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Computational Evaluation of 1,8-Cineole from Cymbopogon Citratus Against Colon Cancer-Associated Protein Targets

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ABSTRACT: Colorectal cancer remains a major global health concern, creating a need for safer and more effective therapeutic candidates. This study evaluated phytochemicals from Cymbopogon citratus against CDK2 and the APC using molecular docking, ADMET profiling, and molecular dynamics simulations. Several compounds, including isoorientin, rutin, chlorogenic acid, luteolin, quercetin, and caffeic acid, showed favorable predicted docking scores. Although 1,8-cineole was not the top-ranked compound, its comparatively favorable ADMET profile supported its selection for further analysis. Docking indicated that 1,8-cineole formed noncovalent interactions with both target structures. During 100 ns molecular dynamics simulations, the complexes maintained overall structural stability, compactness, and controlled conformational fluctuations. Principal component and free energy landscape analyses further supported the presence of stable conformational states. These findings identify 1,8-cineole as a promising computational candidate for further colorectal cancer research. Experimental studies are required to confirm its target interactions and biological activity.

1. INTRODUCTION

Colorectal cancer (CRC) is a worldwide issue in health, as it is one of the most common malignancies identified and the cause of cancer-related mortality in the world. This is likely to be a significant burden to the global population over the next few decades as the world faces the aging of the population, population growth, and the rising prevalence of lifestyle-related risk factors. Even with the improvements in screening, molecular classification and treatment, recurrence of the diseases, resistance to therapeutic treatment, and toxicity of the treatment remain barriers to clinical outcome, which highlights the need to develop new approaches to treatment(1–5).

Colorectal carcinogenesis is a complex, multistage process, which presupposes the creation of genetic and epigenetic alterations disrupting the intestinal epithelial homeostasis, the cellular growth, differentiation, and apoptosis. Loss-of-function changes in the adenomatous polyposis coli (APC) gene are some of the molecular events that have been implicated in the initiation of tumors, and are considered to be a focal event in the classical adenoma-carcinoma progression. APC is a tumor-suppressor protein which helps to regulate canonical Wnt/ β -catenin pathway through regulating of β -catenin stability and Wnt-induced transcription. APC dysfunction may facilitate abnormal β -catenin signaling and intestinal epithelial growth and tumor formation-related genes (6–10). Simultaneously, cyclin-dependent kinase 2 (CDK2) is a serine/threonine kinase, which regulates cell-cycle progression, especially during G1/S-phase, and DNA replication via interactions with cyclins E and A, which makes it a promising target in the study of small-molecule-mediated regulation of cancer-associated proliferation (11–15). The unique, yet complementary functions of APC-related signaling and CDK2-mediated cell-cycle regulation give a reason why they should be studied in the molecular factors of colon cancer.

Surgery, chemotherapy, radiotherapy in certain clinical cases, targeted therapy, and immunotherapy are the current treatment options of colon cancer based on the stage of disease and molecular features. Though there are agents like 5-fluorouracil, oxaliplatin, irinotecan, and molecularly targeted therapy that have enhanced clinical management, they may not be effective due to systemic toxicity, heterogeneity of tumors, acquired resistance, and variability in patient responses(16–22). These drawbacks have heightened the process of seeking structurally differentiated compounds that can interact with cancer-related molecular targets and can be used as leads in subsequent development of therapeutic agents.

There is an increasing interest in medicinal plants as developing sources of bioactive compounds that could have anticancer effects. Flavonoids, phenolic compounds, terpenoids, and other related secondary metabolites have been shown to have various biological activities which include the effects against oxidative stress, inflammation, cellular proliferation and apoptosis (23–26). One of such sources, *Cymbopogon citratus* Stapf which is also known as lemongrass has been of interest due to its heterogeneous phytochemical content and the purported pharmacological functions. It has citral, geraniol, myrcene, and limonene as its constituents though this depends on the origin of the plants used and the conditions under which the extracts and essential oils are extracted. Anticancer-relevant activities of *C. citratus* extracts and selected constituents have been reported in experimental experiments, but there are no general cytotoxic or antiproliferative effects that define their molecular interactions, specificity or target, or pharmacological activity (27–33). Computational study with a specific aim to elucidate the possible role of these phytochemicals in colon cancer-related proteins could thus prove to be useful.

Computational methods that are based on structure offer useful tools to initial screening and prioritization of natural-product candidates. Molecular docking can be used to predict protein-ligand binding modes and profiles, whereas ADMET and pharmacokinetic analyses can be used to give initial evaluations of drug-likeness and pharmacological properties. The conformational behaviour and stability of interaction of the chosen protein-ligand complexes can also be analysed using molecular dynamics (MD) simulations in specific conditions of the simulation. These techniques alone are not sufficient to determine the biological efficacy, but when combined together can yield mechanistic hypotheses and also determine compounds that can be subjected to subsequent experimental testing (34–37).

Although *C. citratus* has been reported to have biological activities, there are gaps in the literature regarding the possible interactions of the phytochemical constituents of *C. citratus* with APC and CDK2 in relation to colon cancer. Thus, the current work was conducted to assess specific *C. citratus* phytochemicals in terms of APC and CDK2 with the help of molecular docking, ADMET/pharmacokinetic prediction, and molecular dynamics simulations. This method was intended to describe the binding interactions of interest predicted, evaluate initial pharmacological characteristics, and the transient behavior of the target protein-ligand complexes and thus aid the prioritization of viable compounds to be further experimented with.

MATERIAL AND METHODS

1.1. Computational Workflow

A structure-based workflow of computational studies was used in order to examine the possible interactions of *Cymbopogon citratus* phytochemicals with human cyclin-dependent kinase 2 (CDK2) and adenomatous polyposis coli (APC). The following workflow was involved in the preparation of ligands and proteins, molecular docking, ADMET prediction, molecular dynamics (MD) simulations, principal component analysis (PCA), and free energy landscape (FEL) analysis. The structures of proteins were found in RCSB Protein Data Bank and the ligand structures were found in PubChem. AutoDock Tools, BIOVIA Discovery Studio, PyMOL and GROMACS were used to prepare, visualize and analyze the interactions(38–40).

1.2. Ligand Preparation

Computational screening of phytochemicals was done to screen thirty-two phytochemicals that had been reported in *Cymbopogon citratus*. Their three-dimensional structures were obtained in PubChem in the SDF format and the two-dimensional chemical structures were made with ChemDraw and are listed in Supplementary Table 1. The structure of the ligands was optimized using geometry followed by the transformation of the ligand structures to the format needed to perform molecular docking(41,42).

1.3. Protein Structure Preparation

Human CDK2 (PDB ID: 2A4L) and APC (PDB ID: 3NMW) were obtained in their experimentally-determined structures in the RCSB Protein Data Bank. The preparation of the protein preparation was done with BIOVIA Discovery Studio. Co-

crystallized ligands and other unnecessary water molecules were eliminated where necessary and the hydrogen atoms were added and the appropriate protonation states assigned. Minimization of energy was carried out to minimize the undesirable steric interactions and set up the structures to be docked(43,44).

1.4. Molecular Docking

The AutoDock Tools were used to prepare the protein and ligand structures into PDBQT format. The blind molecular docking was carried out to investigate potential binding regions on the surfaces of the protein, a rigid receptor and flexible ligands were used. The poses that were obtained were ranked based on the predicted binding energy and the top-ranked complexes were examined with the help of the molecular visualization software to describe hydrogen bonding, hydrophobic contacts, and other noncovalent contacts.

1.5. ADMET and Drug-Likeness Prediction

The ADMETlab 2.0 web server was used to predict the pharmacokinetic, toxicity-related and drug-likeness properties of the chosen phytochemicals. Relevant physicochemical descriptors and predictions were considered in the analysis, which included the absorption, distribution, metabolism, excretion, and toxicity. These were computational estimates that were employed to prioritize compounds to be further analysed(45).

1.6. Molecular Dynamics Simulations

The simulation of the stability of structures and dynamics of the chosen protein-ligand complexes was carried out with the help of GROMACS version 2023.4. The parameters of proteins were set with the help of the CHARMM36 force field and the parameters of compatible ligands were created with the help of an adequate parameterization scheme. The solvation of each system was in a cubic box with a full volume of TIP3P water with a minimum distance of 1.0 nm between the protein and the box walls. The systems were neutralized with addition of counterions(46–48).

The steepest-descent algorithm was used to minimise the energy of the solvated systems over 5000 steps and then equilibrating under NVT and NPT systems at 310 K (100 ps each). Periodic boundary conditions were then used to simulate a 100 ns production under periodic boundary conditions. Hydrogen-containing covalent bonds were kept constant with the help of the LINCS algorithm with a 2fs time of integration. Short-range interactions were also computed with the Verlet cutoff scheme and the cutoff was 1.2 nm whereas the long-range electrostatic interactions were computed with the Particle Mesh Ewald method(49–52).

1.1. Principal Component Analysis

The covariance matrix of positional fluctuations of atoms was used to perform PCA to describe the most prominent overall movements and conformational flexibility of the protein-ligand complexes in the MD trajectories. The eigenvalue decomposition and covariance matrix were worked out with the gmx covar and gmx ana eig modules of GROMACS, respectively. The projections of the two main components (PC1 and PC2) were compared to compare the conformational space explored by the complexes(53).

1.2. Free Energy Landscape

The PC1 and PC2 projections of PCA were used to perform an analysis of the FEL. The conformational probability distribution of the conformational free energy was computed as the relative Gibbs free energy based on:

$$G(X) = -k_B T \ln P(X)$$

with k_B , the Boltzmann constant, T , the temperature of the simulation and $P(X)$ the probability of a given conformational state. Energetically favorable conformational basins were then determined using the resulting landscapes and studied the conformational preferences and transitions of the protein-ligand complexes(54).

3. RESULTS AND DISCUSSION

Molecular docking Analysis

Molecular docking was done to examine how 32 phytochemicals of *Cymbopogon citratus* are expected to behave in terms of their binding behavior with human cyclin-dependent kinase 2 (CDK2; PDB ID: 2A4L) and adenomatous polyposis coli

(APC; PDB ID: 3NMW). The docking scores were converted to predicted binding energies in kcal/mol where more negative scores were more favorable predicted binding based on the scoring function. These values were compared to give a prioritization of the ligand not as a real-world measurement of experimental binding affinity.

The docking outcomes revealed that the binding energies of the phytochemicals screened were predicted to vary (Table S2, Supporting Information). In the case of CDK2 the predicted binding energies were between -4.02 and -10.33 kcal/mol. The best predicted binding score was isoorientin (-10.33 kcal/mol), then luteolin (-9.21 kcal/mol), chlorogenic acid (-8.97 kcal/mol), quercetin (-8.77 kcal/mol) and caffeic acid and rutin (both -8.36 kcal/mol). These findings suggest that a number of oxygenated phytochemicals and especially those containing flavonoids and phenolics showed relatively good predicted interactions with CDK2.

In the case of APC, the trends of binding energy were between -4.31 and -8.88 kcal/mol (Table S3, Supporting Information). Rutin was shown to have the highest predicted binding score of (-8.88 kcal/mol), then isoorientin (-8.34 kcal/mol), chlorogenic acid (-8.09 kcal/mol), luteolin (-7.73 kcal/mol), and geranyl acetate (-6.92 kcal/mol). Other compounds that portrayed relatively good predicted binding scores include Quercetin (-6.90 kcal/mol), citronellyl acetate (-6.81 kcal/mol), alpha-bergamotene (-6.51 kcal/mol) and spathulenol (-6.48 kcal/mol). The variations in the ranking of the ligands of CDK2 and APC indicate that the interaction preferences predicted were target-specific.

Isoorientin, rutin, chlorogenic acid and luteolin were some of the best-ranked phytochemicals across both targets, but in different relative positions in both CDK2 and APC. Isoorientin was the highest predicted binding score with respect to CDK2, and rutin was the high-ranking one with APC. Conversely, 1,8-cineole, which was predicted to bind to CDK2 with a binding energy of -5.29 kcal/mol, and to APC with a binding energy of -5.10 kcal/mol was not in the top-ranked docking compounds. However, it was chosen to be further analyzed by molecular dynamics due to its relatively good ADMET profile. This choice is an indication of a multi-parameter prioritization approach where pharmacokinetic suitability was predicted, and docking performance was factored in, as opposed to picking off the compounds based on docking score.

The docking findings present preliminary structural data that the specific *C. citratus* phytochemicals have a potential to interact well with CDK2 and APC. Nevertheless, docking scores cannot determine binding affinity or any target inhibition or anticancer activity alone. Hence, the interactions that are predicted will further have to be evaluated in terms of residue-level analysis, molecular dynamics simulations.

ADMET

The ADMET profiling was carried out on the ADMETLab 2.0 platform to assess pharmacokinetic, physicochemical, and toxicity-related characteristics of the phytochemicals that were found in *Cymbopogon citratus* (Table 2). The evaluation encompassed molecular weight, lipophilicity, aqueous solubility, topological polar surface area, intestinal absorption, membrane permeability, blood-brain barrier permeability, plasma protein binding, unbound fraction, cytochrome P450 inhibition, and a few toxicity endpoints, such as hERG channel inhibition, Ames mutagenicity, drug-induced liver toxicity, carcinogenicity, and chemical aggregation potential. It is these parameters that were taken into account to find compounds with a relatively good balance of physicochemical suitability, estimated absorption, systemic distribution, metabolic behavior and safety.

The best phytochemicals evaluated had a relatively ideal overall ADMET profile and thus 1,8-cineole was chosen as the lead to carry out further molecular dynamics simulations. Its moderate polar character, low molecular weight, and lipophilicity were in line with physicochemical properties that are likely to be beneficial in membrane permeation and gastrointestinal absorption. The calculated intestinal absorption and membrane permeability properties further indicated that 1,8-cineole could have appropriate pharmacokinetic capabilities to be exposed to systemically, after oral intake. Computational predictions of blood-brain barrier permeability and plasma protein-binding profile also suggested the possibility of tissue distribution but the computational predictions were not to be construed as direct evidence of in vivo bioavailability or tissue accumulation.

The predictions based on toxicity indicated a relatively low likelihood of hERG channel inhibition, Ames mutagenicity, and liver injury due to the drug, in the case of 1,8-cineole. Moreover, it exhibited a relatively low predicted interaction potential with the key cytochrome P450 isoforms indicating a reduced risk of metabolic interference and cytochrome P450-based drug-

drug interactions. The compound was also predicted to have low aggregation tendency that could minimize chances of nonspecific aggregation related binding during computational assays.

Even though 1,8-cineole did not score best in the docking score against either CDK2 or APC, the choice of 1,8-cineole to be subjected to molecular dynamics analysis was made based on the combined analysis of the docking performance and the predicted pharmacokinetics and safety profiles. Therefore, 1,8-cineole was considered a computationally-feasible candidate with an appealing ADMET profile instead of being based on binding-energy ranking. These results justify its further exploration with molecular dynamics simulations and experimental research to reveal its stability, biological implication, and anticancer potential of its interactions with the chosen target proteins.

Binding Interaction Analysis of 1,8-Cineole with APC

The pose of molecular docking revealed that 1,8-cineole was able to fit the modeled binding site of APC (PDB ID: 3NMW) using hydrogen-bonds and hydrophobic interactions (Figure 1). It was found that a typical hydrogen bond existed between the oxygen atom of 1,8-cineole and ARG66, and this could indicate the existence of polar anchoring between the ligand and the protein. Moreover, an alkyl interaction with ARG66 was also found which can also contribute to the accommodation of the ligand in the binding region. Such interactions suggest a positive orientation of predicted binding of 1,8-cineole in the APC structure modeled. But, the biological importance of such an interaction needs to be further confirmed by molecular dynamics simulations.

Binding Interaction Analysis of 1,8-Cineole with CDK2

The docked complex of 1,8-cineole and CDK2 (PDB ID: 2A4L) showed that it had a few non-covalent interactions with hydrophobic residues in the predicted binding region (Figure 2). A π -sigma interaction was observed with PHE80, with further alkyl and π -alkyl interactions observed with LEU134, VAL64, LYS33, ALA144, ALA31 and VAL18. Such hydrophobic interactions can help in the positioning and stabilization of 1,8-cineole in the modeled binding region of CDK2. The fact that there are several contacts indicates that there is good ligand-protein complementary, but the docking pose cannot be sufficient to determine that the compound inhibits CDK2 or that the compound is within the canonical binding site.

Molecular Dynamics Simulation Analysis

GROMACS was used to conduct a 100 ns all-atom molecular dynamics simulation of the APC-1, 8 cineole (PDB ID: 3NMW) and CDK2-1, 8 cineole (PDB ID: 2A4L) complexes to determine their structural stability and conformational changes. Simulations were done with the corresponding apoproteins and taken as references to determine the effect of ligand binding on the dynamics of the protein. Root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), solvent-accessible surface area (SASA), intermolecular hydrogen bonding, principal component analysis (PCA) and free energy landscape (FEL) analysis were used to analyze the trajectories. All these parameters then were analyzed to analyze global stability, residue-level flexibility, structural compactness, solvent exposure, persistence of ligand-protein interactions and the conformation states explored by each system during the simulation.

1. Molecular Dynamics Simulation Analysis of APC-1, 8-Cineole complex

RMSD Analysis

To determine the structural stability of the apoprotein and APC-1,8-cineole complex as a whole, the backbone RMSD profiles were performed to evaluate the structural stability of the complex in the course of the 100 ns long simulation (Figure 3A-B). In both systems there was an initial equilibration phase and the dynamic fluctuations along the trajectory. Most of the simulation had values of RMSD in the range of 0.15-0.45 nm, but there were temporary values of 60-70 nm. After these oscillations, the two systems were back in similar RMSD values towards the end of the simulation.

The change in RMSD of the ligand-bound complex was not steadily increasing or did not exhibit a significant structural deviation as compared to the apoprotein. Despite the fluctuations observed in the complex in the middle and later part of the trajectory, the overall profile of RMSD of the complex was similar to the one of the unbound protein. These observations indicate that 1,8-cineole was able to fit without significant destabilizing effects globally on the modeled APC structure. But the similar RMSD profiles suggest that no significant decrease in global backbone mobility was observed with the binding of

the ligands.

RMSF Analysis

The RMSF profile calculated in residue-wise was used to assess the local flexibility and determine areas that experience an increase in conformational changes (Figure 3C). The fluctuations of most of the residues in both systems were relatively low (generally, less than about 0.30 nm) suggesting that the central regions of the modeled protein were relatively stable during the simulation. The apoprotein systems (ligand-bound and apo-bound) had generally similar patterns of fluctuation throughout most of the sequence.

Greater variability was found towards the terminal regions, especially in the region close to the C-terminal end where the RMSF was about 1.5-1.8nm. This high terminal mobility is normally linked to solvent exposure and lack of extensive structural constraints. Moderate changes in several loop regions were also observed, although there were no large-scale changes in the extent of residue mobility in the ligand bound system. The general indication of the RMSF profile is that 1,8-cineole did not cause a significant further increase in the flexibility of the modeled APC structure, but stabilization of the binding site at the residue level would need a more localized study of the interacting residues.

Radius of Gyration Analysis

To measure the behavior of the protein in the simulation, the radius of gyration was computed to measure the compactness and folding behavior of the protein (Figure 3D). The apoprotein and APC-1,8-cineole complex were found to have relatively constant Rg values with most values being in the range of about 210-220 nm. The profiles had insignificant variations without an increasing or decreasing of the total radius of gyration.

The similarity of the Rg values suggests that the given 1,8-cineole did not affect the global compactness of the protein. The lack of significant change in Rg indicates that there was no significant expansion, unfolding or collapse of the modeled protein structure during the 100 ns simulation due to the ligand binding.

Solvent-Accessible Surface Area Analysis

To examine the change in protein solvent exposure and behavior of the proteins, the solvent-accessible surface area was evaluated (Figure 3E). The values of the SASA of both systems were fluctuating around 155 and 185 nm² during the simulation. Comparatively strong changes were observed in the trajectory of the apoprotein, but the APC-1,8-cineole complex has a rather similar range of SASA following the initial equilibration period.

The fact that there was no significant and sustained change in the SASA indicates that no significant difference was observed in the overall solvent exposure of the modeled APC structure due to the binding of 1,8-cineole. The fluctuations that are observed are in line with normal conformational rearrangement during molecular dynamics simulations as opposed to large scale structural unfolding, or significant exposure of previously buried parts.

Intermolecular Hydrogen-Bond Analysis

Hydrogen-bonding profile between APC and 1,8-cineole was observed to determine the existence of polar interactions in the course of the simulation (Figure 3F). The quantity of hydrogen bonds varied between zero and three with the majority of the trajectory being intermittent formation of one or more hydrogen bonds. The number of hydrogen bonds was occasionally decreased and increased at various points in the simulation, which suggests that polar contacts were not sustained throughout the simulation.

The hydrogen bonding which is intermittent, could also help stabilize and reposition 1,8-cineole in the binding region that was modeled. Nevertheless, the stability of the complex is expected to be determined significantly by hydrophobic and van der Waals (and other nonpolar) interactions rather than hydrogen bonding since 1, 8- cineole has only one oxygen atom in its structure. Thus, dynamic ligand-protein contacts are favored by the hydrogen-bond profile, but not by itself to create consistent high-affinity binding.

Principal Component Analysis

Principal component analysis has been carried out to describe the collective motions that are prevailing in the APC-1,8-cineole complex during the simulation. The trajectory projection on the first and second principal component indicated that

the projection was two-dimensional with a number of different conformational clusters (Figure 4). The initial sampling of the trajectory was over a relatively wide range of conformational states with subsequent emergence of more populated clusters in other regions of the PC1–PC2 space.

The existence of more than one conformational cluster means the protein have more than a single dynamically accessible state in the course of the simulation. The high density of the populated areas implies preferential conformational equilibria, and the interchange of clusters between clusters implies collective changes of structure. These data show that the APC-1,8-cineole complex was dynamically active but probed specific conformational regions, and did not experience structural displacement.

Free Energy Analysis

The projections of PC1 and PC2 were used to build the free energy landscape to determine the conformational states of the APC cineole complex that were energetically accessible (Figure 5). There were several low-energy basins, which are denoted in the blue and green areas, scattered throughout the principal-component space. The largest low energy basin was found in the area of positive PC1 and slightly negative PC2, and other favorable basins were found in the other areas of the conformational landscape.

The fact that there are a number of energy minima indicates that the complex took on a number of energetically favorable conformations during the simulation. These basins can be related to different but reachable structural states related to ligand accommodation and flexibility of the proteins. The specified energy minima, along with the lack of the progressive structural drift in the RMSD, Rg and SASA profiles, confirm the dynamical stability of the modeled APC-1,8-cineole complex. However, the presence of several minima also points to the conformational changeability but not absolute structural rigidity.

2. Molecular Dynamics Simulation of the CDK2–1,8-Cineole Complex

RMSD Analysis

To determine the general structural stability of the CDK2 in the unbound and 1,8-cineole-bound state the backbone RMSD profiles were compared (Figure 6A–B). Both the systems showed a period of equilibration at the beginning of the simulation, after which it was relatively stable. The apoprotein backbone RMSD was also found to be around 0.10-0.28nm with minimal fluctuations between 0.10-0.27nm with the CDK218-cineole complex. When using around 1520ns, RMSD profiles of both systems were similar and there was no gradual increase or significant structural difference.

Protein-fitted RMSD profiles also exhibited the same behavior with the most values falling between about 0.15 and 0.31 nm. In the second half of the simulation, the complex showed a couple of greater fluctuations compared to the apoprotein, but still, the fluctuations were within a very limited range. Generally, the fact that there was no long-term structural drift indicates that 1,8-cineole did not significantly destabilize the modeled structure of CDK2 over the course of the 100ns simulation.

RMSF Analysis

The RMSF profile of the local flexibility of the apoprotein and CDK2-1,8-cineole complex was computed in the residue-wise (Figure 6C). The relative fluctuations in most of the residues in both systems were relatively low (below about 0.20 nm) which suggests that there is limited local mobility of most of the protein structure. The profiles of the fluctuation of the apoprotein and the complex with the ligand were generally comparable, indicating that 1,8-cineole did not significantly change the residue-level flexibility of CDK2.

A greater variation was found in the areas of selection loops or terminals. The apoprotein exhibited a high amplitude fluctuation at around 0.50 nm around the N-terminal region, as compared to the N-terminal region in the ligand bound system which had a relatively smaller amplitude. Other moderate fluctuations were noted at various residues that are scattered across the sequence, as well as around the C-terminal end. These regional differences are in line with the natural variability of loop and terminal regions. The general results of the RMSF indicate that the CDK2-1,8-cineole complex had a stable residue-wise dynamic structure and that there was no global increase in protein flexibility upon ligand binding.

Radius of Gyration Analysis

To measure the compactness and the folding of CDK2 in the course of the simulation, the radius of gyration was computed

(Figure 6D). The apoprotein and CDK2-1,8-cineole complexes had fairly constant values of R_g , most of which were around the range of 2.43–2.49 nm. The trajectories in the profiles exhibited slight variations and no long-term growth or decrease during the 100ns trajectory.

Their similar values of R_g show that the compactness of CDK2 across the world was maintained in the presence of 1,8-cineole. There is no significant change in radius of gyration so it is possible that during the simulation no significant protein expansion, collapse or unfolding was induced by the ligand binding.

Solvent-Accessible Surface Area Analysis

SASA profile was presented in order to determine modifications in protein solvent exposure and conformational behaviour (Figure 6E). The values of SASA of the two systems varied around 245–265 nm². This led to the apoprotein showing slightly higher variability over the course of the trajectory, and the solvent-accessible surface area of the apoprotein changing relatively consistently, especially in the second half of the simulation, which was seen for the CDK2-1,8-cineole complex.

The fact that there was no significant and sustained difference in the SASA of the two systems indicates that there was no significant difference in the total solvent exposure of CDK2 by 1,8-cineole. Their observed variations may be due to normal conformational changes during the simulation and not a large scale structural rearrangement or unfolding.

Intermolecular Hydrogen-Bond Analysis

To measure how long the polar interactions were retained in the simulation, the number of hydrogen bonds between CDK2 and 1,8-cineole was tracked (Figure 6F). The hydrogen-bond profile revealed that mostly the interactions were intermittent and the number of hydrogen bonds tended to go between zero and one. There were occasional increases to two hydrogen bonds at various time points and a temporary higher value was found at the start of the trajectory.

The discontinuity of the hydrogen-bonding pattern indicates that hydrogen bonds can help to accommodate the ligands, but are not maintained throughout the simulation. Given the polar deficit of 1,8-cineole, hydrophobic and van der Waals forces are also likely to play a significant role in the binding of the ligand in the modeled CDK2 binding region. Thus, the hydrogen-bond analysis can be used to support the existence of dynamic ligand-protein interactions as opposed to a stable hydrogen-bond network.

Principal Component Analysis

To describe the main collective motions of the CDK2-1,8-cineole complex in the 100-ns simulation, principal component analysis was done. The projection of the trajectory to the first two major components in 2D showed that there are a few regions that are conformationally populated (Figure 7). A highly populated cluster was seen around the negative PC1 and slightly negative PC2 area with another group of conformational populations pushing towards PC1 positive and PC2 higher values.

Their existence in distinct clusters implies that the complex was able to explore several accessible conformational states in the course of the simulation. The highly populated areas are states of preferential conformations, and the transitions between the state are collective structural rearrangements. The PCA profile is therefore indicative of the CDK2-1,8-cineole complex being dynamically flexible, but with a smaller repertoire of conformational states than previously thought, as opposed to a free structural repositioning.

Free Energy Landscape Analysis

The first two major components were used to build the free energy landscape to identify those conformational states of the complex between CDK2 and 1,8-cineole that are energy favorable (Figure 8). There was a high level of low-energy basin on the landscape in the direction of the negative PC1 and slightly negative PC2 area portrayed by the blue region. Furthermore, other higher-energy and intermediate-energy states stretched in the PC1-PC2 space, which shows that there were other conformational states.

The low-energy basin is dominant indicating that the complex was more likely to be in a stable conformational state throughout the simulation. The presence of the extra surrounding basins implies conformational flexibility and changes between accessible structural states. The FEL results in combination with the stable RMSD, R_g and SASA profiles suggest the

preservation of the overall structural integrity of the CDK2-1,8-cineole complex in the simulated period. The fact that there are several conformational regions, however, means that the complex was not completely rigid but was dynamically active.

All the 100 ns MD simulations showed that both APC-1,8-cineole and CDK2-1,8-cineole complexes were in satisfactory structural stability without significant conformational destabilization. The profiles of the RMSD, Rg and SASA profiles indicated that the global balance and compactness remained intact whereas the RMSF analysis revealed that variations existed predominantly within the flexible terminal and loop areas. Favourable low-energy basins in the FEL analysis and intermittent hydrogen bonding as a characteristic of PCA clusters also indicated the dynamic accommodation of 1,8-cineole in both protein structures models. These results indicate that 1,8-cineole is computationally stable with APC and CDK2, but needs to be experimentally validated to be able to engage and be biologically active.

4. DISCUSSION

4.1. Combined Computational Analysis of *Cymbopogon citratus* Phytochemicals.

The current research has used a combination approach of computation to determine how phytochemicals of *Cymbopogon citratus* may interact with two cellular proliferation- and colorectal cancer-related proteins, CDK2 and armadillo repeat domain of APC. The molecular docking revealed variations in the predicted binding preferences of the screened compounds and ADMET profiling and molecular dynamics was applied to justify the prioritization and dynamic assessment of 1,8-cineole.

The docking outcomes showed that some of the oxygenated phytochemicals, especially isoorientin, the rutin, chlorogenic acid, luteolin, quercetin, and caffeic acid had relatively good predicted binding scores. Isoorientin had the best docking score compared to CDK-2 and rutin the best with the modeled APC domain. The ranking based on the targets implies that the chemical characteristics of the ligands had different interactions with the structural environments of the two proteins. The good performance of various flavonoid and phenolic compounds could be attributed to the presence of more than one oxygen group in their functional groups that can facilitate polar and hydrogen-bonding interactions. However, docking scores are relative to the scoring operation used, and must be considered as relative computational approximations, but not binding affinity.

Despite the fact that 1,8-cineole was not one of the highest-ranked compounds based on the docking score, the compound was chosen to be further analyzed in terms of molecular dynamics due to its relatively good ADMET profile. This choice is significant since docking affinity is not the sole approach that considers absorption, distribution, metabolic activity, toxicity and other pharmacokinetic factors. This prioritization of 1,8-cineole was hence more of a multi-parameter approach, and not necessarily the choice of a compound based on its docking score.

4.2. Pharmacokinetic and Toxicological Relevance of 1,8 -Cineole.

The predictions of the ADMET profile showed that 1,8-cineole had a relatively good physicochemical and pharmacokinetic profile compared to other phytochemicals tested. Its low molecular weight and favorable lipophilicity could facilitate membrane permeation and the potential of systemic exposure is indicated by the predicted intestinal absorption and membrane permeability. The distribution-related properties that were predicted also add to the fact that the compound can be able to access the various tissue compartments. But these findings are in silico estimates, which should not be taken as verbatim that these substances are being in vivo orally bioavailable, accumulating in tissues, having therapeutic exposure.

The predictions based on the toxicity also indicated a comparatively low likelihood of hERG inhibition, Ames mutagenicity, and liver injury induced by the drug. Moreover, the low inhibitory potential of major cytochrome P450 isoforms predicted could show a decreased risk of metabolic interference. Such results justify the priority of computation of 1,8-cineole in further studies. However, the ADMET prediction systems are trained on experimental data, and they can give a false-positive or false-negative prediction hence the safety profile of 1,8-cineole needs to be validated with the help of suitable experimental pharmacokinetic and toxicological studies.

4.3. Predicted Binding Interactions with CDK2 and the APC

Docking analysis indicated that the 1,8-cineole might fit into the binding areas of the model that was constructed of the CDK2 and the APC. PHE80, LEU134, VAL64, LYS33, ALA144, ALA31 and VAL18 of the CDK2 complex were predicted to have π -sigma, alkyl, and π -alkyl interactions with the ligand. These interactions are also in line with the hydrophobicity of

1,8-cineole, and could play a role in its orientation in the modeled binding region.

In the case of the APC structure, an alkyl interaction and a conventional hydrogen bond were observed to be predicted with ARG66. Since 3NMW is the armadillo repeat domain of APC, this particular interaction ought to be viewed within the framework of a determined structural domain as opposed to the complete-length protein of APC. The postulated interaction can show that 1,8-cineole has the ability to bind to a surface area of the APC domain, but fails to activate interference with APC-mediated β -catenin regulation, Asef recognition or Wnt signaling. Additional structural and biochemical studies would be required to identify whether the predicted binding site or not corresponds to a functional protein-protein interaction interface.

It should also be mentioned that in the current study blind docking was employed. The poses predicted, therefore, reveal potential binding sites, but do not define that the 1,8-cineole binds to the canonical ATP-binding pocket of CDK2 or a functionally verified regulatory site of APC. To shed light on the relevance of these predicted interactions in terms of functionality, experimental binding studies and site-specific computational validation would be necessary.

4.4. Dynamic Stability of the 1,8-Cineole Complexes

The 100 ns molecular dynamics simulations were another insight that gave more understanding on the structural behavior of the selected complexes. The APC–1,8-cineole system and the CDK2–1,8-cineole system have relatively stable RMSD profiles without a noticeable steady structural drift or significant destabilization. The similarity of the values of the radius of gyration demonstrated that the global compactness of both proteins modeled was maintained whereas the SASA profiles indicated that binding of a ligand did not significantly change the overall solvent exposure of the protein.

The RMSF curves indicated that a majority of residues had comparatively minor variations with the increased mobility being linked with terminal and chosen loop segments. Such trends are compatible with the normal protein flexibility and do not reflect the overall destabilization after binding to a ligand. The hydrogen-bond analyses showed that polar interactions were not continuous but intermittent and not the form of a hydrogen-bonding network. This finding makes sense in the case of 1,8-cineole, which has just one oxygen atom and should not depend on hydrophobic or van der Waals forces to a great extent to accommodate the ligand.

The PCA and FEL results also suggested that both complexes simulated had defined conformational regions and energetically favorable states during the simulations. Different conformational clusters and low-energy basins indicate that the complexes had a dynamic flexibility and were inclined to occupy the conformational states available. Collectively, these results suggest the computational stability of the modeled complexes, but do not in and of themselves indicate good binding affinity or biological activity.

4.5. Biological Implication and Study limitations.

CDK2 also takes part in the cell-cycle event, specifically, the G1/S transition and the DNA replication, and its deregulation has been linked to the abnormal cellular proliferation. Hence, the anticipated 1,8-cineole/CDK2 interaction can be used as an initial structural foundation to consider its potential applicability to the proliferation-related pathways. Nevertheless, the current findings do not reveal the inhibition of CDK2, cell-cycle arrest, and anticancer effects.

On the same note, APC is a tumor-suppressor protein which helps regulate the stability of β -catenin, Wnt signaling, cell adhesion, migration among other cellular functions. Since the current study was based on the armadillo repeat domain structure which is depicted by the PDB ID 3NMW, the results can be applied to the interaction with this modeled domain alone. Adhesion to this domain is incomparable to recovery of APC tumor-suppressor activity or through direct Wnt/ β -catenin pathway inhibition.

There are also a number of limitations to be taken into consideration. First, molecular docking offers predicted binding poses and scoring approximates as opposed to experimentally measured affinities. Second, blind docking adds more uncertainty to the relevance of the binding sites predicted to be functional. Third, ADMET and toxicity predictions are algorithm estimates, and must be experimentally confirmed. Fourth, the molecular dynamics calculations were carried out on a single chosen compound and throughout a finite time of the simulation. Further studies, such as replicate simulations, binding free-energy calculations, contact persistence, and experimental validation of results would reinforce the conclusions. Last, biochemical analyses, cellular analyses, and relevant colorectal cancer paradigms should be done to identify whether 1,8-cineole has any

significant activity on CDK2-mediated cell-cycle regulation or the APC-mediated signaling pathways.

Table 1: Target Proteins and their respective functions

Protein	Protein Description	Protein Function	PDB ID
CDK2	Cyclin-dependent kinase 2	CDK2 is a serine/threonine protein kinase that plays an important role in cell-cycle progression, particularly during the G1/S transition and DNA synthesis. It forms active complexes with cyclins E and A and phosphorylates several regulatory proteins involved in cell-cycle control. Dysregulation of CDK2 activity has been associated with uncontrolled cellular proliferation and cancer progression.	2A4L
APC	Adenomatous polyposis coli protein	PC is a tumor-suppressor protein involved in the regulation of the Wnt/ β -catenin signaling pathway, cell adhesion, cytoskeletal organization, and cellular proliferation. Through its interactions with β -catenin and other regulatory proteins, APC contributes to the control of β -catenin-dependent gene expression. Loss or mutation of APC is strongly associated with colorectal cancer development.	3NMW

Table 2: Predicted ADMET Properties of Selected *Cymbopogon citratus* Phytochemicals

Compound	MW	Logp	TPSA	HBD	HBA	Caco2	HIA	BBB	CYP3A4_Inh	Ames
1,8-Cineole	154.14	2.168	9.23	0	1	-4.58	0.0029	0.9649	0.0032	0.4993
Alpha-Bergamotene	204.19	5.325	0	0	0	-4.548	0.0013	0.9229	0.3381	0.0822
Alpha-Copaene	204.19	4.561	0	0	0	-4.625	0.0023	0.2077	0.6899	0.2979
Alpha-Pinene	136.13	4.514	0	0	0	-4.723	0.0061	0.4068	0.2498	0.0159
Alpha-Terpineol	154.14	2.968	20.23	1	1	-4.559	0.0187	0.6865	0.1031	0.2908
Caffeic-Acid	180.04	1.19	77.76	3	4	-4.94	0.3012	0.0018	0.0012	0.2738
Caryophyllene	204.19	4.389	0	0	0	-4.531	0.0444	0.0505	0.1542	0.2877
Chlorogenic-Acid	354.1	1.036	164.75	6	9	-6.426	0.1063	0.0002	0	0.3861
Citral	152.12	3.284	17.07	0	1	-4.486	0.0903	0.2212	0.4534	0.4304

Citronellyl-Acetate	198.16	3.799	26.3	0	2	-4.804	0.0019	0.9121	0.192	0.1997
Dipentene	136.13	4.541	0	0	0	-4.581	0.0009	0.9848	0.0623	0.1917
Eugenol	164.08	2.321	29.46	1	2	-4.57	0.0346	0.1062	0.9983	0.4683
Furfural	96.02	0.564	30.21	0	2	-4.641	0.3184	0.4643	0.0034	0.4495
Geraniol	154.14	3.428	20.23	1	1	-4.426	0.6089	0.0366	0.3024	0.228
Geranyl-Acetate	196.15	3.816	26.3	0	2	-4.405	0.1456	0.0773	0.0258	0.4148
Isoeugenol	164.08	2.265	29.46	1	2	-5.102	0.0368	0.0362	0.3812	0.4513
Isoorientin	448.1	0.572	201.28	8	11	-6.239	0.6354	0.0019	0.4235	0.8027
Isopulegol	154.14	2.792	20.23	1	1	-4.694	0.0029	0.7007	0.0134	0.4237
Isovaleraldehyde	86.07	1.098	17.07	0	1	-4.468	0.0209	0.9741	0.0529	0.1308
Isovaleric-Acid	102.07	1.058	37.3	1	2	-4.698	0.0416	0.5488	0	0.2464
Limonene	136.13	4.541	0	0	0	-4.581	0.0009	0.9848	0.0623	0.1917
Linalool	154.14	2.512	20.23	1	1	-4.721	0.2887	0.0142	0.1756	0.3694
Linalyl-Acetate	196.15	3.321	26.3	0	2	-4.699	0.0158	0.5716	0.8252	0.333
Luteolin	286.05	2.247	111.13	4	6	-5.192	0.0146	0.0115	0.9976	0.6495

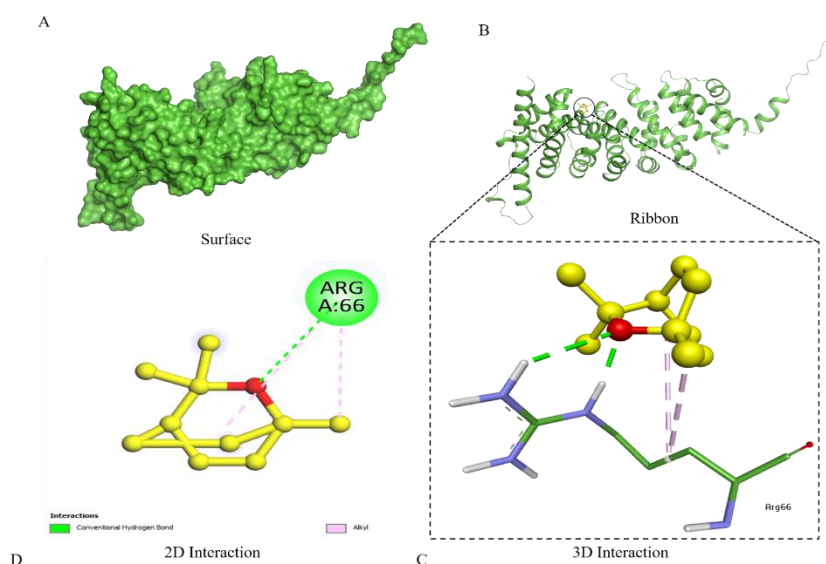


Fig. 1: Binding interactions of APC with 1,8-cineole

A) Surface representation of docked complex B) Ribbon representation of docked complex C) 3D representations of docked complex D) 2D representations of docked complex

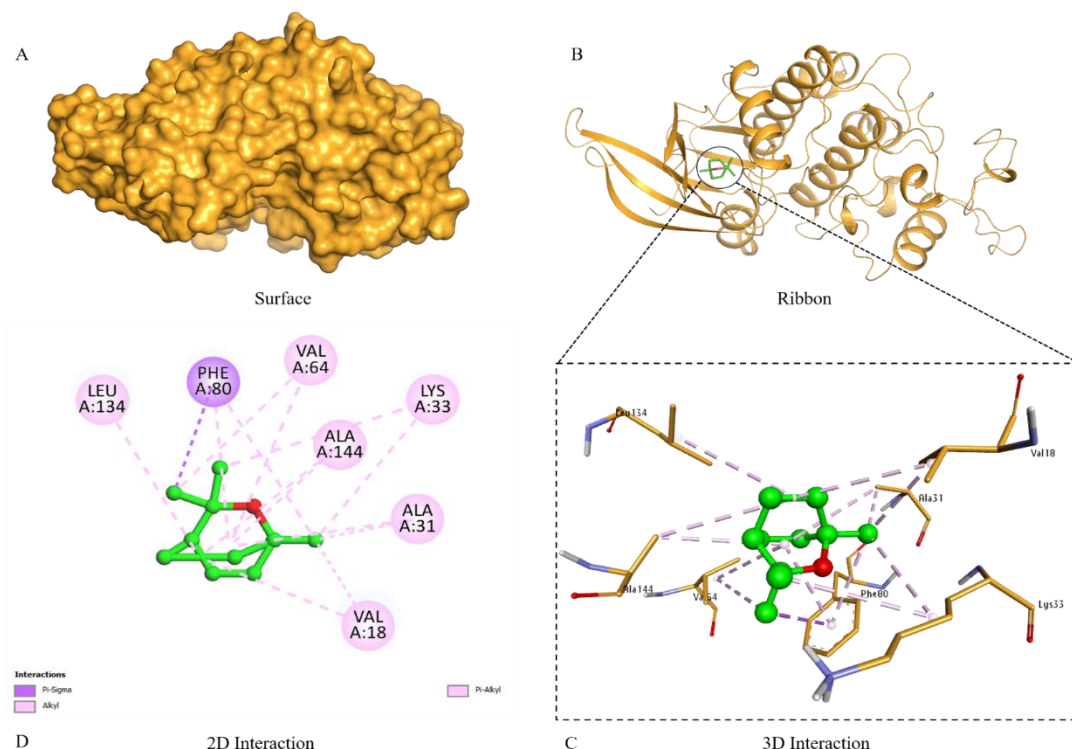


Fig. 2: Binding interactions of CDK2 with 1,8-cineole

A) Surface representation of docked complex B) Ribbon representation of docked complex C) 3D representations of docked complex D) 2D representations of docked complex

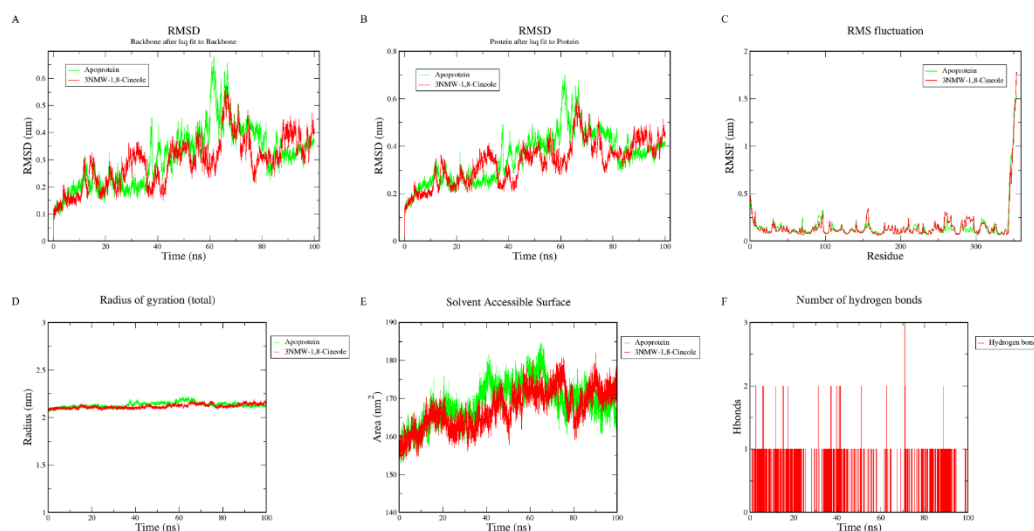


Fig. 3: Shows a simulation of molecular dynamics of apoprotein and APC (3NMW) with 1,8-cineole complex. (A) RMSD of Backbone apoprotein and complex; (B) RMSD of whole protein apoprotein and complex; (C) RMSF of apoprotein and complex; (D) Radius of gyration (total) of apoprotein and complex; (E) SASA of apoprotein and complex; (F) Hydrogen bond analysis

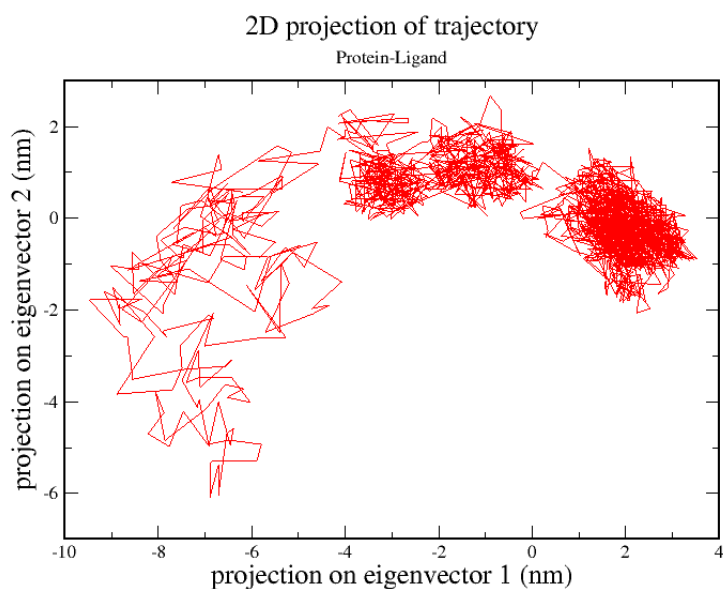


Fig. 4: 2D projection of the motion of 3NMW-1,8-cineole complex constructed by plotting the first two principal components (PC1 and PC2) in the conformational space.

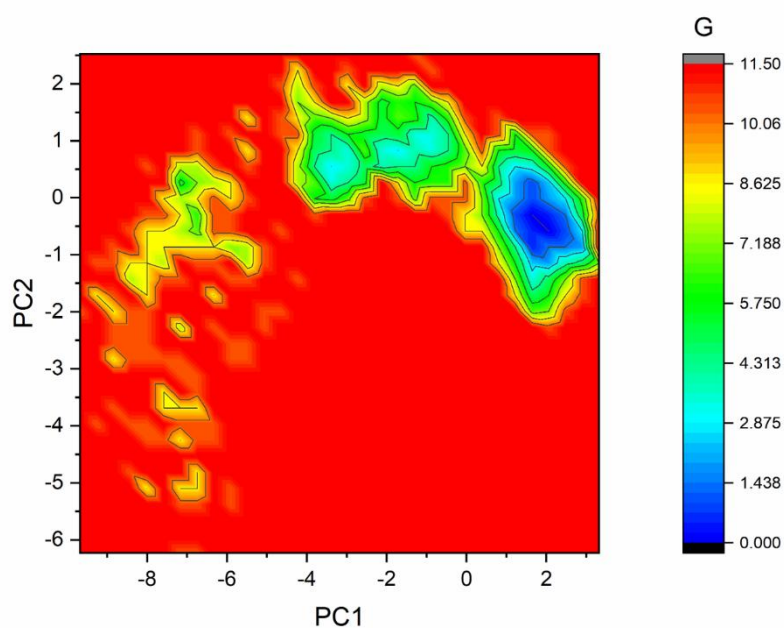


Fig. 5: The free energy landscapes (FEL) of 3NMW-1,8-cineole complex

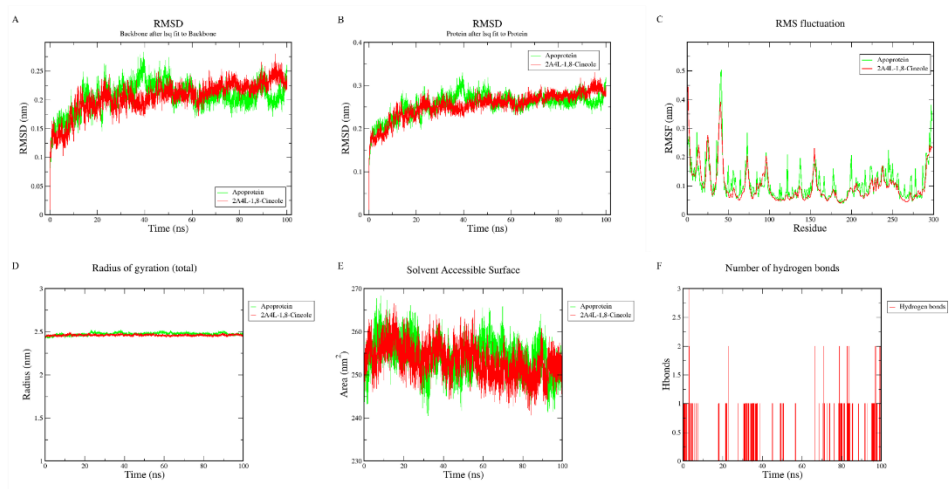


Fig. 6: Shows a simulation of molecular dynamics of apoprotein and CDK2 (2A4L) with 1,8-cineole complex. (A) RMSD of Backbone apoprotein and complex; (B) RMSD of whole protein apoprotein and complex; (C) RMSF of apoprotein and complex; (D) Radius of gyration (total) of apoprotein and complex; (E) SASA of apoprotein and complex; (F) Hydrogen bond analysis

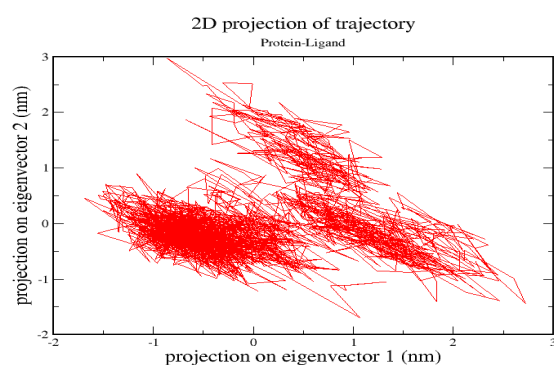


Fig. 7: 2D projection of the motion of 2A4L-1,8-cineole complex constructed by plotting the first two principal components (PC1 and PC2) in the conformational space.

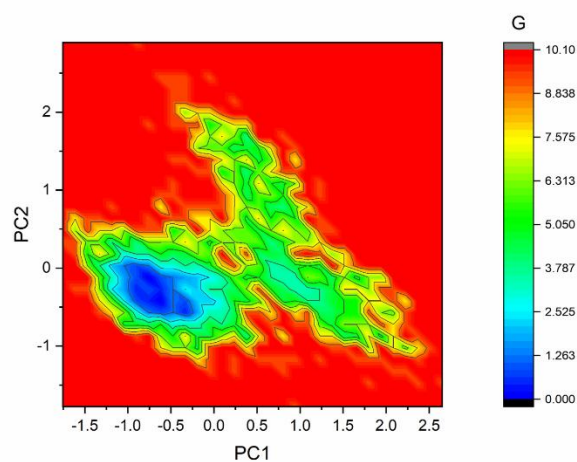


Fig. 8: The free energy landscapes (FEL) of 2A4L-1,8-cineole complex

5. CONCLUSION

The current research involved an interactive computational workflow to screen *C. citratus* phytochemicals on CDK2 and the APC. An array of flavonoid and phenolic compounds had good predicted docking scores, and 1,8-cineole was selected to undergo further analysis due to a relatively good profile of ADMET. Molecular docking has revealed the presence of noncovalent interactions with both of the modeled targets, and 100 ns of molecular dynamics simulations suggested that the APC-1,8-cineole and CDK2-1,8-cineole complexes did not lose their overall structural stability and conformational integrity. The results justify the 1,8-cineole as a computationally prioritized candidate that needs further research. Nonetheless, the outcomes are predictive and do not determine target inhibition, restoration of APC activity, Wnt-pathway regulation, or anticancer activity. The predicted interactions need to be confirmed by biochemical, cellular, pharmacokinetic and in vivo studies to establish the therapeutic relevance of 1,8-cineole in colorectal cancer.

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