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Short Communication

Network pharmacology, molecular docking, and molecular dynamics analyses to explore the molecular mechanism of paclitaxel in atherosclerosis therapy

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Abstract

Atherosclerosis is a chronic arterial disease and the leading cause of vascular death. Paclitaxel has long been recognized as an anticancer agent, but recent studies have shown that paclitaxel can also potentially reduce the progression of atherosclerosis. The aim of this study was to explore the molecular mechanism of paclitaxel as an atherosclerosis therapy using in silico study. Pharmacokinetic and pharmacodynamic analyses of paclitaxel were conducted using SwissADME, ProTox v3.0, and SCFbio websites. Cytoscape software was used to construct a network of protein-protein interactions, and the key proteins involved in paclitaxel-related atherosclerosis were identified, including AKT serine/threonine kinase 1 (AKT1), Jun N-terminal kinase (JNK), and Endothelin 1 (ET1). These key proteins were then subjected to molecular docking and molecular dynamic simulation using MOE and Yasara applications. Pharmacokinetic and pharmacodynamic analyses revealed that paclitaxel has good distribution, metabolism, and excretion properties. However, paclitaxel has shortcomings in absorption, toxicity, and water solubility. According to the results of molecular docking, paclitaxel showed consistent results as the most potential inhibitor of AKT1 (-9.59 kcal/mol), ET1 (-9.16 kcal/mol), JNK (-8.72 kcal/mol) when compared to the control ligands. Molecular dynamics simulations also confirmed the interaction stability between paclitaxel with AKT1, ET1, and JNK, with paclitaxel-AKT1 demonstrating the highest conformational stability (Carbon-α Root Mean Square Deviation <3.0 Å). Even though our in-silico results are promising, more experimental studies are required to confirm the efficacy of paclitaxel as an atherosclerosis therapy.

Keywords: Atherosclerosis, molecular docking, molecular dynamics, paclitaxel, network pharmacology

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Introduction

Cardiovascular disease (CVD) is still the leading cause of death worldwide. In the last 3 decades, the number of CVD cases has almost doubled, and the mortality rate is expected to continue to rise until 2030 [1]. Two-thirds of them are caused by heart attack and stroke. One of the primary causes of cardiovascular diseases (CVDs), such as heart failure, stroke, myocardial infarction (MI), and claudication, is atherosclerosis. Atherosclerosis is a chronic arterial disease and the

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leading cause of vascular death. The process begins with endothelial dysfunction caused by disruptions to the processes that regulate vascular homeostasis. This dysfunction compromises the normal function of the endothelial cells, making the vascular walls more susceptible to damage and disease progression [1,2].

Vascular walls are vulnerable to oxidative stress, leukocyte adhesion, lipid infiltration, vasoconstriction, and platelet activation when endothelial cells are unable to maintain homeostasis [2]. These factors contribute to forming fatty streaks, considered the earliest visible manifestation of atherosclerosis. This streak, primarily composed of lipids and foam cells, marks the initial stage of atheromatous plaque development, a process characterized by the accumulation of low-density lipoprotein (LDL) particles that become oxidized and trigger an inflammatory response [2]. Over time, the fatty streak forms a more complex structure known as an atheroma. Atheroma plaque is a lipid-rich core surrounded by a fibrous cap composed of smooth muscle cells, collagen, and other extracellular matrix components.

As the plaque matures, it grows, narrowing the affected artery and reducing blood flow [3]. The fibrous cap stabilizes the plaque but can also become fragile and prone to rupture, particularly under increased stress, such as high blood pressure or turbulent blood flow. The rupture of an atheromatous plaque exposes its pro-thrombotic contents to the bloodstream, leading to the formation of a blood clot (thrombus). This clot can cause partial or total occlusion of the artery, resulting in acute events such as myocardial infarction or stroke [3]. Furthermore, the progression of atherosclerosis involves the continued recruitment of inflammatory cells, smooth muscle cell migration, and extracellular matrix remodeling, all of which contribute to the thickening of the arterial wall and the eventual formation of plaques that may lead to chronic ischemic conditions or acute cardiovascular events [1-3].

Various therapies have been developed to treat atherosclerosis, but current atherosclerosis therapy is still less than effective. This ineffectiveness is due to multiple factors, including the often-late detection, the complexity of the disease, and individual variations in response to treatment [4]. Patient adherence to lifestyle changes and medication is also usually low, while some therapies have significant side effects. Despite many advances in research and technology, the understanding and treatment of atherosclerosis are still evolving. Therefore, safer and more effective therapeutic alternatives are needed, and early prevention efforts remain an important strategy to improve therapeutic effectiveness [4,5].

Currently, no drug is available for subclinical atherosclerosis. Synthetic drugs are inadequate for preventing atherosclerosis in its early stages due to their limited indications, severe side effects, and high treatment costs. Naturally derived anti-atherosclerotic medications would, therefore, be an alternative. One natural ingredient that has attracted the attention of researchers is paclitaxel. Paclitaxel has long been recognized as an anticancer agent, but recent studies have shown that paclitaxel can also potentially reduce the progression of atherosclerosis [6,7]. Paclitaxel has been used in stent therapy to prevent restenosis by inhibiting smooth muscle cell proliferation and stabilizing microtubules, which reduce plaque formation and inflammation in the arterial wall [7]. This suggested that an exploratory effort is needed to determine the potential of paclitaxel as a therapy for atherosclerosis.

Along with the development of science and technology, in silico methods have been developed and widely applied for drug development and discovery. Computational-based approaches are promising in optimizing drug development and revolutionizing clinical research [8]. This method has the advantages of reducing costs and time, using tools and materials, and using experimental animals in experiments [8]. This method can also predict the pharmacokinetic properties of a compound, target proteins of disease pathophysiology related to a compound, and various components before in vitro, in vivo, preclinical, and clinical testing. The important role of in silico methods in drug discovery is why a preliminary study is needed in this research. Therefore, the aim of this study was to investigate and validate the molecular mechanisms through which paclitaxel exerts its therapeutic effects in the treatment of atherosclerosis by employing network pharmacology, molecular docking, and molecular dynamics analyses.

Methods

Network pharmacology and enrichment analysis

The protein-protein interaction (PPI) analysis was performed by submitting the UniProt IDs of identified proteins to the STRING database (version 12.0). Using the multiple protein input option, the study was specifically conducted for *Homo sapiens* organisms. The PPI network data was exported in TSV format for further analysis. Network visualization and analysis were then performed using Cytoscape software (V.3.10.3) to evaluate protein significance based on their centrality, which is influenced by the connectivity of the node (protein) [9]. Additionally, pathway enrichment analysis was conducted using the ShinyGO database to identify enriched Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) terms, providing insights into the biological processes and molecular functions associated with the identified proteins with the false discovery rate (FDR) limited to below 1×10^{-2} to prioritize the most significant possible mechanisms [10].

Pharmacokinetic and pharmacodynamic prediction

ProTox v3.0 website was used to predict the toxicity of paclitaxel based on the Lethal dose 50 (LD_{50}) value in mg/kg body weight unit (mg/kg BW). (https://tox.charite.de/protox3/index.php; accessed: 10th December 2024). LD_{50} refers to the dose of a substance required to cause death in 50% of a test population. Class I compounds are deadly if swallowed ($LD_{50}\leq5$ mg/kg BW), class II compounds are deadly if swallowed (5 mg/kg BW $<LD_{50}\leq50$ mg/kg BW), class III compounds are toxic if swallowed (50 mg/kg BW $<LD_{50}\leq300$ mg/kg BW), class IV compounds are harmful if swallowed (300 mg/kg BW $<LD_{50}\leq2000$ mg/kg BW), class V compounds may be harmful if swallowed (2000 mg/kg BW $<LD_{50}\leq5000$ mg/kg BW), and class VI compounds are non-toxic ($LD_{50}>5000$ mg/kg BW) [11]. The SwissADME website (http://www.swissadme.ch/index.php; accessed: 10th December 2024) was utilised to ascertain the characteristics of the paclitaxel's absorption, distribution, metabolism, and excretion (ADME). Using Lipinski's rule of five criteria, the compound's drug-likeness was assessed on the SCFbio website (http://www.scfbio-iitd.res.in/; accessed: 10th December 2024) [12]. There are five rules of Lipinski's rule of five, including molecular weight (<500 Dalton), LogP (≤5), molar refractivity (40–130 cm^3/mol), H-bond donors (<5), and H-bond acceptors (≤10). Paclitaxel is considered a drug-like compound if it complies with at least 4 out of 5 rules.

Ligand and protein preparation

The 3D structure of paclitaxel was obtained from the PubChem database. The PDB web server (https://www.rcsb.org/; accessed: 10th December 2024) was used to retrieve the 3D structure of all target proteins (ET1, AKT1, and JNK) (**Table 1**). Biovia Discovery Studio v.2021 isolated the control ligand from each target protein's 3D crystal structure. The MOE v2022.02 application was then used to conserve, neutralize, and refine all ligands and proteins to an RMS gradient of 0.001 kcal/mol/Å2 [13].

Molecular docking

The MOE v2022.02 application was used to perform molecular docking and 2D/3D visualization. The MOE application's Site Finder tool automatically matched the molecular docking site to the target protein's active site (**Table 1**). The results of the molecular docking include binding affinity (kcal/mol), root mean square deviation (RMSD) (Å), and 2D/3D visualization. Paclitaxel has the potential as a multiple pathway inhibitor of atherosclerosis if the binding affinity of paclitaxel is more negative (lower) than the control ligand with an RMSD value <2.5 Å. Additionally, the type and interaction similarity between paclitaxel and the control ligand in the target protein's active site were used to prove that paclitaxel has the potential as a specific inhibitor for each target protein.

Molecular dynamics simulation

YASARA Dynamics v4.3.13 was used to perform molecular dynamics simulations. Each sample was first loaded into the program by choosing the Set Target and Macro & Movie options from the Options menu. The molecular dynamics simulations were run using a macro input, with the

variable section containing values such as a physiological pH of 7.4, NaCl 0.9%, 1 atm, and temperature of 310 K. Forcefield was set using AMBER14, cell shape is a cube with size 10 extension, and model cell boundary periodic was used as the system set. The macro md_run set the simulation for 50,000 ps (50 ns). The RMSD of Carbon-α was computed using the "MD_analysis" macro. The molecular dynamics result was visualized using ORIGINPro 2024 (OriginLab, Massachusetts, United States). The molecular dynamics technique complied with a prior study's advice [13].

Table 1. Protein, protein data bank identifier (PDB ID), control ligand, and the active site's amino acid residue of target protein

Protein	PDB ID	Control ligand (PubChem ID)	Amino acid residue
AKT1	3MVH	Ipatasertib (24788740)	LEU156, GLY157, LYS158, VAL164, ALA177, LYS179, GLU198, THR211, MET227, GLU228, TYR229, ALA230, GLY233, GLU234, PHE236, PHE237, GLU278, ASN279, MET281, LYS289, THR291, ASP292, TYR437, PHE438, ASP439, PHE442
ET1	5X93	Sitaxentan (216235)	PRO88, PRO89, CYS90, GLN91, PRO93, ILE94, LYS97, GLU98, PHE100, LYS101, ASN104, SER108, ASP147, HIS150, ALA154, ILE155, ASN158, LYS161, LEU162, GLU165, ASP166, TRP167, VAL177, PRO178, GLN181, LYS182, SER184, VAL185, THR188, GLU236, PHE240, MET245, TYR247, LEU252, ARG253, ILE254, CYS255, LEU256, LEU257, ALA270, LYS273, ASP274, LEU277, PHE332, TRP336, LEU339, ARG343, LYS346, TYR350, GLN352, ARG357, LE372, ASN373, ALA375, SER376, ASN378, SER379
JNK	1PMN	Imidazole-pyrimidine (447872)	LYS68, ILE70, GLY71, SER72, GLY73, ALA74, GLN75, GLY76, ILE77, VAL78, ALA80, ALA91, ILE92, LYS93, LYS94, LEU95, SER96, ARG97, PRO98, GLN100, THR103, HIS104, LYS106, ARG107, ALA108, ARG110, GLU111, MET115, ILE124, LEU126, LEU144, VAL145, MET146, GLU147, LEU148, MET149, ASP150, ALA151, ASN152, GLN155, HIS187, ASP189, LYS191, SER193, ASN194, VAL196, LEU206, ASP207, PHE208, GLY209, LEU210, ALA211, YR223 VAL224 VAL225 THR226 ARG227 ARG230

Results

Protein-protein interaction (PPI) analysis

The PPI network revealed a complex interplay between paclitaxel and key proteins involved in atherosclerosis pathways. Based on their degree centrality, FOS, EDNRB, EDN1, AKT1, and JUN (all with a degree centrality of 6) were identified as highly connected hub proteins (**Figure 1** and **Table 2**).

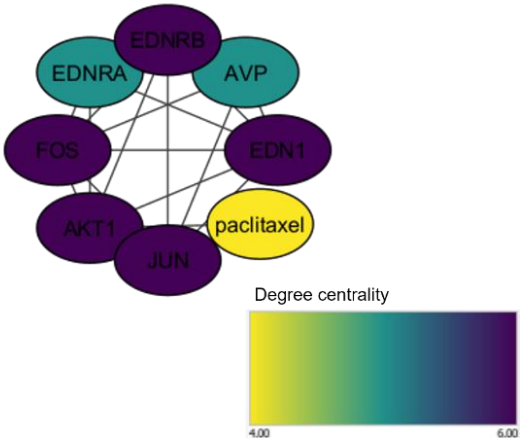


Figure 1. Protein-protein interaction (PPI) network for paclitaxel in the atherosclerosis pathway. Node colour indicated the degree of interaction, ranging from yellow (lowest) to purple (highest). Darker purple nodes represented key proteins with a higher degree of centrality, suggesting their critical role in network functionality and the potential mediation of paclitaxel's therapeutic effects.

Table 2. Network pharmacology centrality values of paclitaxel in atherosclerosis pathways

Name	Betweenness centrality	Closeness centrality	Degree
JUN	0.213889	0.75	6
FOS	0.011111	0.642857	6
EDN1	0.011111	0.642857	6
EDNRB	0.011111	0.642857	6
EDNRA	0.005556	0.6	5
AKT1	0.213889	0.75	6
AVP	0.005556	0.6	5

Enrichment analysis

Our enrichment analysis revealed potential therapeutic mechanisms of paclitaxel in combating atherosclerosis. As presented in **Figure 2**, the enrichment analysis based on biological process demonstrated that paclitaxel plays a significant role in blood vessel diameter maintenance and vasoconstriction, with notably high fold enrichment (>500) in vascular regulation processes. Furthermore, our investigation based on KEGG enrichment showed that paclitaxel works through the relaxin signalling pathway, which exhibited the highest fold enrichment among cellular signalling pathways (**Figure 2d**) [14,15].

Our molecular function analysis revealed that paclitaxel operates through multiple interconnected mechanisms, including the TNF signalling pathway, cAMP signalling, and endothelin receptor signalling (**Figure 2b**). Additionally, cellular component analysis identified a potential link between paclitaxel and the transcription factor AP-1 complex, which exhibited the most significant FDR value (**Figure 2c**).

Pharmacokinetic and pharmacodynamic prediction

Based on Lipinski's rule of five, paclitaxel has molecular weight =312 Dalton (<500 Dalton), LogP value =-0.053 (≤5), molar refractivity =77.146 (40-130), H-bond donors =5 (≤5), and H-bond acceptors =6 (≤10). Paclitaxel does not violate any of the rules. According to the absorption prediction, paclitaxel has a low amount of absorption in the human intestine (**Table 3**). Based on the CaCO-2 permeability indicator, paclitaxel has a low permeability value of 0.0623×10^{-6} cm/s. Paclitaxel was unable to pass across the blood-brain barrier (BBB). The Log S value of -6.66 indicates that paclitaxel is also considered poorly water-soluble. To predict the metabolism of the compounds, their availability as an inhibitor of the metabolic enzymes commonly found in the liver, namely Cytochrome P450 family 2 subfamily D member 6 (CYP2D6), Cytochrome P450 family 1 subfamily A member 2 (CYP1A2), Cytochrome P450 family 2 subfamily C member 19 (CYP2C19), and Cytochrome P450 family 3 subfamily A member 4 (CYP3A4) was assessed. Paclitaxel does not act as a CYP2D6, CYP1A2, CYP2C19, and CYP3A4 inhibitor, suggesting that the peptide will not alter the concentration of other drugs that are dependent on the CYP2D6, CYP1A2, CYP2C19, and CYP3A4 enzymes for its activation of elimination. The results also indicate that paclitaxel does not function as an organic cation transporter 2 substrate. Lastly, based on the level of toxicity, paclitaxel is classified as class III toxicity (toxic if swallowed), with an LD_{50} value of 134 mg/kg (**Table 3**).

Molecular docking

Molecular Docking of AKT1

The molecular docking results showed that paclitaxel (-9.59 kcal/mol) had a more negative binding affinity than Ipatasertib (-7.41 kcal/mol) as the control ligand. Also, the RMSD value of paclitaxel (1.42 Å) is below 2 Å (**Table 4**). The 2D visualisation showed that paclitaxel formed three interactions with the AKT1 active site: two hydrophilic acidic interactions (Glu278, Asp292) and one hydrophilic polar interaction (Gly157). Meanwhile, Ipatasertib forms only one interaction with the AKT1 active site: hydrophilic acidic interaction (Asp292) (**Figure 4**). This shows that paclitaxel and Ipatasertib form the same interaction at the AKT1 active site, which is at the amino acid residue Asp292.

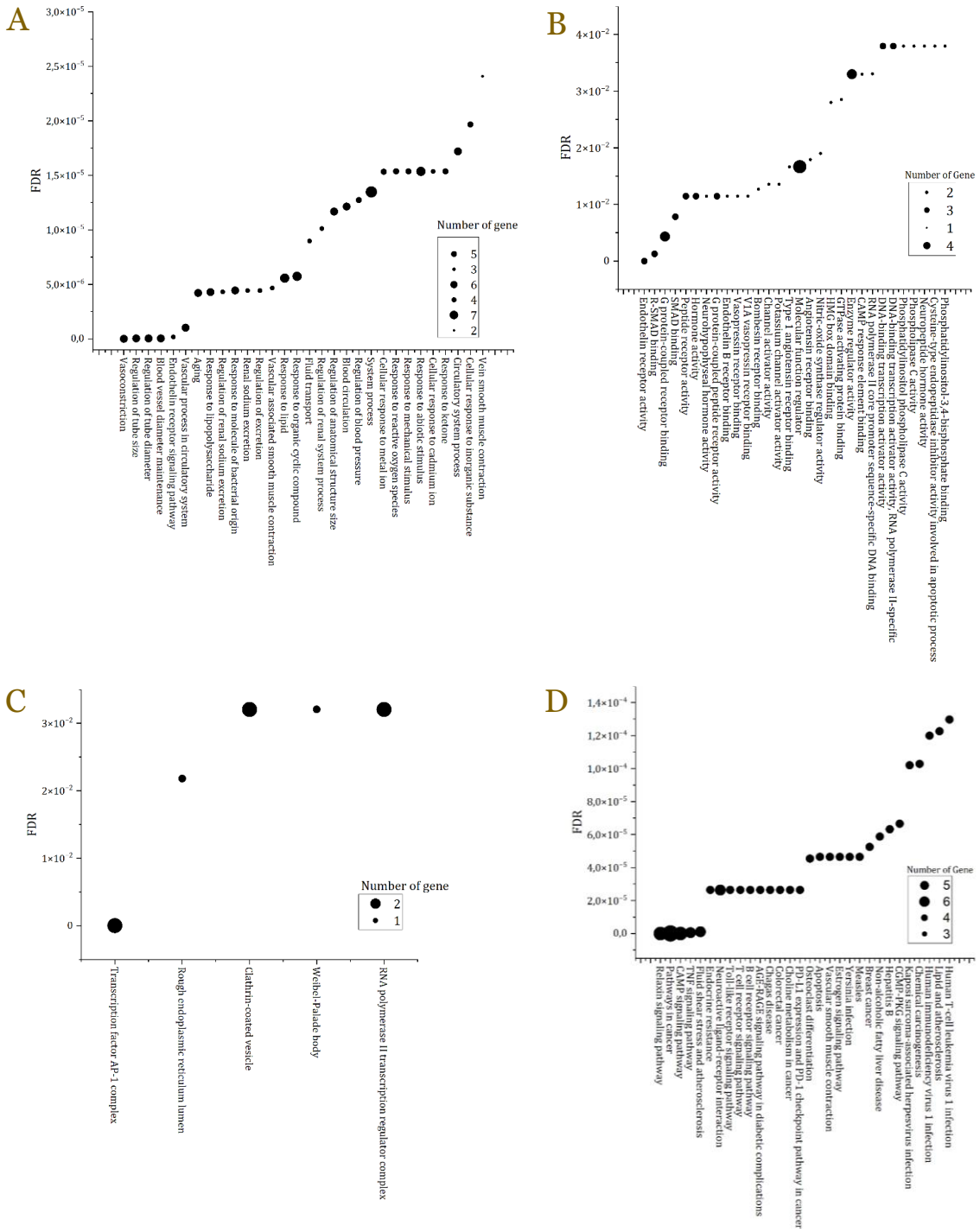


Figure 2. Gene ontology enrichment analysis results: biological process (A); molecular function (B); cellular component (C); and KEGG (D).

Molecular docking of ET1

The molecular docking results showed that paclitaxel (-9.16 kcal/mol) has a more negative binding affinity than sintaxenthan (-7.79 kcal/mol) and an RMSD value smaller than 2 Å (1.60 Å) (**Table 4**). Paclitaxel forms four interactions with the active site of ET1 protein: three hydrophilic basic interactions (Lys161, Lys182, and Arg343) and one hydrophobic greasy interaction (Leu277). Meanwhile, sitaxenthan, as a control ligand, formed four interactions: two hydrophilic basic interactions (Lys182 and Arg343) and one hydrophobic greasy interaction (Leu277) (**Figure 5**). Paclitaxel and sitaxenthan have three similarities in the interaction on the active site amino acid residues of ET1 protein, namely Lys182, Leu277, and Arg343.

Table 3. Pharmacokinetic and pharmacodynamic properties of paclitaxel

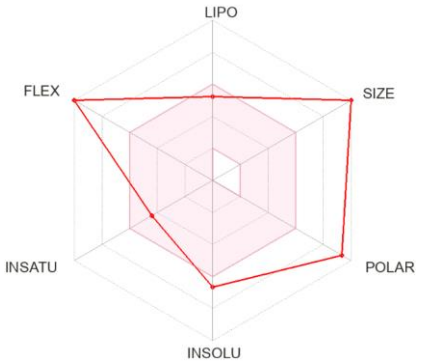
Paclitaxel	Properties	Results
	Physicochemical	
	Molecular weight (<500 Dalton)	312 Dalton
	LogP (≤5)	-0.053
	Molar refractivity (40–130)	77.146
	H bond donors (<5)	5
	H bond acceptors (≤10)	6
	Lipinski's rule of five	Yes, zero violations
	Pharmacokinetics	
	Water solubility (Log S)	-6.66 (Poorly soluble)
	CaCO-2 permeability (in 10^{-6} cm/s)	0.623 (Low permeability)
	GI absorption	Low
	BBB permeant	No
	CYP1A2 inhibitor	No
	CYP2C19 inhibitor	No
	CYP2C9 inhibitor	No
	CYP2D6 inhibitor	No
	CYP3A4 inhibitor	No
	Renal OCT2 substrate	No
	Toxicity class (LD50)	Class III (134 mg/kg)

Table 4. Molecular docking results between paclitaxel and control ligands of AKT1, ET1, and JNK

Target protein	Ligand	Molecular docking results	
		Binding affinity (kcal/mol)	RMSD (Å)
AKT1	Ipatasertib	-7.41	1.46
	Paclitaxel	-9.59	1.42
ET1	Sintaxenthan	-7.79	1.42
	Paclitaxel	-9.16	1.60
JNK	Imidazole-pyrimidine	-8.50	1.35
	Paclitaxel	-8.72	1.80

RMSD: root mean square deviation

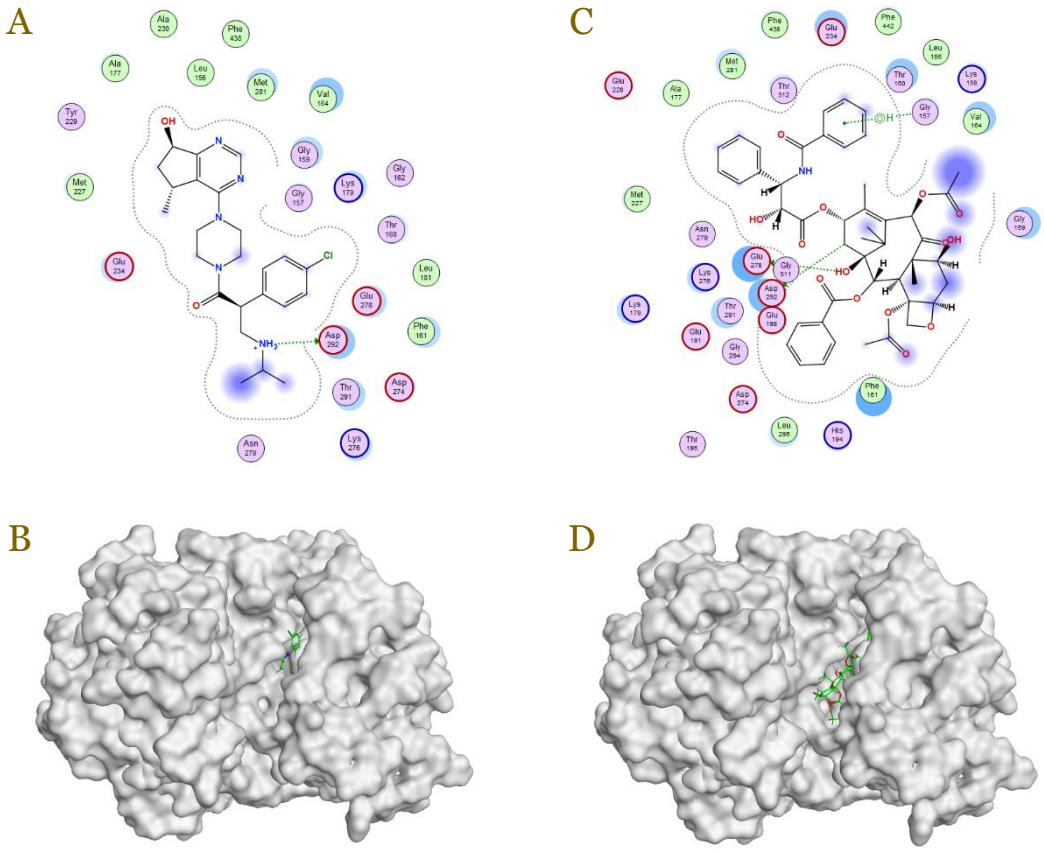


Figure 4. Two and three-dimensional (2D and 3D) visualisation of ipatasertibin (A, B) and paclitaxel (C, D) in the active site of AKT1.

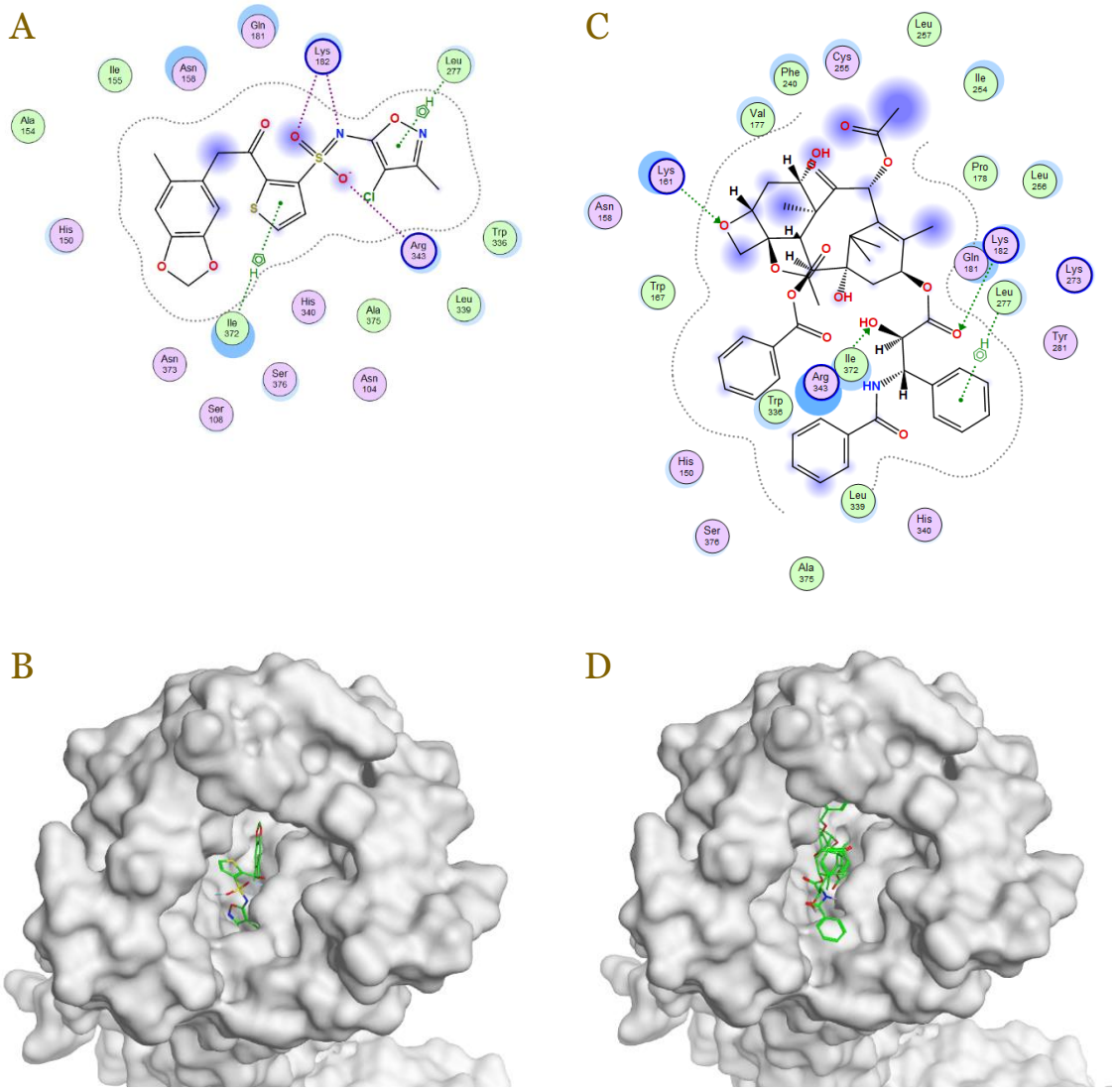


Figure 5. Two and three-dimensional (2D and 3D) visualisation of sitaxentan (A, B) and paclitaxel (C, D) in the active site of ET1.

Molecular docking of Jun N-terminal kinase (JNK)

Paclitaxel (-8.72 kcal/mol) had more negative binding affinity than imidazole-pyrimidine (-8.50 kcal/mol) and RMSD value smaller than 2 Å (1.80 Å) (**Table 4**). Paclitaxel formed three interactions: two hydrophilic polar interactions (Gln75 and Asn152) and one hydrophilic basic interaction (Lys191) (**Figure 6**). Meanwhile, imidazole-pyrimidine forms two interactions as a control ligand: one hydrophilic polar interaction (Gln75) and one hydrophobic greasy interaction (Met146). Between them, paclitaxel and imidazole-pyrimidine have one similarity in the interaction at the amino acid residue of the active site of the JNK protein, Gln75.

Molecular dynamics simulation

The molecular dynamics simulation results (**Figure 7**) showed the RMSD values of paclitaxel's C-alpha atoms (green) during 50 ns for three target proteins. Focusing on the core carbon atoms of amino acid residues, C-alpha RMSD is a crucial metric for assessing conformational changes and paclitaxel backbone stability [16]. Paclitaxel-AKT1 demonstrated the highest conformational stability, maintaining Cα RMSD values below 3.0 Å throughout the simulation and exhibiting lower fluctuations than other complexes. This suggests its stiff backbone structure may help retain its functional shape throughout atherosclerosis treatment. On the other hand, paclitaxel-ET1 exhibits the most fluctuation with a C-alpha RMSD of 4.0 Å (**Figure 7**).

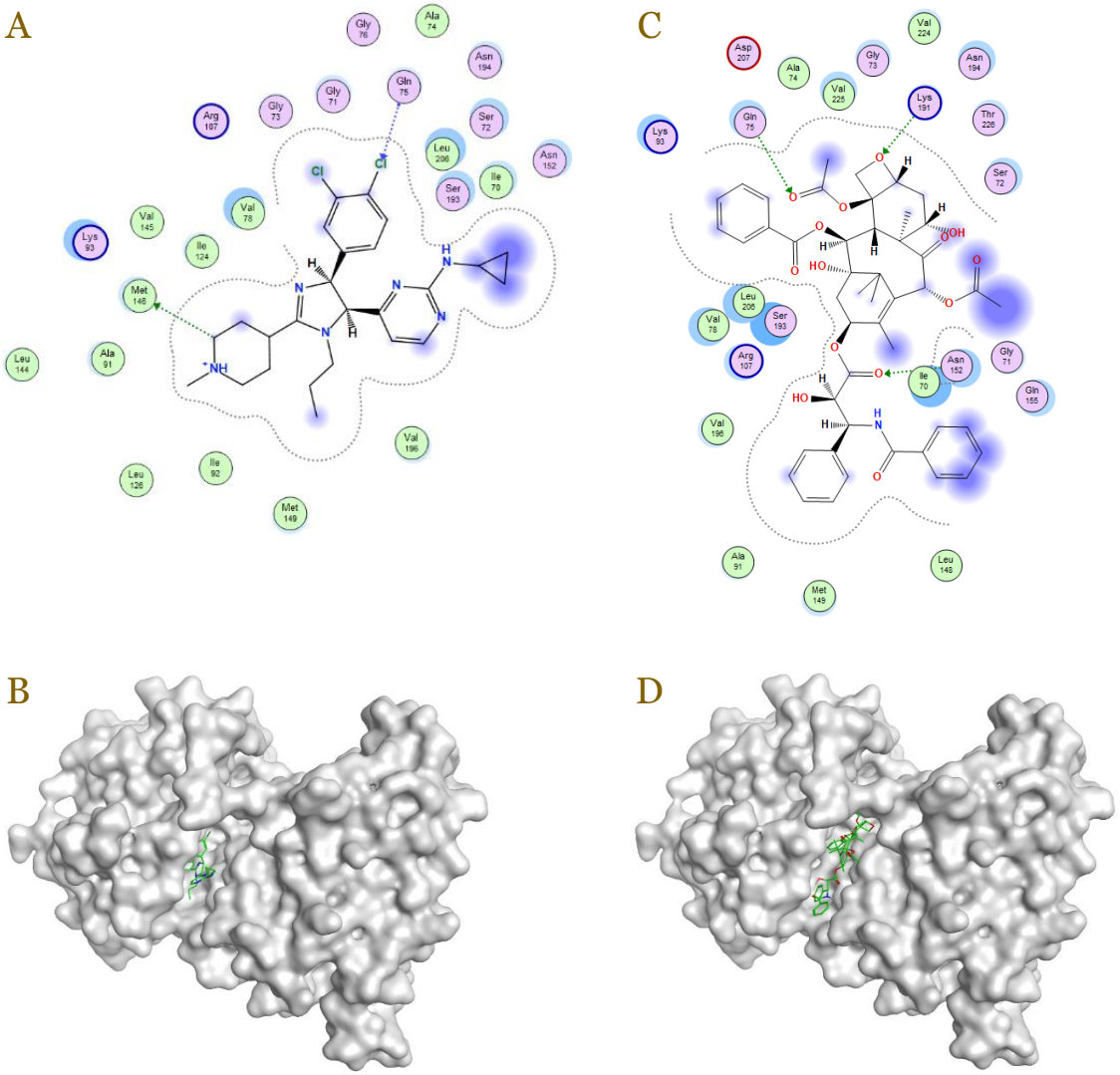


Figure 6. Two and three-dimensional (2D and 3D) visualisation of imidazole-pyrimidine (A, B) and paclitaxel (C, D) in the active site of JNK.

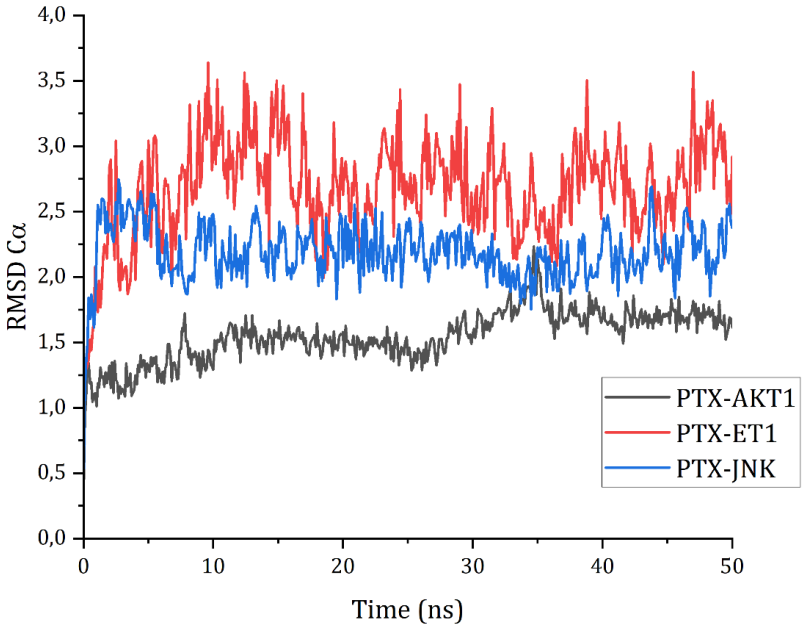


Figure 7. Molecular dynamics simulation results of the paclitaxel with ET1, AKT1, and JNK.

Discussion

This present study demonstrated the therapeutic potential of paclitaxel as an atherosclerosis therapy through a combination of pharmacokinetic and pharmacodynamic analysis, network pharmacology, molecular docking, and molecular dynamics simulations. Based on the pharmacokinetics and pharmacodynamics analysis, paclitaxel is classified as a drug-likeness compound with good distribution, metabolism, and excretion properties. However, paclitaxel has shortcomings in absorption, toxicity, and water solubility. Therefore, paclitaxel is not a good candidate for oral administration due to its limited intestinal absorption, so intravenous delivery is a better suitable route. In addition, careful dose determination is required in its application due to its high toxicity level (class III).

In the present study, the results of network pharmacology analysis showed that paclitaxel could inhibit three signalling pathways in atherosclerosis: endothelin signalling via ET1 (EDN1), cellular survival pathways through AKT1, and transcriptional regulation via JUN/JNK. AKT1 is a protein that regulates smooth muscle cell proliferation and migration, an important component in atherosclerotic plaque formation [17]. Chronic AKT1 activation promotes foam cell production, supports macrophage survival, and increases the migration and proliferation of vascular smooth muscle cells (VSMCs), contributing to the development of atheromatous plaque [17]. In the present study, paclitaxel (-9.59 kcal/mol) can replace Ipatasertib (-7.41 kcal/mol) and act as a specific competitive inhibitor of AKT1 by sharing the same amino acid residue with Ipatasertib in Asp292. These results predicted that paclitaxel may prevent or treat atherosclerosis by inhibiting the active site of the AKT1 protein. Inhibiting AKT1 may help reduce the inflammatory response within the arterial walls, a key factor in atherosclerotic plaque formation [17,18].

Endothelin-1 (ET1) has several roles related to cardiovascular homeostasis, including vascular constriction, modulation of platelet aggregation, and regulation of smooth muscle cell growth [19]. ETA and ETB are two different G protein-coupled receptors that ET1, a multisource derivative, activates [20]. Additionally, the ETB receptor mediates vasodilation by releasing prostacyclin or nitric oxide (NO). When ET1 is released from endothelial cells to the VSMCs of the arterial media, it activates neutrophils, mast cells, and monocytes, regulating the production of various cytokines implicated in the inflammatory cascade [21]. Therefore, ET1 may represent a novel therapeutic target for the treatment and prevention of atherosclerosis. The present in silico study showed that paclitaxel (-9.16 kcal/mol) could replace sintaxenthan (-7.79 kcal/mol) as a specific competitive inhibitor of the ET1 protein by interacting with the similar amino acid with sitaxenthan at the active site of ET1 (Lys182, Leu277, and Arg343).

Beyond its effects on AKT1 and ET1, paclitaxel also targets the JNK pathway, which plays a crucial role in inflammation, metabolic reprogramming, and apoptosis in atherosclerosis. JNK, known as c-Jun N-terminal kinase, plays several cell processes, including inflammation, metabolic reprogramming, and apoptosis [22]. In the majority of cells, JNK activity is tightly controlled. Consequently, dysregulated JNK signalling may result in the development of diseases, one of which is atherosclerosis [22,23]. According to previous studies, overactivation of JNK accelerates the development of atherosclerosis [23,24]. Additionally, inhibition of JNK can mitigate atherosclerosis progression, inhibit foam cell production, and reduce endothelial cell injury [22]. According to the present study, paclitaxel could inhibit the JNK protein specifically by acting as a JNK active site competitive inhibitor. Paclitaxel (-8.72 kcal/mol) has more negative binding affinity than imidazole-pyrimidine (-8.50 kcal/mol) and shares a similar interaction in the amino acid residue at the active site of ET1 protein (Gln75). These results suggested that paclitaxel could reduce the development and advancement of atherosclerosis.

Molecular dynamics simulations support the molecular docking results of this study to demonstrate the stability of paclitaxel in the framework of molecular dynamics simulations. RMSD values provide critical insight into whether a ligand maintains its binding mode during molecular dynamic simulation. In this study, paclitaxel anchorage showed a favourable interaction between considerable conformational shift and bond relaxation, staying below 4.0 Å. An RMSD value described the conformational shift in a macromolecule that changes into a receptor after coming into contact with a specific ligand [16].

One limitation of this study is its reliance on an in-silico approach, which cannot capture the physiological dynamics observed in in vitro or in vivo conditions. This limitation potentially

makes it less representative of real-world applications. Validation through in vitro or in vivo research is necessary to verify the effectiveness of the aforementioned drugs on atherosclerosis. Validation is essential because it determines accuracy by comparing model outputs with experimental data.

Conclusion

Paclitaxel exhibited favourable distribution, metabolism, and excretion properties but poor absorption and low water solubility. Paclitaxel consistently produced the best results compared to the control ligands because of its high binding affinity and structural stability as a multitarget inhibitor of AKT1, ET1, and JNK proteins. However, more in vitro and in vivo studies are required to confirm its effectiveness as a treatment for atherosclerosis.

Ethics approval

Not required.

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Competing interests

All the authors declare that there are no conflicts of interest.

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Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

Declaration of artificial intelligence use

We hereby confirm that no artificial intelligence (AI) tools or methodologies were utilised at any stage of this study, including during data collection, analysis, visualisation, or manuscript preparation. All work presented in this study was conducted manually by the authors without the assistance of AI-based tools or systems.

How to cite

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