 2004). Based on the prior report, eleven bioactive components were identified in the samples tested. From the results of data analysis in Table 1, it can be seen that the 7 compounds selected as ligands from avocado seeds (*Persea americana* Mill.), namely epicathecin, catechin, atropin, hiosiamin, scopolamine, trans-5-O-caffeoyl-D-quinic acid, and norhiosiamin, have met the established Lipinski rule. This finding indicated that the compounds can penetrate the membrane by passive diffusion and be formed into oral preparations. It is known that the Lipinski rule shows the solubility of certain compounds in penetrating the membrane by passive diffusion (Pollastri, 2010). Test compounds are said to meet the requirements to be formed into oral preparations if there is no more than one violation of the Lipinski rule (Ahmad et al., 2023; Lipinski, 2004).

In drug discovery and development, adsorption, distribution, metabolism, excretion (ADME) properties, and drug toxicity are essential factors that must be evaluated. In this study, ADME and toxicity parameters were examined, including human intestinal absorption (HIA), Caco-2 cellular permeability, plasma protein binding (PPB), blood-brain barrier (BBB), mutagenicity test, and carcinogenicity test. Based on Table 2, the pharmacokinetic properties such as absorption (HIA, Caco-2 permeability), distribution (PPB, BBB), and carcinogen of eleven tested compounds were obtained.

Human intestinal absorption (HIA) and Caco-2 cell permeability are parameters used to predict absorption rates. The HIA classification is divided into three categories: 0% to 20% indicate poor absorption, 20% to 70% indicate sufficient absorption, and 70% to 100% indicate good absorption capacity. The compounds atropine, hyoscyamine, scopolamine, and norhyoscyamine were classified in a good HIA category. On the other hand, the compounds epicatechin, catechin, procyanidin A1, procyanidin A2, and trans-5-O-caffeoyl-D-quinic acid had fair HIA values, while procyanidin B1 had poor HIA feature. On the other hand, Caco-2 is used to predict the permeability of Caco-2 cells derived from human colon adenocarcinoma, and there are multiple routes for drug transport across the intestinal epithelium. Caco-2 values are interpreted according to the criteria: values less than 4 indicate low permeability, 4 to 70 indicate moderate permeability and values greater than 70 indicate high permeability (Abdullah et al., 2021; Karim et al., 2023). The compounds that have moderate permeability are procyanidin A1, procyanidin A1, procyanidin B1, atropine, hyoscyamine, scopolamine, trans-5-O-caffeoyl-D-quinic acid, and norhyoscyamine. Protein Plasma Binding (PPB) is the reversible bonding of a compound with proteins in the blood (Testa et al., 2006). Protein Plasma Binding indicates that the drug molecule binds strongly to plasma proteins. PPB value less than 90% can be interpreted that the drug molecule binds weakly to plasma proteins and vice versa (Hasan dan Herowati, 2024). The compounds epicatechin, catechin, procyanidin A1, procyanidin A2, and procyanidin B1 had good PPB values. The BBB is a protective membrane that prevents the central nervous system from being entered by toxins and pathogens in the blood. Of the eleven compounds tested, no compound had a good BBB value. The eleven compounds had BBB values <2, indicating poor BBB values and can penetrate the blood-brain barrier, which can harm the body (Wu et al., 2023). Meanwhile compounds that are mutagenic or can cause mutations in DNA or cells are epicatechin, catechin, scopolamine, and trans-5-O-caffeoyl-D-quinic acid, and norhyosciamine, also carcinogenic properties that can cause or promote cancer were obtained from compounds of epicatechin gallate, procyanidin A1, procyanidin A2, procyanidin B1, atropine, hyoscyamine, scopolamine, and norhyoscyamine when tested on mice and rats.

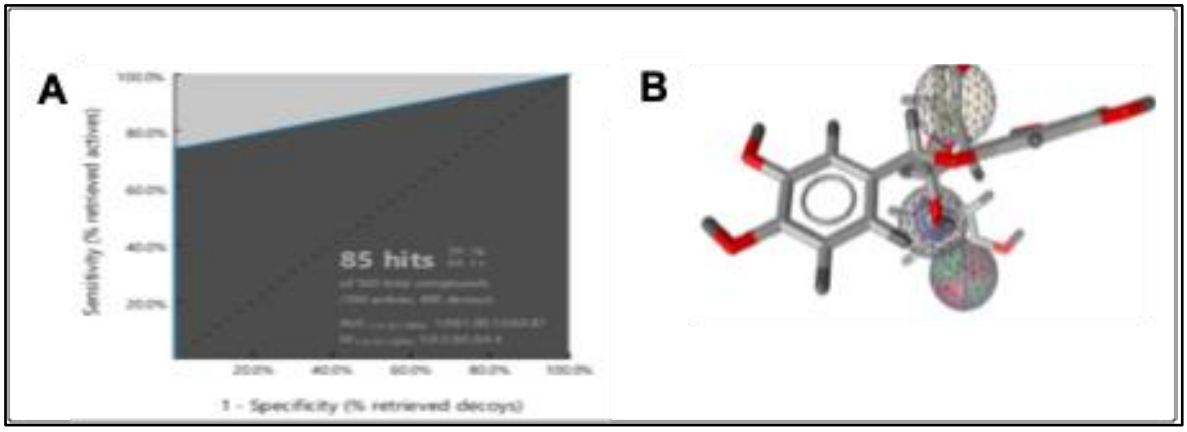



**Figure 1.** A) ROC Validation Curve; B) Pharmacophore Screening Results of Prosianidin B1 Compounds.

Furthermore, in this study, pharmacophore modeling or screening was also performed. Pharmacophore screening has the same function of maintaining the same spatial arrangement, leading to biological activity carried out on the same target, namely estrogen alpha receptor (ER-α). A good AUC-ROC value for a pharmacophore model was more significant than 0.5, and a GH value of more than 0.7. Pharmacophore modeling in LigandScout can be performed without knowing the structural data of the protein-ligand complex or with poor quality. AUC values range from 0 to 1. A pharmacophore model is improving and can distinguish between active and decoys (or inactivecompounds) if the AUC-ROC value obtained is close to 1. Data analysis was carried out on 10 test compounds, namely epicatechin, catechin, procyanidin A1, procyanidin A2, procyanidin B1, scopolamine, trans-5-O-caffeoyl-D-quinic acid, hiosiamin, norhiosiamin, and atropine and then observed the pharmacophore fit score. The AUC value that met the requirements was above 0.70. Thus, model 1, with a value of 0.87, was chosen as the best model to be continued in screening test compounds. In screening test compounds, only one hit compound was obtained, the procyanidin B1, with a pharmacophore fit score of 45.09. If the pharmacophore fit score is > 50%, then the feature has good activeness, while the feature is poor if the pharmacophore fit score is 30-50%. The pharmacophore fit score is related to the level of activeness of a feature to the receptor (Muchtaridi et al., 2017). That means the procyanidine B1 compound obtained from screening test compounds is less active against its receptor.

After obtaining a hit compound in pharmacophore screening, molecular docking is then performed. Molecular docking is a computational method used to describe the interaction between a molecule, such as a ligand, and a receptor or protein. Conformation is stable if the amount of Gibbs free energy is small, whereas if the Gibbs energy value obtained is considerable, the complex formed is less stable. The affinity of the ligand-protein complex will be better with the more negative Gibbs energy value obtained, so the activity is expected to be better. The ability to inhibit the performance or interaction of the enzyme with the substrate is indicated by the value of the inhibition constant or Ki, with a smaller Ki value, the possibility of active side interaction on the ligand with the receptor is maximized, and the bond formed is strong (Dewi and Ginarsih, 2021).

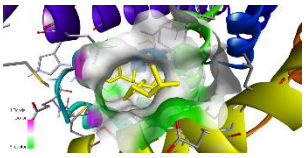
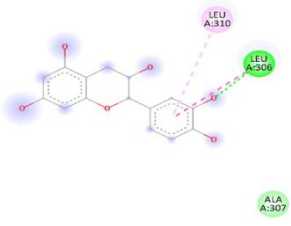
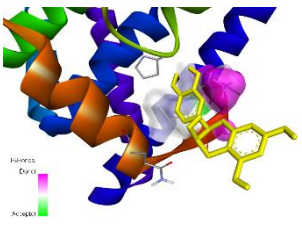
Based on the results obtained in Table 3, it was concluded that the catechin compound has the best interaction because it has the smallest binding energy value among other compounds. The decrease in the binding affinity value indicated the ease with which the biological activity interacts with the target protein binding site compared to the comparator ligand. Active compounds are expected to interact with the target receptor if they have the same or lower binding affinity value as the comparator compound (Naufa et al., 2021).

Table 3 shows that the hit compound obtained from the pharmacophore screening stage, namely procyanidin B1, had a high enough binding energy value of +2.50, so it cannot be used as a candidate compound. This is because procyanidin B1 is less likely to bind to the target receptor compared to catechins,

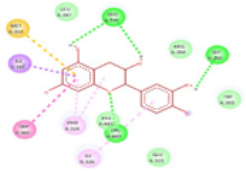
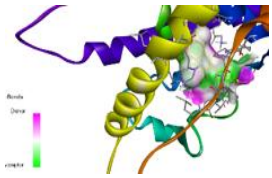
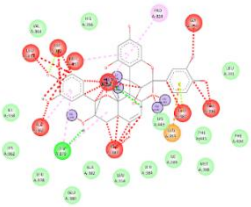
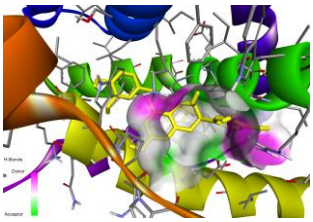
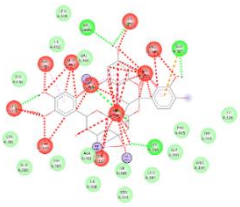
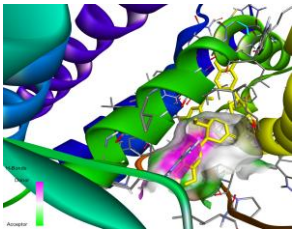
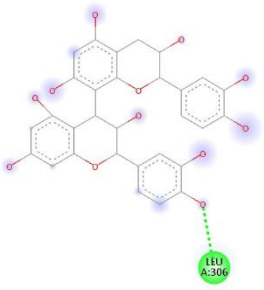
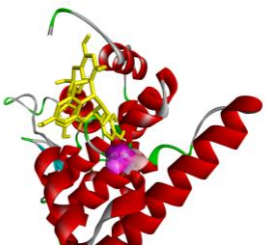
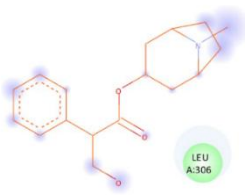
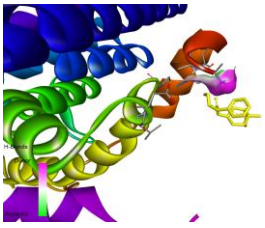
which are more easily bound due to their lower binding energy value. The molecular docking results are then visualized to determine the interactions and bonding modes of each compound (Table 3). Interactions between receptors and ligands can occur through hydrogen bonds, van der Waals bonds, and other types of bonds, such as alkyl and pi-alkyl bonds. Hydrogen and van der Waals bonds are crucial in the interaction between receptors and ligands (Ratu et al., 2021). The compounds with the smallest binding energy values, namely catechins, hiosiamines, and atropine, had more hydrogen and van der Waals bonds than the hit compound procyanidine B1 in the pharmacophore screening. In 2D visualization, catechin had 3 hydrogen bonds and 4 van der Waals bonds, hiosiamin had 1 hydrogen bond and 2 van der Waals bonds, and atropine had 1 van der Waals bond. When compared, procyanidine B1 only has one hydrogen bond, making it not bond strongly enough to the receptor. Interestingly, only catechin showed similar binding to the amino acid residue compared to the native ligand, specifically at ARG394 and LEU387, making it possible to bind partly to a similar pocket in ER-α with a high docking score. Based on these findings, it demonstrated a quite different phenomenon from the pharmacophore screening and the molecular docking, as procyanidine B1 was found as the hit compound, but after evaluating the molecular docking analysis, the interaction required higher energy to bind to the receptor. Still, our results demonstrate the potential of avocado seeds to be further explored for their anticancer activities, particularly in relation to those that overexpress ER-α.

In conclusion, the activity produced by avocado seeds is a combination of the effects of each bioactive compound so that every selected compound is still included in each test. In addition, the compounds used are also obtained from natural materials that are more complex than synthetic compounds, so the results may not always qualify for each test. Thus, testing for all compounds is still needed as a basis for the development of each compound that will be used for the database in future research.

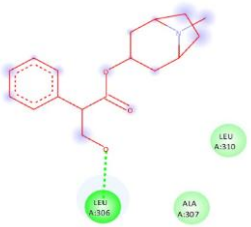
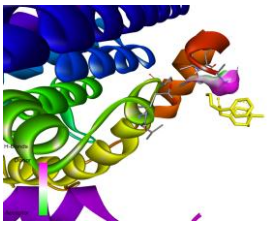
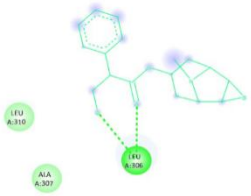
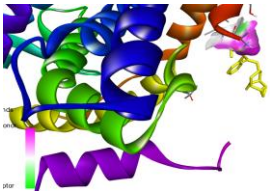
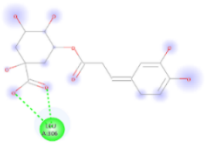
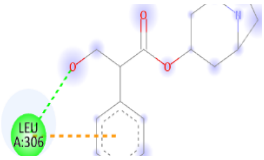
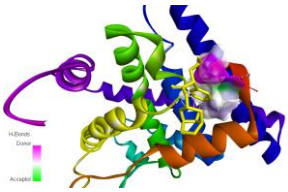
**Table 3.** Molecular Docking and Visualization Output

| Compound | Binding Energy (kkal/mol) | Inhibition Constant (µM) | 2D Visualization | 3D Visualization |
|---|---|---|---|---|
| *Native Ligand* | - | - |  |  |
| *Epicatechin* | +0.21 | - |   |  |

Lanjutan Tabel 3.

| Compound | Binding Energy (kkal/mol) | Inhibition Constant (µM) | 2D Visualization | 3D Visualization |
|---|---|---|---|---|
| *Catechin* | -5.15 | 168.53 |  |  |
| *Prosianidin A1* | +314.45 | - |  |  |
| *Procyanidin A2* | +247.79 | - |  |  |
| *Procyanidin B1* | +2.32 | - |  |  |
| *Atropine* | -0.07 | 895.47 |  |  |

Lanjutan Tabel 3.

| Compound | Binding Energy (kkal/mol) | Inhibition Constant (μM) | 2D Visualization | 3D Visualization |
|---|---|---|---|---|
| *Hiosiamine* | -0.10 | 841.670 |  |  |
| *Scopolamine* | +0.11 | - |  |  |
| *Trans-5-O-caffeoyl-D-quinate* | +1.50 | - |  |  |
| *Norhiosiamine* | +0.02 | - |  |  |

## Conclusion

Our study concluded that catechin in Avocado seeds has the best interaction and is possibly the potential candidate as an anticancer targeted against ERα. To validate the anticancer ability of avocado seeds, especially targeting ERα, a series of laboratory tests are needed, including *in vitro* and *in vivo* tests.

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