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Research Article

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Identification of Hsp90 inhibitors from *Ananas comosus* potential phytochemicals for lung cancer treatment

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ABSTRACT

Lung cancer is a significant global health issue, with thousands of lives lost each year. One potential approach to preventing lung cancer is the use of heat shock protein 90 (Hsp90) inhibitors, which have been shown to induce substantial cell death in both chemo-sensitive and chemo-resistant small cell lung cancer cells. In this study, we conducted in silico computational molecular docking of pineapple phytochemicals with Hsp90 to investigate their potential inhibitory effects on Hsp90 and, consequently, their ability to prevent lung cancer. Our findings demonstrate that the phytochemicals found in *Ananas comosus*, specifically caffeic acid, ferulic acid, 4-Hydroxycinnamic acid, Sinapic acid, and D-Galacturonic Acid, exhibit notable inhibitory activity against Hsp90. Beyond their Hsp90 inhibition, these phytochemicals also demonstrate promising biological activities, serving as effective agents against neoplastic conditions, particularly lung cancer, and displaying pro-apoptotic properties. Moreover, the ADME (Absorption, Distribution, Metabolism, and Excretion) and toxicological assessments conducted on these compounds yielded satisfactory results. These findings suggest that pineapple phytochemicals may have potential in the development of novel therapeutic strategies for lung cancer prevention.

Keywords: Pineapple, *Ananas comosus*, Hsp90 inhibitors, Lung cancer.

INTRODUCTION

Lung cancer is a complex and devastating disease that continues to be a significant global health concern. As the predominant cause of both global cancer incidence and mortality, it accounted for approximately 2 million diagnoses and 1.8 million deaths in 2020 alone[1]. The disease is characterized by uncontrolled cell growth in the lung tissue, often leading to the formation of malignant tumors[2]. Diverse categories of lung cancer exist, including adenocarcinoma (affecting glandular cells), squamous cell carcinoma (SCC), non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC). Each variant exhibits distinctive characteristics, leading to specific approaches in their diagnosis and treatment[3]. The etiology of lung cancer is complex and multifactorial, with various elements contributing to the development of the disease. While smoking tobacco remains the single most important risk factor for lung cancer. However, non-smoking-related factors such as exposure to environmental carcinogens, genetic predisposition and exposure to environmental carcinogens such as asbestos, silica, diesel exhaust and radon also play significant role in the pathogenesis of lung cancer[4]. Understanding the fundamental molecular mechanisms and genetic alterations associated with the development and progression of lung cancer is crucial for the identification of effective target[5]. Recent advancements in molecular biology, genomics, and immunology have revolutionized the field of lung cancer research, leading to the development of targeted therapies[6]. A specific focus involves heat shock protein 90 (Hsp90), a molecular chaperone essential for the proper folding and stability of numerous oncogenic kinases responsible for signaling pathways and the proliferation of lung cancer cells[7]. Hsp90 participate in various cellular processes and regulatory pathways such as apoptosis, cell cycle control, cell viability, protein folding and degradation[8]. It also regulates the activity of heat shock factor-1 (HSF-1), the master regulator of the heat shock response, and is involved in the development of serious conditions like cancer[9] and neurodegenerative diseases [10]. Due to its significance in cellular function and disease development, Hsp90 is a promising target for the treatment of various diseases, including lung cancer[11]. Hsp90 inhibition prevents lung cancer by disrupting the function of Hsp90. Studies indicate that inhibiting Hsp90 leads to significant cell death in both chemosensitive and chemoresistant small cell lung cancer cells[12]. Additionally, Hsp90 inhibitors have been shown to degrade mutant ErbB2, mutant B-Raf, or mutant or overexpressed c-Met, which are proteins driving lung cancer, further contributing to the prevention of cancer progression[13]. Plant-derived natural products have been identified as important sources for potent anticancer agents, with more than 60% of anticancer drugs showing high efficiency in clinical use derived from natural sources[14]. *Ananas comosus* phytochemicals have gained attention for their potential anticancer properties. It contains various phytochemicals such as furaneol, ferulic acid, caffeic acid, 4-hydroxy cinnamic acid and myristic acid[15]. Among them, bromelain which is richly present in pineapple has been shown to have synergistic

effects with other anticancer agents and potentiate the antitumor effect of cisplatin[16] in triple-negative breast cancer[17]. In addition, phytochemicals present in pineapple has been found to induce apoptosis and disrupt the survival of cancer cells by blocking the Akt and attenuating MUC1 oncoproteins and Bcl2[18]. Targeting Hsp90 has been shown to inhibit proliferation and induce apoptosis through the AKT1/ERK pathway in lung cancer[19]. Several clinical trials have been conducted to evaluate the effectiveness of HSP90 inhibitors in the context of lung cancer. These trials have focused on various HSP90 inhibitors and their potential in the treatment of non-small cell lung cancer (NSCLC) and other types of lung cancer[20]. The Institute of Cancer Research in London has been involved in the development of HSP90 inhibitors, such as AUY922, and has conducted clinical trials to demonstrate the safety and clinical activity of these inhibitors in drug-resistant breast and lung cancer[21].

GLOBAL PREVALENCE OF LUNG CANCER

Globally, lung cancer poses a significant public health challenge, with approximately 2 million diagnoses and 1.8 million fatalities recorded in 2020[22]. It stands as the second most prevalent cancer worldwide and holds the top spot among cancers affecting men, while ranking as the second most common among women[23]. Although smoking tobacco remains the primary risk factor, contributing to the majority of cases, non-smokers can also be affected[24]. Other risk factors encompass exposure to secondhand smoke, occupational hazards, air pollution, and pre-existing chronic lung conditions[25]. The global incidence of lung cancer is on the rise, especially in developing nations where increased access to tobacco and industrialization play a role[26]. Despite ongoing efforts, lung cancer maintained its position as the leading cause of cancer-related deaths worldwide in 2020, with colorectal, liver, and stomach cancers[27]. The prevalence of lung cancer varies across countries, with Hungary having the highest age-standardized rates (ASR) of lung cancer in 2020[28]. The burden of lung cancer is growing in almost every country, highlighting the need for comprehensive and integrated approaches to prevention and control measures. Around 40% of cancer cases could be prevented by tackling risk factors related to diet, nutrition, and physical activity[29]. Figure 1 depicts graphical representation of top countries with lung cancer cases.
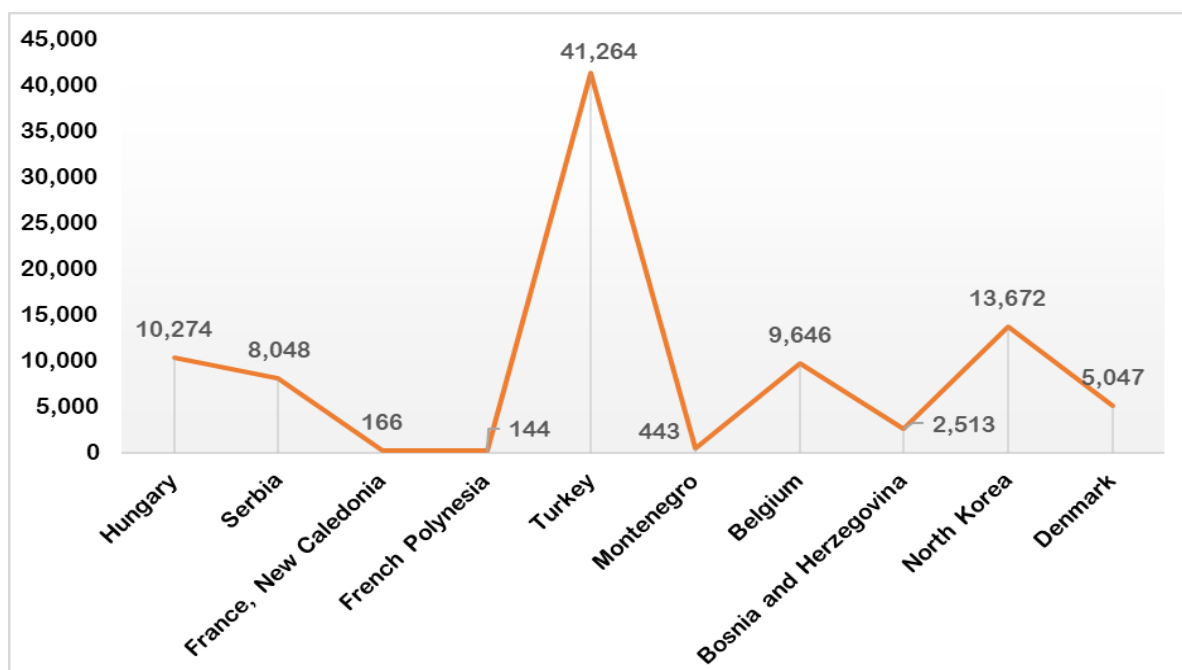

Figure 1: A graph illustrating the top countries with the highest number of lung cancer cases

MATERIAL AND METHODS

Protein preparation

The investigation utilized the Protein Database (https://www.rcsb.org/) to procure the PDB file corresponding to the Crystal Structure of the human Hsp90-alpha N-domain, distinguished by its unique PDB ID: 5XRE. The Protein Data Bank (PDB) serves as a comprehensive repository containing data on experimentally ascertained structures of proteins and nucleic acids. In the subsequent stages of analysis, procedures for preparing the protein were implemented, involving the removal of water molecules and associated ligands. This task was effectively carried out using PyMOL[30], an open-source software tool well-known for its proficiency in generating molecular visualizations. The strategic utilization of PyMOL made it an optimal choice for facilitating the docking preparation process.

Evaluation of phytochemicals present in *Ananas* extract

The assessment of phytochemicals in *Ananas* was conducted utilizing the Indian Medicinal Plants, Phytochemistry And Therapeutics 2.0 (IMPPAT 2.0) database[31]. IMPPAT stands out as a meticulously curated database, assembled through the digitization of data from over 100 traditional Indian medicine books, 7000+ published research articles, and various other pertinent resources. IMPPAT 2.0 represents the most extensive digital repository on phytochemicals found in Indian medicinal plants to date, marking a substantial improvement and expansion over its predecessor, IMPPAT 1.0.

Ligand retrieval and preparation

The molecular structures of the selected phytochemicals were obtained in sdf file format from the PubChem database, a valuable repository that provides comprehensive information on chemical compounds, including structures, formulas, and molecular weights. In

the ligand preparation phase for subsequent analysis, the OpenBabel tool[32] within PyRx 0.8[33] was employed. OpenBabel is widely utilized in molecular docking studies for ligand preparation. The ligand energy underwent minimization using the mmff94 force field, a method chosen for its effectiveness in achieving stable and reliable ligand structures. Subsequently, the ligands' sdf file format was converted to pdbqt format, rendering the ligands executable and poised for docking. This conversion step played a pivotal role in ensuring compatibility and streamlining the subsequent exploration of ligand-receptor interactions in molecular modeling.

Prediction of biological activity of the compound

To predict the biological actions of the selected molecules, the researchers utilized the PASS web server (http://www.pharmaexpert.ru/passonline)[34]. Utilizing intricate atom neighbor descriptors, PASS analysis aids in deciphering the potential effects of a drug solely based on its molecular formula, underscoring the complex relationship between its biological function and chemical arrangement.

Molecular Docking

A molecular docking analysis was carried out to explore the interactions between the phytochemicals and the Hsp90-alpha N-domain. For the execution of molecular docking, AutoDock Vina[35] tool was employed which comes integrated with PyRx 0.8. This enabled a comprehensive exploration of potential binding interactions between the ligands and the macromolecule, offering valuable insights into their binding affinities and orientations.

Visualization of Docking Results

After executing the molecular docking analysis, we identified the protein-ligand complex characterized by the most favorable negative score, indicative of a strong affinity. This optimal binding pose was then selected for further investigation using Discovery Studio 4.5[36]. The software facilitated the visualization and exploration of the binding mode, enabling a detailed examination of ligand-receptor interactions. Through this comprehensive analysis, we uncovered crucial molecular interactions that govern the ligand's high binding affinity to the Hsp90-alpha N-domain. Our focus was specifically on

visualizing phytochemicals that demonstrated both a commendable docking score and possessed drug-likeness properties.

Molecular descriptors of chosen phytochemicals

Properties such as the physicochemical nature, lipophilicity, water solubility, and drug-likeness of the chosen compounds underwent analysis utilizing the SWISS ADME webserver[37]. Key factors considered for assessing physicochemical properties included the number of hydrogen acceptors, number of hydrogen donors, and topological polar surface area (TPSA). For evaluating lipophilicity and water solubility, XLOGP3 and ESOL values were taken into account, respectively. Drug-likeness properties were evaluated based on the Veber rule[38] and Lipinski rule[39].

Prediction of absorption, distribution, metabolism, and toxicity

The assessment of predictions pertaining to absorption, distribution, metabolism, and toxicity for the chosen compound was carried out using admetSAR[40]. An online tool, accessible at http://lmmd.ecust.edu.cn/admetsar2/, was employed to scrutinize a diverse range of parameters. These parameters played a crucial role in the prediction process, enriching our holistic comprehension of the compound's characteristics in relation to absorption, distribution, metabolism and toxicity.

RESULT

Prediction of biological activity of compounds

The PASS webserver was utilized to validate the anticipated biological effects. Biological activity such as hsp90 inhibitor, anti-neoplastic (lung cancer), and apoptosis agonist were taken into consideration. Out of all assessed compounds, ergosterol peroxide, bromelain, myristic acid, and flavoxanthin lack hsp90 inhibitor property while rest shown to have hsp90 inhibition property. The Pa value for hsp90 inhibitor ranged between 0.098 to 0.183, for antineoplastic activity it ranged between 0.128 to 0.742 and for apoptosis agonist, it was observed to range between 0.269 to 0.992. When the Pa value surpasses the Pi value, it indicates a probable presence of the specified biological activity. The summarized outcomes are presented in table 1.

Table 1: Biological activity of selected ligands as predicted by PASS

| Ligand | Biological activity | | | | | |
| | HSP90 inhibitor | | Antineoplastic | | Apoptosis agonist | |
	Pa	Pi	Pa	Pi	Pa	Pi
Ethyl acetate	0.111	0.034	0.274	0.046	0.300	0.127
Butane-2,3-diyl diacetate	0.183	0.063	0.497	0.014	0.269	0.147
Ergosterol peroxide	---	---	0.341	0.033	0.992	0.002
4-Hydroxycinnamic acid	0.138	0.036	0.158	0.094	0.458	0.005
Bromelain	---	---	0.353	0.030	0.310	0.025
Myristic acid	---	---	0.362	0.020	0.342	0.102
Sinapic acid	0.118	0.047	0.349	0.031	0.730	0.012
Flavoxanthin	---	---	0.949	0.004	0.750	0.011
Furaneol	0.102	0.059	0.742	0.019	0.836	0.006
tert-Butanol	0.098	0.046	0.128	0.124	0.326	0.112
1-Triacontanol	0.103	0.041	---	---	0.306	0.124
Ferulic acid	0.152	0.026	0.268	0.047	0.702	0.015
Caffeic acid	0.140	0.033	0.192	0.074	0.711	0.014
D-Galacturonic Acid	0.121	0.045	0.411	0.022	0.550	0.032

Table 2: Docking score of selected phytochemicals with their molecular weight (MW) and pubchem ID

Ligands	Pubchem ID	MW (g/mol)	Docking score (kcal/mol)
Ethyl acetate	8857	88.11	-3.8
Butane-2,3-diyl diacetate	66193	174.19	-5.5
Ergosterol peroxide	5351516	428.6	-9.9
4-Hydroxycinnamic acid	637542	164.16	-7.1
Bromelain	44263865	1026.9	-7.5
Myristic acid	11005	228.37	-6.1
Sinapic acid	637775	224.21	-6.5
Flavoxanthin	5281238	584.9	-10
Furaneol	19309	128.13	-5.1
tert-Butanol	6386	74.12	-3.5
1-Triacontanol	68972	438.8	-6.7
Ferulic acid	445858	194.18	-7.2
Caffeic acid	689043	180.16	-7.0
D-Galacturonic Acid	439215	194.14	-5.4

Docking score of the compounds

The docking study involved utilizing the Crystal Structure of the human Hsp90-alpha N-domain, identified by PDB ID: 5XRE. Autodock Vina, accessed through PyRx 0.8, served as the tool for analysis. To prepare both the protein and the ligand for docking, UCSF Chimaera's Dockprep feature was employed. The protein was transformed into a macromolecule, and the chosen compounds underwent initial minimization using the mmff94 forcefield. Subsequently, the compounds were converted to pdbqt format using OpenBabel within PyRx. For the docking procedure, a grid box with dimensions of 44.47 Å × 44.08 Å × 44.80 Å was employed, centred at coordinates (-33.06, 14.64, 20.40). The exhaustiveness level was set to the default value of 8. Specific details regarding the ligands or compounds and their respective docking scores are provided in Table 2.

Evaluation of pharmacological and toxicological properties

The assessment of pharmacological and toxicological properties phytochemicals thorough analysis of physicochemical properties, lipophilicity, water solubility, drug-likeness and ADME/t values. The evaluation was done usin SWISSADME and admetSAR. The summarized outcomes are presented in Tables 3 and 4. The pivotal criteria influencing a compound's potential as a drug candidate, encompassing topological polar surface area (TPSA), molecular weight (MW), ESOL (solubility), xlog3 value, and drug-likeness parameters such as Lipinski's rule and Veber rule were considered. Ethyl acetate, with two hydrogen acceptors and no hydrogen donors, exhibited moderate lipophilicity (XLOGP3 = 0.73) and limited water solubility (ESOL = -0.71). Meeting both Veber and Lipinski drug-likeness criteria, it displayed attributes conducive to drug development. Butane-2,3-diyl diacetate, characterized by four hydrogen acceptors and a TPSA of 52.60 Å, showcased moderate lipophilicity (XLOGP3 = 0.87) and some hydrophobicity (ESOL = -1.14), meeting drug-likeness criteria. Ergosterol peroxide, with three hydrogen acceptors and a TPSA of 38.69 Å, demonstrated high lipophilicity (XLOGP3 = 6.71) and limited water solubility (ESOL = -6.46), meeting both Veber and Lipinski criteria. 4-Hydroxycinnamic acid, featuring three hydrogen acceptors and a TPSA of 57.53 Å, exhibited moderate lipophilicity (XLOGP3 = 1.46) and some

hydrophobicity (ESOL = -2.02), meeting drug-likeness criteria. Bromelain, a complex compound with 29 hydrogen acceptors, 18 hydrogen donors, and a Total Polar Surface Area (TPSA) of 483.41 Å, exhibits distinctive physicochemical characteristics. It possesses a notably high degree of hydrophilicity, indicated by a lipophilicity value (XLOGP3) of -11.65, along with good water solubility (ESOL = 2.32). However, bromelain does not meet both Veber and Lipinski drug-likeness criteria. The high number of hydrogen acceptors and donors, coupled with its large TPSA, may present challenges in the context of drug development, highlighting the need for careful consideration of its pharmacological applications. Myristic acid, possessing two hydrogen acceptors and a TPSA of 37.30 Å, displayed high lipophilicity (XLOGP3 = 6.11) and limited water solubility (ESOL = -4.31). While not meeting the Lipinski rule, it complied with the Veber rule. Sinapic acid, characterized by five hydrogen acceptors and a TPSA of 58.12 Å, demonstrated moderate lipophilicity (XLOGP3 = 1.46) and some hydrophobicity (ESOL = -2.16), meeting drug-likeness criteria. Flavoxanthin, featuring three hydrogen acceptors and a TPSA of 49.69 Å, showcased high lipophilicity (XLOGP3 = 10.06) and limited water solubility (ESOL = -9.21), meeting the Veber rule but not the Lipinski rule. Furaneol, with three hydrogen acceptors and a TPSA of 31.22 Å, displayed moderate lipophilicity (XLOGP3 = 0.68) and some hydrophobicity (ESOL = -1.06), meeting drug-likeness criteria. tert-Butanol, possessing one hydrogen acceptor and a TPSA of 20.23 Å, showed low lipophilicity (XLOGP3 = 0.53) and moderate hydrophobicity (ESOL = -0.63), meeting drug-likeness criteria. 1-Triacontanol, featuring one hydrogen acceptor and a TPSA of 20.23 Å, exhibited very high lipophilicity (XLOGP3 = 14.70) and limited water solubility (ESOL = -9.97), not meeting both Veber and Lipinski criteria. Ferulic acid, with four hydrogen acceptors and a TPSA of 51.63 Å, displayed moderate lipophilicity (XLOGP3 = 1.51) and some hydrophobicity (ESOL = -2.11), meeting drug-likeness criteria. Caffeic acid, characterized by four hydrogen acceptors and a TPSA of 77.76 Å, exhibited moderate lipophilicity (XLOGP3 = 1.15) and some hydrophobicity (ESOL = -1.89), meeting drug-likeness criteria. D-Galacturonic Acid, featuring seven hydrogen acceptors and a TPSA of 127.45 Å, displayed hydrophilicity (XLOGP3 = -2.34) and good water solubility (ESOL = 0.50), meeting drug-likeness criteria. All compounds possess drug-likeness property except bromelain, myristic acid, flavoxanthin, and 1-Tricontanol.

Table 3: Physicochemical properties, lipophilicity, water solubility, and drug-likeness of Ananas phytochemicals as predicted by SWISSADME server

LIGAND	Physicochemical Properties			Lipophilicity	Water Solubility	Drug-likeness	
	Accept H	Donor H	TPSA (Å)			Veber	Lipinski
				XLOGP3	ESOL		
Ethyl acetate	2	0	26.30	0.73	-0.71	YES	YES
Butane-2,3-diyl diacetate	4	0	52.60	0.87	-1.14	YES	YES
Ergosterol peroxide	3	1	38.69	6.71	-6.46	YES	YES
4-Hydroxycinnamic acid	3	2	57.53	1.46	-2.02	YES	YES
Bromelain	29	18	483.41	-11.65	2.32	NO	NO
Myristic acid	2	1	37.30	6.11	-4.31	NO	YES
Sinapic acid	5	2	58.12	1.46	-2.16	YES	YES
Flavoxanthin	3	2	49.69	10.06	-9.21	YES	NO
Furaneol	3	1	31.22	0.68	-1.06	YES	YES
tert-Butanol	1	1	20.23	0.53	-0.63	YES	YES
1-Triacontanol	1	1	20.23	14.70	-9.97	NO	NO
Ferulic acid	4	2	51.63	1.51	-2.11	YES	YES
Caffeic acid	4	3	77.76	1.15	-1.89	YES	YES
D-Galacturonic Acid	7	5	127.45	-2.34	0.50	YES	YES

Table 4: Absorption, distribution and metabolism profile of chosen phytochemicals as predicted by admeSAR

Parameters	Caffeic acid	4-Hydroxycinnamic acid	Ferulic acid	Sinapic acid	D-Galacturonic Acid
ABSORPTION					
Human oral bioavailability	Positive	Negative	Positive	Positive	Negative
Human intestinal absorption	Positive	Positive	Positive	Positive	Positive
P-glycoprotein substrate	Negative	Negative	Negative	Negative	Negative
P-glycoprotein inhibitor	Negative	Negative	Negative	Negative	Negative
DISTRIBUTION					
Subcellular localization	Mitochondria	Mitochondria	Mitochondria	Mitochondria	Mitochondria
METABOLISM					
CYP2C9 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP2D6 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP3A4 substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate	Non-substrate
CYP1A2 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP2C9 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP2D6 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
CYP2C19 inhibition	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor

Table 5: Toxicity prediction of selected phytochemicals

Parameters	Caffeic acid	4-Hydroxycinnamic acid	Ferulic acid	Sinapic acid	D-Galacturonic Acid
Carcinogenicity	Inactive	Inactive	Weak/low	Inactive	Inactive
Hepatotoxicity	Inactive	Inactive	Inactive	Inactive	Inactive
Ame's mutagenesis	Inactive	Inactive	Inactive	Inactive	Inactive
Respiratory toxicity	Inactive	Inactive	Inactive	Inactive	Inactive

In the assessment of ADME (Absorption, Distribution, Metabolism, and Excretion) and toxicological properties, only phytochemicals demonstrating both favorable docking scores and drug-likeness properties were subjected to analysis (Table 4).

Toxicity prediction was performed using the admetSAR server, considering parameters such as carcinogenicity, hepatotoxicity, Ame's mutagenicity, and respiratory toxicity. Strikingly, all selected compounds demonstrated an absence of such toxicities, affirming their safety for potential use, according to the assessments conducted by the admetSAR server Table 5.

Protein-ligand interaction

Interaction between phytochemicals having hsp90 inhibition property, good docking score and drug-likeness were assessed using Discovery Studio. For Caffeic acid, Van der Waals interactions involve Phe22, Asn51, Met98, Ile104, Leu107, Gly108, Tyr139, Phe170, Thr184, and Val186. Additionally, a hydrogen bond with Leu103 is reported, characterized by a bond length of 2.44 Å. 4-Hydroxycinnamic acid engages in Van der Waals interactions with Phe22, Asn51, Met98, Leu103, Leu107, Gly108, Tyr139, Phe170, Thr184, Val186, while a hydrogen bond with Trp162 has a bond length of 2.05 Å. Ferulic acid, with similar Van der Waals interactions, forms a hydrogen bond with Trp162 at a bond length of 2.11 Å. Sinapic acid exhibits Van der Waals interactions with Leu48, Ser52, Ala55, Asp53, Leu107, Tyr139, Thr184, Val186, and a hydrogen bond with Asn51 at a bond length of 2.87 Å. D-Galacturonic Acid engages in Van der Waals interactions with Leu48, Ala55, Met48, Phe138, Val150, Thr184, Val186, and forms hydrogen bonds with Asn51, Ser52, and Asp93, characterized by bond lengths of 2.21 Å, 2.97 Å, and 2.36 Å,

Table 6: Interaction between target molecule and chosen phytochemicals

Ligand name	Interaction	Amino acids	Bond length (Å)
Caffeic acid	Van der Waals	Phe22, Asn51, Met98, Ile104, Leu107, Gly108, Tyr139, Phe170, Thr184, Val186	**---**
	Hydrogen bond	Leu103	2.44
		Trp162	2.05
4-Hydroxycinnamic acid	Van der Waals	Phe22, Asn51, Met98, Leu103, Leu107, Gly108, Tyr139, Phe170, Thr184, Val186	---
	Hydrogen bonding	Trp162	2.05
Ferulic acid	Van der Waals	Phe22, Asn51, Met98, Leu103, Gly108, Tyr139, Phe170, Thr184, Val186	---
	Hydrogen bond	Trp162	2.11
Sinapic acid	Van der Waals	Leu48, Ser52, Ala55, Asp53, Leu107, Tyr139, Thr184, Val186	---
	Hydrogen bond	Asn51	2.87
D-Galacturonic Acid	Van der Waals	Leu48, Ala55, Met48, Phe138, Val150, Thr184, Val186	---
	Hydrogen bond	Asn51	2.21, 2.97
		Ser52	2.36
		Asp93	2.23
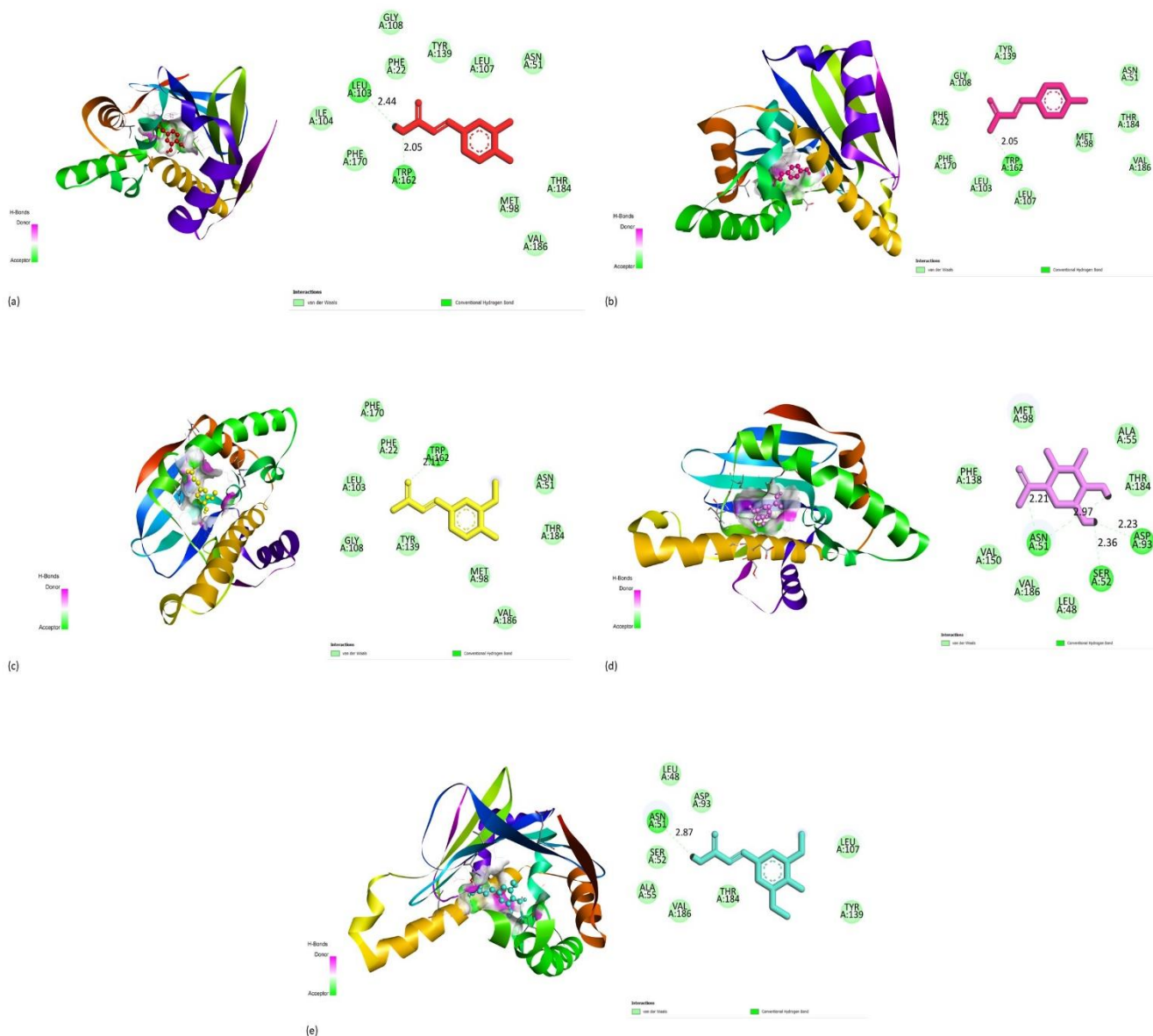
Figure 2 (a-e): Interaction between target protein and hit compounds- (a) Caffeic acid (b) 4-Hydroxycinnamic acid (c) Ferulic acid (d) D-Galacturonic Acid (e) Sinapic acid

respectively. These interactions highlight the specificity and diversity of molecular binding events, providing insight into the ligand-protein interactions within the studied system. Table 6 summarizes the result while figure 2 (a-e) depicts 2D representation of the interaction.

DISCUSSION

The presented study explores the potential of pineapple phytochemicals, including caffeic acid, ferulic acid, 4-Hydroxycinnamic acid, Sinapic acid, and D-Galacturonic Acid, as inhibitors of heat shock protein 90 (Hsp90) for the prevention of lung cancer. Hsp90, a crucial molecular chaperone, plays a significant role in the stabilization and function of various client proteins implicated in cancer development and progression. The in silico computational molecular docking conducted in this investigation reveals notable inhibitory activity of these phytochemicals against Hsp90, suggesting a potential mechanism for their anti-cancer properties. Beyond their inhibitory effects on Hsp90, the study highlights the compounds' promising biological activities, including efficacy against neoplastic conditions and pro-apoptotic properties. In discussing these findings, it is pertinent to consider the existing literature on Hsp90's role in lung cancer, emphasizing how targeting this molecular chaperone could offer a promising avenue for therapeutic intervention. The broader biological activities of the identified pineapple phytochemicals, beyond Hsp90 inhibition, prompt discussions on the specific cellular and molecular pathways influenced by these compounds, providing a more comprehensive understanding of their potential mechanisms of action in preventing lung cancer. Moreover, the study underscores the translational potential of these compounds by highlighting the favorable results from absorption, distribution, and metabolism assessments, coupled with promising toxicological profiles. This suggests that the identified phytochemicals not only exhibit in silico biological activity but also possess characteristics that make them suitable candidates for further preclinical and clinical investigations.

CONCLUSION

In conclusion, the findings of this study suggest that pineapple phytochemicals, particularly caffeic acid, ferulic acid, 4-Hydroxycinnamic acid, Sinapic acid, and D-Galacturonic Acid, hold promise as potential candidates for the development of novel therapeutic strategies for preventing lung cancer. However, it is crucial to acknowledge the need for further experimental validations, including in vitro and in vivo studies, to confirm the inhibitory effects on Hsp90 and elucidate the underlying mechanisms of action. Additionally, clinical studies are warranted to assess the safety and efficacy of these compounds in human subjects, ultimately advancing their potential role in lung cancer prevention.

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