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IN-SILICO EVALUATION OF CHAMAZULENE AS A POTENTIAL INHIBITOR OF KRÜPPEL-LIKE FACTOR 5 IN PANCREATIC CANCER: MOLECULAR DOCKING, PHARMACOKINETIC AND TOXICITY PROFILING AND MOLECULAR DYNAMICS SIMULATION

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ABSTRACT: Background: Pancreatic ductal adenocarcinoma (PDAC) remains one of the most aggressive and treatment-resistant cancers, often driven by aberrant KRAS signalling. Kruppel-like factor 5 (KLF5), a downstream transcription factor in this pathway, has emerged as a potential therapeutic target. Chamazulene, a bioactive sesquiterpene derived from *Matricaria chamomilla*, known for its anti-inflammatory and antioxidant properties, but its anticancer potential remains unexplored. **Objective:** To evaluate the drug-likeness, toxicity, and KLF5-targeting potential of Chamazulene using an integrated *in-silico* approach. **Methods:** Chamazulene's physicochemical and pharmacokinetic properties were assessed *via* SwissADME and PreADMET tools. Toxicity predictions were obtained using the GUSAR server. Molecular docking against homology-modelled KLF5 was performed using AutoDock Vina, and binding interactions were visualized. The top-scoring complex was further analyzed through 100-nanosecond molecular dynamics simulation using Desmond to assess structural stability under physiological conditions. **Results:** Chamazulene demonstrated favorable drug-likeness, high gastrointestinal absorption, BBB permeability, and a bioavailability score of 0.55. It showed no predicted hepatotoxicity or mutagenicity and had a high lethal dose (LD_{50}) value (>5000 mg/kg), although carcinogenic potential was flagged. Docking revealed a stable interaction with KLF5 (-5.9 kcal/mol), with hydrogen bonding to Tyr272 and favorable hydrophobic contacts. Molecular dynamics (MD) simulations confirmed complex stability, with RMSD values below 2 Å and preserved secondary structure. **Conclusion:** Chamazulene shows strong potential as a KLF5 inhibitor, with promising pharmacokinetic and structural interaction profiles. Further *in-vitro* and *in-vivo* validation is essential to confirm its therapeutic role in pancreatic cancer.

INTRODUCTION: Pancreatic cancer remains one of the most aggressive and lethal malignancies worldwide, ranking as the seventh leading cause of cancer-related deaths, with a five-year survival rate of less than 10% [1].

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Among its subtypes, pancreatic ductal adenocarcinoma (PDAC) accounts for over 90% of cases and is frequently characterized by early metastasis, late diagnosis, and resistance to conventional chemotherapy [2].

The persistent activation of oncogenic KRAS signalling pathways has been identified as a central driver of Tumorigenesis in PDAC, making it a prime target for therapeutic intervention [3, 4]. One downstream effector of KRAS signalling is Kruppel-like factor 5 (KLF5), a zinc finger

transcription factor that regulates genes involved in cell proliferation, survival, and epithelial transformation [5, 6, 7]. Overexpression of KLF5 has been documented in multiple solid tumors, including pancreatic, colorectal, and breast cancers, and is associated with poor prognosis and therapeutic resistance [8, 9, 10]. Inhibiting KLF5 has thus emerged as a promising strategy for attenuating tumor progression, particularly in KRAS-mutated malignancies [2, 11, 12, 13].

Natural products have long been a source of bioactive compounds with diverse pharmacological activities, offering unique structural scaffolds for drug development [14, 15]. Chamazulene, a sesquiterpene derivative commonly found in chamomile (*Matricaria chamomilla*), has been reported to exhibit anti-inflammatory, antioxidant, and cytoprotective properties [14].

Despite its known bioactivity, the anticancer potential of Chamazulene its ability to modulate transcription factors like KLF5 remains unexplored. This study was undertaken to assess the therapeutic potential of Chamazulene as a KLF5 inhibitor using an *in-silico* approach. We employed molecular docking, ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiling, and molecular dynamics (MD) simulations to evaluate its pharmacological suitability, binding affinity, and structural stability within the KLF5 binding pocket [16, 17, 18].

This computational strategy aims to provide preliminary evidence supporting Chamazulene as a candidate for further preclinical development in pancreatic cancer therapeutics.

MATERIALS AND METHODS: This study was designed to evaluate the drug-likeness, toxicity, binding affinity, and dynamic stability of Chamazulene, a naturally occurring sesquiterpene, as a potential inhibitor of Kruppel-like factor 5 (KLF5). The methodology integrated pharmacokinetic and toxicological prediction, molecular docking, and molecular dynamics (MD) simulation using widely accepted computational tools [11, 16, 17, 19].

Ligand Preparation: The 2D structure of Chamazulene (PubChem CID: 10719) was obtained from the PubChem database. It was converted into a 3D structure using MarvinSketch, followed by energy minimization using Avogadro (version 1.2.0) with the MMFF94 force field to optimize geometry and ensure conformational stability [13]. The optimized structure was saved in PDB format for further computational analysis.

ADMET and Toxicological Profiling: Pharmacokinetic and drug-likeness predictions were performed using SwissADME and PreADMET online tools [18, 20]. Evaluated parameters included Lipinski's Rule of Five compliance, bioavailability score, gastrointestinal absorption, blood-brain barrier (BBB) permeability, P-glycoprotein substrate status, and cytochrome P450 enzyme inhibition (CYP3A4, CYP2C19, and CYP2D6). *In-silico* toxicity profiling was carried out using the GUSAR server [18], which provided predictive insights into hepatotoxicity, immunotoxicity, mutagenicity, carcinogenicity, respiratory toxicity, and oral LD_{50} (rat model). These assessments aimed to evaluate the compound's therapeutic safety profile.

Target Selection, Homology Modelling, and Molecular Docking: KLF5 was selected as the molecular target due to its known involvement in oncogenic signalling, particularly in KRAS-driven cancers [12, 13, 21].

The FASTA sequence of human KLF5 (UniProt ID: Q13887) was retrieved and submitted to the SWISS-MODEL server for homology modelling [17]. The best-scoring model based on GMQE and QMEAN scores was selected for docking studies.

The protein structure was prepared using AutoDock Tools (version 1.5.7) [11] by adding polar hydrogens, Gasteiger charges, and defining torsions. AutoDock Vina (version 1.2) [16] was employed for molecular docking. The docking grid was centered on the predicted ligand-binding site of KLF5, and exhaustiveness was set to 8. The docking results were evaluated based on binding energy, hydrogen bond interactions, and occupancy of the active site pocket. Visualization and interaction analysis were performed using PyMOL (version 2.5) and Discovery Studio Visualizer [17].

Molecular Dynamics Simulation: To assess the structural stability and behaviour of the

Chamazulene-KLF5 complex under physiological conditions, a 100-nanosecond MD simulation was conducted using the Desmond module within the Schrödinger Suite (version 2023-1) [17, 19].

The docked complex was placed in an orthorhombic simulation box and solvated using the TIP3P water model. The system was neutralized with Na^+ and Cl^- counterions, and simulations were run under NPT ensemble conditions at 300 K and 1 atmospheric pressure.

Before the production run, the system underwent energy minimization and two-stage equilibration (NVT and NPT). The simulation was monitored for trajectory stability using Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF). Additionally, hydrogen bond occupancy, secondary structure retention, and protein–ligand interaction profiles were analysed using Maestro's Simulation Interaction Diagram tool. Key structural frames were visualized using PyMOL [17].

RESULTS:

Drug-Likeness and ADMET Profiling: Chamazulene's physicochemical and pharmacokinetic properties were evaluated using *in-silico* tools [11, 16, 18]. The compound complied with Lipinski's Rule of Five, demonstrating favorable oral bioavailability with a molecular weight of 184.28 g/mol, log P of 4.24, and one hydrogen bond donor and acceptor each [11, 18]. Its structural simplicity and low rotatable bond count enhance its drug-likeness.

Pharmacokinetic profiling revealed high gastrointestinal absorption and a bioavailability score of 0.55. Chamazulene was predicted to cross the blood-brain barrier (BBB), indicating potential central nervous system activity. However, it exhibited inhibition of major cytochrome P450 enzymes (CYP3A4, CYP2C19, CYP2D6), which could impact metabolic stability and raise drug interaction concerns [11, 18].

The compound also showed 97.7% plasma protein binding, with a short half-life (0.113 hours) and high total clearance (8.017 mL/min/kg), suggesting rapid systemic elimination and highlighting the need for optimization to improve pharmacokinetics **Table 1.**

TABLE 1: DRUG-LIKENESS AND ADMET PROPERTIES OF CHAMAZULENE

Parameter	Value
Molecular Weight	184.28 g/mol
Log Po/w	4.24
H-bond Donors / Acceptors	1 / 1
Bioavailability Score	0.55
BBB Penetration	Yes
CYP Inhibition	CYP3A4, 2C19, 2D6
Plasma Protein Binding (PPB)	97.7%
Half-life (t_{1/2})	0.113 hours
Total Clearance	8.017 mL/min/kg

Toxicity Profile: *In-silico* toxicological screening predicted a favourable safety profile for Chamazulene, with no hepatotoxicity, mutagenicity, or immunotoxicity, and a low respiratory toxicity score (0.017). However, carcinogenic potential was flagged, warranting further experimental evaluation. The predicted oral LD_{50} (>5000 mg/kg in rats) supports low acute toxicity **Table 2.**

TABLE 2: PREDICTED *IN-SILICO* TOXICITY PROFILE OF CHAMAZULENE

Toxicological Parameter	Result
Respiratory Toxicity	0.017 (Safe)
Hepatotoxicity	Inactive
Carcinogenicity	Active
Immunotoxicity	Inactive
LD_{50} (Oral, Rat Model)	>5000 mg/kg

Molecular Docking Analysis: Molecular docking against the Krüppel-like factor 5 (KLF5) protein revealed a best binding affinity of −5.9 kcal/mol. Key interactions included a hydrogen bond with Tyr272 (3.75 Å) and hydrophobic contacts with Thr269 and Arg273, stabilizing Chamazulene within the KLF5 binding pocket. Docking poses consistently ranged from −5.3 to −5.9 kcal/mol, indicating reproducible binding **Table 3.**

TABLE 3: SUMMARY OF MOLECULAR DOCKING PARAMETERS OF CHAMAZULENE WITH KLF5

Docking Parameter	Value
Best Binding Energy	−5.9 kcal/mol
Lowest Ranked Pose Energy	−5.3 kcal/mol
Hydrogen Bond Interaction	Tyr272 (3.75 Å)
Additional Interactions	Hydrophobic, van der Waals
Binding Site Occupancy	Favourable (central pocket)

A visual representation of the docking pose, highlighting hydrogen bonding and interaction residues, is provided in **Fig. 1.**

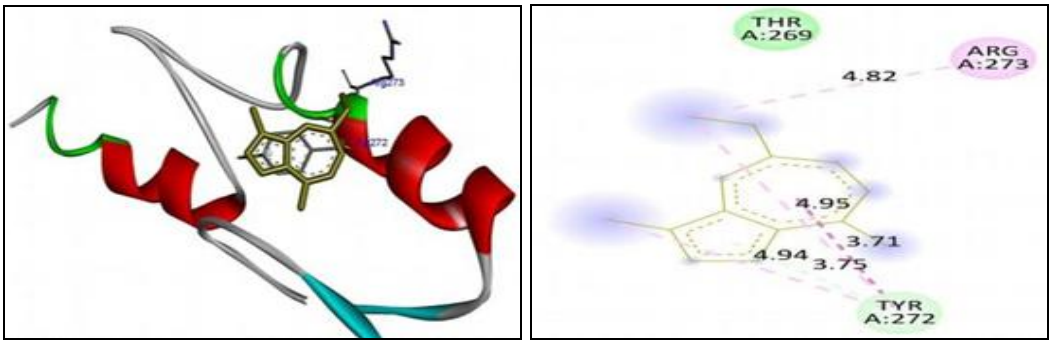

FIG. 1: MOLECULAR DOCKING POSE SHOWING INTERACTION OF CHAMAZULENE WITH THE LIGAND-BINDING DOMAIN OF KLF5. (Left) 3D interaction view within the binding cavity. (Right) Hydrogen bonding distances with key residues (TYR272, THR269, ARG273).

Molecular Dynamics Simulation: A 100 ns molecular dynamics simulation of the Chamazulene–KLF5 complex showed stabilization within 10 ns, with protein backbone RMSD under 2.0 Å and ligand RMSD below 2.5 Å throughout. Active site residues displayed low RMSF (< 1.5 Å), indicating a stable binding interface. The protein maintained its structural integrity, apart from expected flexibility in terminal and loop regions.

A summary of key metrics from the simulation is provided in **Table 4.**

TABLE 4: KEY MOLECULAR DYNAMICS PARAMETERS FOR THE CHAMAZULENE–KLF5 COMPLEX

Metric	Observation
Ligand RMSD	< 2 Å (Stable)
RMSF at Active Site	< 1.5 Å

These findings are further supported by RMSD and RMSF trajectory profiles shown in **Fig. 2** and **Fig. 3**, respectively.

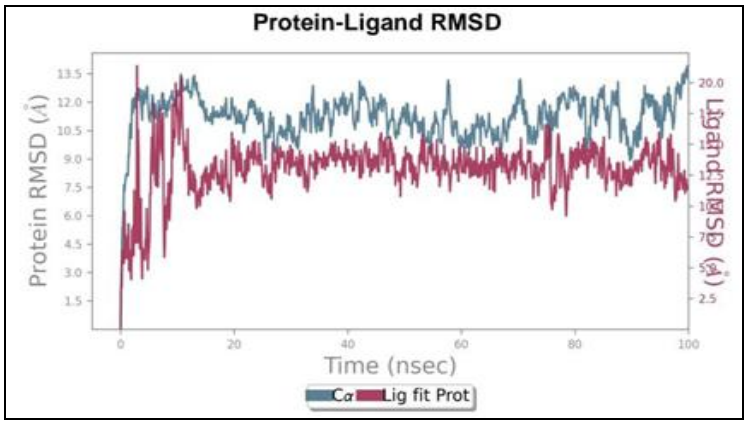

FIG. 2: PROTEIN-LIGAND RMSD OVER 100 NS. Note: Blue: protein Cα RMSD; Red: ligand RMSD (lig-fit-prot). RMSD values remained stable after 10 ns.

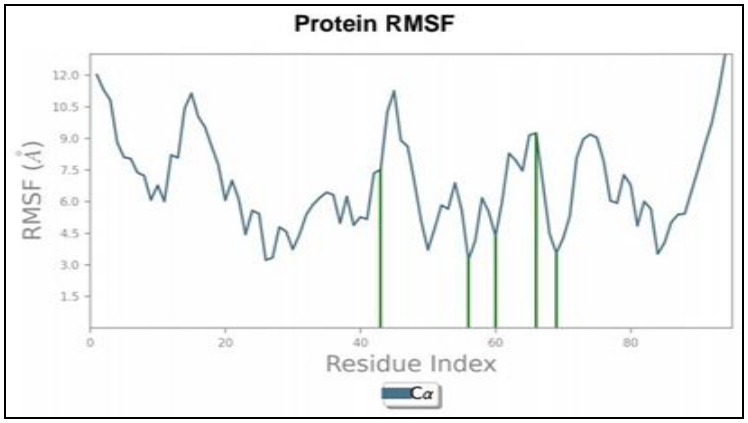

FIG. 3: RMSF PLOT OF KLF5 RESIDUES SHOWING LOCALIZED FLUCTUATIONS. Note: Binding site residues demonstrated low flexibility (< 1.5 Å), indicating stable ligand–receptor interaction.

DISCUSSION: The present *in-silico* investigation aimed to explore the therapeutic potential of Chamazulene, a naturally occurring sesquiterpene, as an inhibitor of the oncogenic transcription factor KLF5. Using a multi-tiered computational approach, including ADMET profiling, molecular docking, and molecular dynamics (MD) simulations, the study provides preliminary but compelling evidence supporting the candidacy of Chamazulene for further preclinical exploration in the context of pancreatic cancer.

Chamazulene demonstrated favorable drug-likeness, complying with all key parameters of Lipinski's Rule of Five, and exhibited a high gastrointestinal absorption and BBB permeability profile, suggesting that it can be effectively absorbed and potentially act on intra-tumoral targets. The bioavailability score of 0.55 is consistent with previous studies suggesting moderate oral availability for lipophilic terpenoids [14, 20, 22]. Additionally, the compound was found to inhibit cytochrome P450 enzymes such as CYP3A4, CYP2C19, and CYP2D6, which may influence its metabolic fate and necessitates further evaluation for drug–drug interaction potential in combination settings [18, 20].

The toxicity profile of Chamazulene was favorable, with predicted inactivity in hepatotoxicity, mutagenicity, and immunotoxicity assays. A high LD_{50} value (>5000 mg/kg) and a low respiratory toxicity score further suggest that Chamazulene exhibits low acute toxicity [18, 19]. Yet, a flagged signal for carcinogenicity warrants careful *in-vitro* validation before clinical consideration. These findings are consistent with prior work showing that several azulene derivatives possess low systemic toxicity while maintaining pharmacological efficacy [14].

The molecular docking results revealed that Chamazulene binds to the central hydrophobic pocket of KLF5 with a minimum binding energy of -5.9 kcal/mol, which is within the range reported for other phytochemical-KLF interactions [11, 13, 14]. The observed hydrogen bond interaction with Tyr272, alongside van der Waals and hydrophobic stabilization, implies a stable and specific binding mode [12, 21, 23, 24]. This interaction profile is notable, as Tyr272 lies within a region crucial for DNA-binding activity in zinc finger domains, suggesting that Chamazulene may exert functional inhibition by disrupting KLF5's transcriptional role [5].

Further validation through a 100-nanosecond MD simulation reinforced the stability of the ligand-receptor complex. RMSD values for both the protein backbone and the ligand stabilized within 10 ns, indicating equilibrium throughout the trajectory. Binding site residues demonstrated limited fluctuation, with RMSF values below 1.5 Å, which reflects a low degree of conformational drift and stable protein-ligand interaction under physiological conditions. Similar simulation patterns have been reported in successful lead optimization studies targeting transcription factors such as NF-κB and STAT3 [6, 19].

The retention of secondary structural elements (α-helices and β-strands) throughout the simulation further validates the conformational integrity of KLF5 in the presence of Chamazulene. These findings support the feasibility of Chamazulene not only as a passive binder but as a conformationally stable inhibitor. While these results are promising, it is important to note that computational predictions, though informative, must be corroborated through experimental studies such as surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), and cell-based functional assays.

This study underscores the potential of Chamazulene as a pharmacologically favourable and structurally compatible inhibitor of KLF5. Given the central role of KLF5 in KRAS-mediated signalling and epithelial transformation, the modulation of this target by natural compounds may offer a novel avenue for intervention in KRAS-driven pancreatic cancer.

Strengths of the Study: This study provides a computational perspective by integrating multiple *in-silico* tools including SwissADME, AutoDock Vina, and Desmond in evaluating the therapeutic potential of Chamazulene. By combining drug-likeness prediction, molecular docking, and molecular dynamics simulation, we were able to capture not only how well Chamazulene binds to KLF5, but also how stable that interaction remains under simulated physiological conditions.

The study's workflow follows reproducible, open-access methods, making it a strong foundation for future experimental research.

Limitations of the Study: While the computational approach provides valuable early insights, it cannot fully replicate the complexity of real biological systems. Factors like enzyme regulation, tissue distribution, immune response, and *in-vivo* metabolism are beyond the scope of prediction models. Additionally, the flagged carcinogenic potential, though only computationally inferred, highlights the need for experimental safety validation. Further wet-lab studies including *in-vitro* binding assays and *in-vivo* efficacy models are essential to confirm the biological relevance of these findings.

CONCLUSION: This study highlights Chamazulene as a promising natural compound with potential to inhibit KLF5, a key player in pancreatic cancer progression. Through molecular docking and simulation, we found that it binds stably and favourably to the target site, with good drug like and safety profiles predicted *in-silico.* While these results are encouraging, they represent an early step in the drug discovery process. To move forward, experimental validation through *in-vitro* and *in-vivo* studies is essential to confirm Chamazulene's biological activity, safety, and real-world therapeutic potential.

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CONFLICT OF INTEREST: The Authors declare no conflict of interest.

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