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Molecular Docking Study of Phenolic Compounds from the Ethanolic Extract of Olive Leaves (*Olea europaea* L.) as Potential Treatment for Preeclampsia

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ABSTRACT

Preeclampsia is a pregnancy-related disorder characterized by hypertension and proteinuria and is closely associated with oxidative stress, inflammation, endothelial dysfunction, and apoptosis. Olive leaves (*Olea europaea* L.) are rich in phenolic compounds with well-documented antioxidant and anti-inflammatory properties, making them a promising source of natural therapeutic agents. This study aimed to evaluate the potential of phenolic compounds from the ethanolic extract of olive leaves as candidates for treating preeclampsia using a molecular docking approach. The two-dimensional structures of selected phenolic compounds, including kaempferol, luteolin, and oleuropein, were obtained from the PubChem database and prepared as ligands. Target proteins associated with the pathophysiology of preeclampsia were prepared using AutoDock Tools by removing water molecules and separating native ligands. Molecular docking simulations were conducted to analyze binding affinities and interaction patterns between the phenolic compounds and the target proteins. The results demonstrated that all tested compounds exhibited favorable binding energies and formed stable interactions with key amino acid residues at the active sites of the target proteins. Among the compounds evaluated, oleuropein showed the strongest binding affinity, followed by luteolin and kaempferol. These findings suggest that phenolic compounds from the ethanolic extract of olive leaves have potential as therapeutic agents for preeclampsia, possibly through antioxidant and anti-inflammatory mechanisms. However, further *in vitro* and *in vivo* studies are required to validate these computational findings and confirm their biological efficacy.

INTRODUCTION

Pregnancy is a special situation for women as future mothers. During pregnancy, there are physical changes that affect her life. Problems that are often encountered during pregnancy include nausea and vomiting, anemia, chronic energy deficiency, hypertension, and preeclampsia (Lagadec *et al*., 2018). Many pregnant women experience preeclampsia. Preeclampsia is a clinical condition of pregnancy that arises after 20 weeks of pregnancy, characterized by the onset of hypertension, proteinuria, hematological complications, and uteroplacental disorders. Preeclampsia is one of the leading causes of morbidity and mortality, responsible for 42% of maternal deaths, and kills approximately 76,000 women each year (Mihalceanu *et al*., 2019). Globally, approximately 12% of mothers die from preeclampsia alone, affecting 5-10% of all pregnancies (Ryan *et al*., 2021). The incidence of preeclampsia in Indonesia is very high, at 24%, affecting 2-8% of pregnant women, and accounts for 9% of maternal deaths, while in Lampung province, there was an increase in 2022 of 344 cases (25%) (Kemenkes RI, 2019).

The classic causes that dominate preeclampsia are placental/trophoblastic ischemia and hypoxia, oxidative stress, genetics, immune dysregulation, and vascular endothelial injury. Oxidative stress is an imbalance in the amount of oxidants and antioxidants in the body. One of the markers of oxidative stress in preeclampsia patients is the increase in lipid

peroxide/Malondialdehyde (MDA) levels (Christenson *et al*., 2023). In preeclampsia, Soluble Fms-Like Tyrosine Kinase-1 (sFlt-1) levels are more dominant, by binding to molecules that result in decreased free circulating levels of VEGF and PIGF. Inflammatory status and epithelial damage are also thought to be the main reasons for increased Neutrophil gelatinase-associated lipocalin (NGAL) levels in preeclampsia. NGAL levels increase in pregnant women due to resulting placental hypoxia and ischemia that cause oxidative stress and apoptosis (Ives *et al*., 2020). Excessive activation of apoptosis in the placenta of preeclamptic women inhibits trophoblast invasion into the spiral artery with increased trophoblast apoptosis (Zhang *et al*., 2019).

Treatment of preeclampsia is more difficult than prevention. Treatment methods that have been carried out by administering methyldopa (Qi *et al*., 2022). Currently, the side effects have caused many pregnant women to turn to herbal medicine treatment (Gatford *et al*., 2020). Herbal medicine development is one of the strategies that can be used because it has few side effects. Recently, the search for herbal medicines has become more widespread, one of which is due to the low and safe side effects. Herbal medicine can also be used as a supporting treatment or as an alternative therapy (Paramita *et al*., 2022). One that has received attention is olive leaf/Olea Europaea L (OEL).

Olive leaf (*Olea Europaea L*) is one of the plants that has antioxidant and antiangiogenic effects that can improve oxidative stress conditions. Antioxidant and antiangiogenic functions can improve endothelial dysfunction that occurs in preeclampsia. Olive leaves contain bioactive compounds, including flavonoids and polyphenols. Olive leaves can also reduce endothelial dysfunction, be anti-inflammatory, antioxidant, angiogenic, and antithrombotic (Silvestrini *et al.,* 2023). Oxidative stress in preeclampsia is severe due to reduced antioxidants, starting from the failure of trophoblast invasion during the implantation process, causing placental hypoxia or ischemia, then causing various cell damage, including placental endothelial cell dysfunction (Subandrate *et al*., 2017). Administration of OEL extract is used as an adjuvant/co-adjuvant therapy, in addition to standard therapy, to maximize its effectiveness. Oleuropein in olive leaves can be a strategy for the prevention and treatment of hypertension. In addition to blood pressure-lowering effects, studies also show that oleuropein has potential cardioprotective, anti-inflammatory, antioxidant, and anticancer activities (Pirkovic *et al*., 2023).

Olive leaves were reportedly extracted using ethanol solvent. The resulting ethanol extract has antioxidant effects and anti-inflammatory effects (Khairunnisa, 2017). There are various kinds of natural compounds contained in olive leaves, including flavonoids and polyphenols. According to research on the identification of phenol components in olive leaves, the results show that the compounds with the greatest antioxidant effect are flavonol rhamnoglucoside compounds, rutin, flavan-3-ol catechin, and flavone luteolin (Ozarowski *et al*., 2021). Research shows that OEL administration significantly eliminates oxidative stress due to its antioxidant properties and can improve kidney and liver dysfunction (Abugomaa & Elbadawy, 2020). To determine the potential of OEL, which can be used as an antioxidant candidate for PE, it can be done by the in silico method, namely by molecular docking (Chigurupati *et al*., 2021). Molecular docking is an *in silico* method based on computational chemistry. This method can be used to find the most appropriate interaction pattern between ligand molecules and receptors. Currently, research using computational methods is very important in various aspects of research in the biological and medical fields. One of the benefits of using this method can be seen in various drug discovery and manufacturing processes (McNutt *et al*., 2021). This research aims to identify flavonoid and phenol compounds in olive leaves by tethering them to the soil.

METHOD

The methodology of this research was based on molecular docking simulations of the test compounds with the target molecule, molecular dynamics simulations, and toxicity prediction of the tested compounds. All experimental protocols were approved by the ethics committee of the Faculty of Medicine Universitas Sebelas Maret, Indonesia.

RESULTS

The molecular targets used in this study were soluble Fms-like tyrosine kinase-1 (sFlt-1; PDB ID: 6JQR), neutrophil gelatinase-associated lipocalin (NGAL; PDB ID: 3TF6), malondialdehyde (MDA; PDB ID: 6VJ3), and caspase-3 (PDB ID: 3KJF). The protein structures were downloaded from the RCSB Protein Data Bank (PDB) in pdb format. Based on the origin criteria, all macromolecules were derived from *Homo sapiens*. Resolution values represent the crystallographic resolution of the macromolecules (Å). Root mean square deviation (RMSD) values were used to evaluate ligand conformational similarity, and the docking method was considered valid if RMSD values were less than 2 Å. Native ligands were small molecules co-crystallized with the target proteins and served as reference ligands with similar biological functions to the test compounds.

DISCUSSION

Preparasi Ligan Uji

The two-dimensional structures of the three olive leaf extract compounds, kaempferol, luteolin, and oleuropein, were generated using SMILES strings or IUPAC names obtained from PubChem

Preparasi target makromolekul

AutoDock Tools version 1.5.6 was used to prepare the target proteins. Initially, water molecules were removed. The target protein and its native ligand were identified and separated. The ligand was saved individually in PDB format. The remaining target macromolecule was then subjected to hydrogen addition and charge assignment and saved in protein data bank, partial charge, and atom type (pdbqt) format.

Preparation of Test Ligands

Native ligands obtained from previous steps were cleaned and prepared following the same procedure as the target proteins, including hydrogen addition and charge assignment, and were saved in pdbqt format.

Preparation of Target Macromolecules

The prepared target proteins in pdbqt format were duplicated into individual folders for each test compound. Target proteins and ligands were loaded into AutoDock Tools 1.5.6, and grid boxes were generated based on validated ligand-binding coordinates. Grid parameter files (gpf) were saved and executed using AutoGrid4 via the command-line interface. This process was repeated for each test compound.

Validation of the Molecular Docking Method

Validation of the molecular docking method was performed using native ligands to determine their binding conformations. Binding interactions between reference ligands and receptor binding sites were compared with those of redocked ligands. The crystallographic structure was evaluated using RMSD values, and the docking protocol was considered acceptable if RMSD ≤2 Å.

Molecular Docking Process

Grid results for each test compound were used for molecular docking. Docking preparation was carried out using AutoDock Tools 1.5.6 by loading the grid files, ligands, and target proteins. Docking simulations were performed with 100 runs and saved as docking parameter files (dpf). AutoDock4 was executed via the command-line interface, generating docking log files (dlg).

Analysis of the Formed Molecular Interactions

Selected docking results with the best binding affinity were saved in pdb format and analyzed using PyMOL. Additional interaction analysis was conducted using ProteinPlus by uploading the PDB files.

Pharmacokinetic Profile Prediction

Pharmacokinetic properties were predicted using SwissADME by inputting the SMILES strings of all test ligands. The predicted parameters included bioavailability, P-glycoprotein (P-gp) substrate, gastrointestinal absorption, and blood–brain barrier permeability.

Prediksi uji toksisitas

Toxicity prediction was performed using pkCSM by inputting the SMILES strings of all test ligands. The evaluated toxicity parameters included AMES toxicity, maximum tolerated dose, hERG inhibition, oral rat acute toxicity, hepatotoxicity, skin sensitization, Tetrahymena pyriformis toxicity, and minnow toxicity.

Molecular Docking Results

Docking results demonstrated binding interactions between four macromolecular targets MDA, sFlt-1, caspase-3, and NGAL and the test compounds oleuropein, kaempferol, and luteolin. Docking of oleuropein, kaempferol, and luteolin with sFlt-1 and caspase-3 showed weaker binding affinity compared to native ligands, as none of the test compounds exhibited lower binding energy values than the native ligands. In contrast, luteolin showed stronger docking results with NGAL than the native ligand, as indicated by a lower binding affinity energy. Additionally, oleuropein exhibited better docking results with MDA compared to the native ligand, evidenced by lower binding affinity energy and shared amino acid residues.

Oleuropein dengan Antioksidan (MDA)

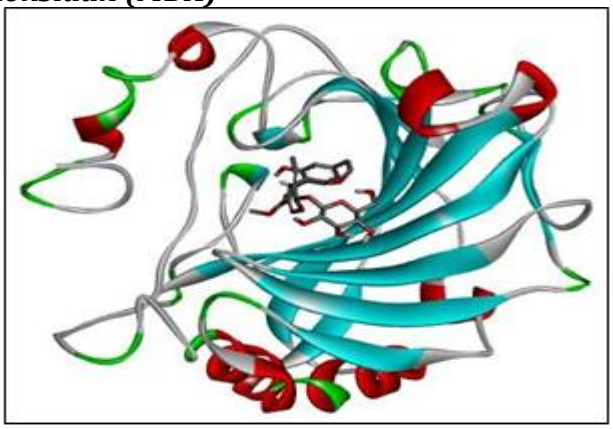

Figure 1. Molecular docking of Oleuropein to MDA

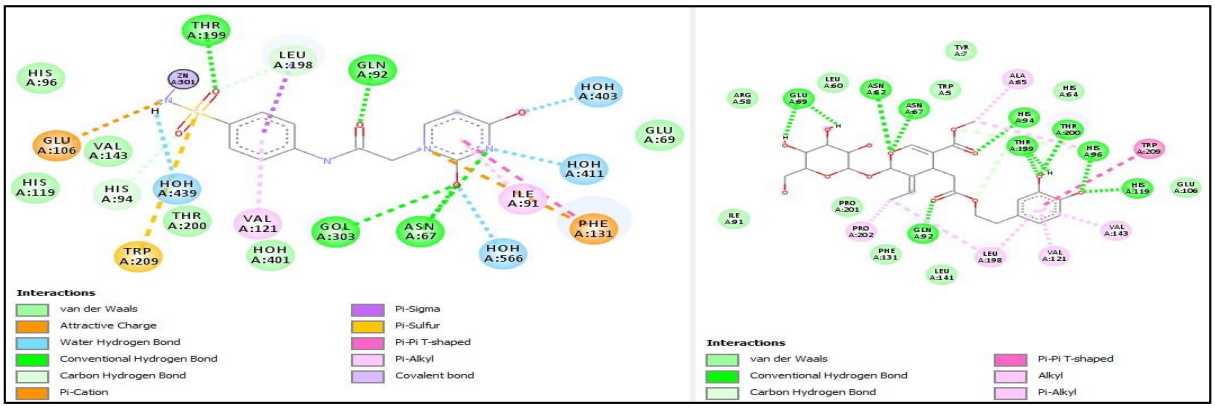

Figure 2. Interaction diagram of native ligand (right) compared to Oleuropein (left)

Luteolin dengan Apoptosis (NGAL)

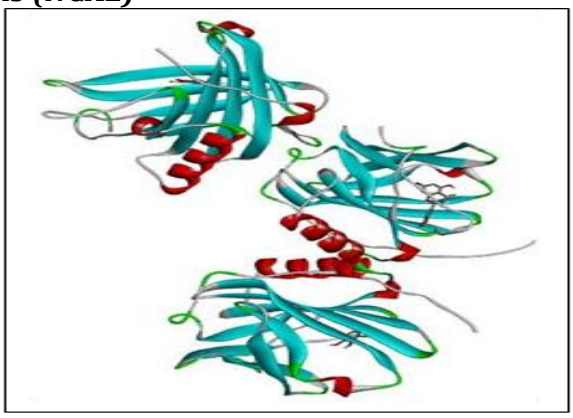

Figure 3. Molecular docking of Luteolin to NGAL

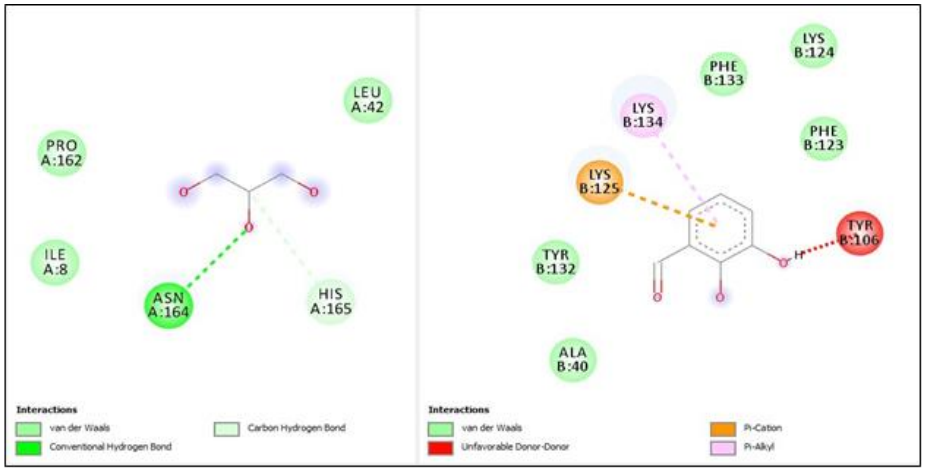

Figure 4. Interaction diagram of native ligand (right), compared to Luteolin (left)

Oleuropein Toxicity Evaluation

Oleuropein was found to be non-mutagenic in bacteria based on the AMES toxicity test. The estimated safe low dose for humans (Phase I clinical trial) was 0.118 log mg/kg/day. Oleuropein did not inhibit hERG I, indicating no cardiotoxicity; however, it showed inhibition of hERG II. The predicted dose of Olea europaea L. at 2.862 mol/kg represents the highest dose that can technically still be administered to experimental animals (rats). A predicted dose of 4.682 log mg/kg did not induce liver cell damage. Oleuropein did not cause skin allergy or contact dermatitis. At a predicted dose of 0.285 log µg/L, oleuropein inhibited 50% of *Tetrahymena pyriformis* growth.

Furthermore, oleuropein at a predicted dose of 4.431 log mM was classified as non-acutely toxic.

Kaempferol Toxicity Evaluation

Kaempferol was non-mutagenic in bacteria according to the AMES toxicity test. The estimated safe high dose for humans (Phase I clinical trial) was 0.531 log mg/kg/day. Kaempferol did not inhibit hERG I or II, indicating no cardiotoxic effects. The predicted dose of kaempferol at 2.449 mol/kg represents the highest technically administrable dose in experimental animals (rats). A predicted dose of 2.505 log mg/kg did not cause liver cell damage. Kaempferol did not induce skin allergy or contact dermatitis. At a predicted dose of 0.312 log μg/L, kaempferol inhibited 50% of *Tetrahymena pyriformis* growth. Kaempferol at a predicted dose of 2.885 log mM was classified as non-acutely toxic.

Luteolin Toxicity Evaluation

Luteolin was found to be non-mutagenic in bacteria based on the AMES toxicity test. The estimated safe high dose for humans (Phase I clinical trial) was 0.499 log mg/kg/day. Luteolin did not inhibit hERG I or II, indicating no cardiotoxicity. The predicted dose of luteolin at 2.455 mol/kg represents the highest technically administrable dose in experimental animals (rats). A predicted dose of 2.409 log mg/kg did not induce liver cell damage. Luteolin did not cause skin allergy or contact dermatitis. At a predicted dose of 0.326 log μg/L, luteolin inhibited 50% of *Tetrahymena pyriformis* growth. Luteolin at a predicted dose of 3.169 log mM was classified as non-toxic.

Relationship Between MDA and Olive Leaf Extract in Preeclampsia

Preeclampsia is a clinical pregnancy condition that occurs after 20 weeks of gestation and is characterized by hypertension, proteinuria, uteroplacental disorders, complications, and organ damage (Turner, 2010). One herbal plant that may serve as an adjunctive therapy to prevent preeclampsia is olive leaf extract. The major bioactive compound in olive leaves is oleuropein. Structurally, oleuropein contains ortho-diphenolic groups capable of scavenging reactive oxygen species (ROS) through hydrogen donation and stabilizing oxygen radicals via intramolecular hydrogen bonding (Nediani et al., 2019).

In vitro, olive leaf extract dose-dependently inhibited copper sulfate–induced LDL oxidation, as assessed by reduced thiobarbituric acid–reactive substances and lipid peroxide byproducts. In vivo, rabbits fed a diet rich in olive leaf extract exhibited higher serum antioxidant levels capable of preventing LDL oxidation, along with reduced free and esterified total cholesterol compared to animals receiving a standard diet (Silvestrini et al., 2023).

Oleuropein content in dried olive leaves ranges from 6–14%, while ethanol extracts of olive leaves contain approximately 20% oleuropein. Studies indicate that the most beneficial phenolic compounds in olive leaves include oleuropein, hydroxytyrosol, and tyrosol. Other compounds identified include rutin, hesperidin, quercetin, kaempferol, apigenin, luteolin, gallic acid, catechin, catechol, ferulic acid, and vanillic acid (Acar-Tek & Agagunduz, 2020). Oleuropein has been shown to inhibit LDL oxidation and may serve as a preventive and therapeutic strategy for hypertension. It also inhibits endothelial activation, monocyte adhesion, and platelet aggregation within physiologically relevant concentrations, suggesting anti-atherogenic and cardiovascular protective effects. In addition to its antihypertensive effects, oleuropein exhibits cardioprotective, anti-inflammatory, antioxidant, anticancer, antiangiogenic, and neuroprotective activities (Nediani et al., 2019). Oleuropein is also associated with anti-cancer effects through tumor necrosis factor inhibition and exhibits antiproliferative and pro-apoptotic properties (Medina et al., 2019). While oleuropein acts primarily by inhibiting oxidation, hydroxytyrosol suppresses lipid peroxidation and enhances endogenous antioxidant defense systems (Acar & Agagunduz, 2020).

Oxidative stress represents an imbalance between oxidants and antioxidants in the body. One biomarker of oxidative stress in preeclampsia is increased lipid peroxidation, particularly

malondialdehyde (MDA). Oxidative stress is also characterized by reduced endogenous antioxidants due to their excessive utilization in neutralizing free radicals (Guerby et al., 2021). Substantial evidence indicates that oxidative stress plays a crucial role in the pathogenesis of preeclampsia by disrupting the balance between reactive oxygen species (ROS) and tissue antioxidant defense systems (Michalczyk et al., 2020).

Three ligands were successfully docked to four potential macromolecular targets to identify interactions between ligands and target proteins. Molecular docking analysis was used to assess binding spontaneity and ligand stability toward target macromolecules based on ΔGbinding values and interactions with amino acid residues (Muttaqin, 2019). More negative ΔGbinding values indicate stronger binding interactions, as lower energy is required for ligand–receptor complex formation. The similarity of amino acid residues interacting with both native ligands and test ligands suggests that plant-derived compounds may have therapeutic potential (Ananta & Santoso, 2018). Molecular docking results revealed that four target macromolecules—sFlt-1, caspase-3, NGAL, and MDA exhibited favorable ΔGbinding values with compounds from olive leaf extract, with several test compounds showing lower ΔGbinding values than native ligands.

Oleuropein is a potent inhibitor of the human epidermal growth factor receptor, a protein often overexpressed in pathological conditions. Olea europaea L. significantly reduced systolic and diastolic blood pressure in animal models of preeclampsia (de Alwis et al., 2022). Its antihypertensive effects support the traditional use of olive leaves in treating mild to moderate hypertension. Recent studies provide significant insights into the mechanisms by which oleuropein reduces blood pressure (Putnik et al., 2019). Oleuropein protects the hypothalamus from oxidative stress by enhancing mitochondrial function through activation of Nrf2-mediated signaling pathways. These effects were observed when supplementation occurred either before or after the onset of hypertension, indicating that oleuropein is a promising strategy for the prevention and treatment of hypertension. Beyond hypertension, oleuropein has demonstrated cardioprotective, anti-inflammatory, antioxidant, anticancer, antiangiogenic, and neuroprotective activities, highlighting its therapeutic potential for various human disorders (Nediani et al., 2019).

Relationship Between sFlt-1 and Olive Leaf Extract in Preeclampsia

Molecular docking results of sFlt-1 with oleuropein, kaempferol, and luteolin indicated binding interactions between the protein and native ligand; however, no hydrogen bonds were formed between the protein and the test ligands. Soluble Fms-like tyrosine kinase-1 (sFlt-1) is a potent inhibitor of vascular endothelial growth factor (VEGF). sFlt-1 acts as an antagonist of VEGF and placental growth factor (PlGF) by binding and preventing their interaction with endogenous receptors (Rana et al., 2019). Levels of sFlt-1 in pregnant women with preeclampsia are increased approximately sixfold compared to normal pregnancies. Several factors are associated with the molecular mechanisms underlying sFlt-1 release in preeclampsia. Although hypoxia has been considered a major trigger, evidence suggests that primary placentation defects are more strongly associated with oxidative stress than hypoxia. Inflammatory stimuli that induce sFlt-1 release into the maternal circulation exert a greater effect than hypoxic conditions (Qu & Khalil, 2020).

Relationship Between Caspase-3 and Olive Leaf Extract in Preeclampsia

Cerebral ischemic injury results in two forms of cell death: necrosis and apoptosis. Apoptosis is a genetically regulated process that allows cells to die with minimal inflammation or release of genetic material. Caspase-mediated apoptosis is initiated by the release of cytochrome c from mitochondria through activation of the apoptosome complex, which subsequently activates caspase-3 (Yalman et al., 2021). Increased cell death is an expected marker in patients with preeclampsia. Villous trophoblasts possess mechanisms to maintain homeostasis and limit excessive apoptosis (Cho et al., 2020).

Relationship Between NGAL and Olive Leaf Extract in Preeclampsia

Recent studies have identified NGAL as a biomarker responsive to tissue stress and nephron injury, enabling early detection of acute kidney damage. NGAL has also been shown to predict preeclampsia prior to clinical diagnosis. Elevated NGAL concentrations in the blood of women with preeclampsia are likely a consequence of generalized endothelial dysfunction characteristic of the disease. This endothelial cell injury leads to increased NGAL levels in maternal circulation. NGAL was initially identified as a glycoprotein in human neutrophils complexed with MMP-9, and its expression is regulated in various inflammatory conditions involving endothelial cell injury (Zdziechowska et al., 2020).

Docking results demonstrated binding interactions between NGAL and the test compound luteolin, evidenced by the formation of hydrogen bonds between the protein and ligand. The binding interaction of luteolin with apoptosis-related proteins correlated with its docking score and biological activity. NGAL activity was inhibited by luteolin in a dose-dependent manner with IC_{50} values, indicating suppression of NGAL activity (Abdullah et al., 2018).

CONCLUSION

This study demonstrates that olive leaf extract contains promising levels of flavonoids and phenolic compounds with strong antioxidant activity based on the DPPH assay. Molecular docking results identified four potential target macromolecules, with MDA-oleuropein and NGAL–luteolin complexes exhibiting the lowest ΔGbinding values compared to native ligands. Toxicity prediction indicated that olive leaf extract is non-mutagenic based on the AMES test and, at doses up to 4000 mg/kg, does not induce cardiotoxicity, liver or kidney damage, allergic reactions, increased blood pressure, or acute toxicity.

AUTHOR'S DECLARATION

Authors' contributions and responsibilities

YA: Writing Original Draft, Conceptualization, Data Collection
Y : Formal Analysis

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Personal expenses

Availability of data and materials

All data and supporting materials for this study are available and can be requested directly from the corresponding author.

Competing interests

The authors declare no competing interests.

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