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# K-RAS -A POTENTIAL INDICATOR FOR TRACKING FLAVONOIDS (QUENTIN, HESPERIA AND FOLIC ACID) AS POTENTIAL PATHWAYS

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**ABSTRACT**

Majorly, cancer is driven by KRAS mutations, which can activate oncogene pathways like RAF-MEK-ERK, PI3-AKT and RALGDS pathways, targeting flavonoids like quercetin, curcumin, hesperidin, and folic acid to show anti-cancer potential through interactions with KRAS G-quadruplex DNA protein. This study investigates the molecular binding and dynamics of Hesperidin that showed the best interactions to target pathways using computational approaches. The molecular docking was performed using Schrödinger Suite-2021 on KRAS proteins (PDB: 1LFD, 1VWH, 6X7B). Ligands were optimized via LigPrep, and docking was evaluated using Glide-XP. MM-GBSA free energy and ADMET screening assessed ligand stability and drug-like properties. MD simulations (100 ns) analyzed protein-ligand complex stability. A docking study revealed strong binding for isoflavones, with G-scores from -6.39 to -14.92. Hesperidin showed the strongest affinity, interacting with residues like Asp128 and Tyr54. MM-GBSA confirmed stability, and ADMET screening showed favorable pharmacokinetics. MD simulations indicated RMSD stabilization (~3 Å), affirming complex robustness. Hesperidin demonstrated superior binding and stability, indicating its potential in targeting ARKS-driven cancer. These findings support further in vivo and clinical investigations into isoflavones as therapeutic agents.

**Keywords:** K-RAS, MD Simulation, RAF-MEK-ERK, PI3-AKT, RAL-GDS Pathways.
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## INTRODUCTION

Cancer is one of the leading causes of death globally compared the other prevalent cancers, with an estimated 2.4 lakhs deaths by 2035. The current treatments are surgery, chemotherapy, pharmacotherapy and radiotherapy, which focus on the tumor site depending on the different stages of cancer. Cellular apoptosis involves the regulation of genes with proteins under physiological conditions to pave the way for cellular signaling pathways with the release of effective amino acids to enhance anti-cancer activity. Hence, this mechanism can be illustrated by the involvement of certain types of isoflavones like Quercetin, Hesperidine, and Folic acid initiating the RAF-MEK-ERK, PI3-AKT, and RAL-GDS pathways for effective anti-cancer activity.[1] Computational molecular modeling plays an integral part for understanding the binding capability of the ligands with the desired proteins and amino acids for studying their affinity rates. Protein-protein interactions with the ligand moieties enhance the docking simulation used to compare the binding affinity of ligands to understand their molecular activities. To discover the protein targets following the ARKS signalling pathway, along with its regulatory amino acid action is a novel pharmacological approach.[2] Protein interactions are important for several cellular biological processes, activating pathways of which their disruption is a leading cause of cancer. The use of


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isoflavones to modulate the pathways is important to illustrate the docking mechanism to enhance the anti-cancer activity effect. In addition, since protein/gene molecules–ligand compound interactions play an important role in drug development, this research investigates molecular docking capacities and dynamic simulation studies.[3]

Molecular dynamics simulations have been extensively used for illustrating different mechanics of protein and ligand binding conformational changes. Drug release pathways are illustrated by different catalytic mutations to target specific proteins at molecular sites that are studied by dynamics screening of ligand–protein interactions.[4] The interactions between peptides and receptors are supported by molecular modelling approaches, which help to characterise the peptides with their receptor's binding sites to activate different metabolic pathways.[5] Molecular docking was used to understand the binding affinity of the ligands and illustrate the protein-ligand interaction with the desired pathways responsible for the KRAS signalling pathway. Flavourless in the form of Hesperidin, Quercetin and Folic acid are the ligands responsible for the KRAS signalling activation. Hesperidin molecular dynamics was performed since it gave the best binding energies with ligand and co-ligand and, in turn, activated the KRAS RAF-MEK pathway by the release of amino acids such as ASN_23, LEU_25, SER_27, TYR_43, SER_43, ALA_46, VAL_47, ASN_49, GLU_51, etc illustrated further Fig.-5b, of which the highest hydrogen bonding was found to be of ASP_128. [6] KRAS is a RAS family oncogene with Trespasses molecules responsible for the activation of KRAS signalling pathways: RAF/Mel/Er, Pi3/Akt/Pdk1 and Ralgds pathways that switch proteins to activate FTP-bound molecules into inactive GDP-bound states. KRAS affects cellular activities such as cell growth, cell differentiation between healthy and tumorous cells and survival through down-regulation of the KRAS pathway through the desired reactions between ligand and proteins.[7] Activation of mutations in the KRAS gene prevents hydrolysis of GTP, making the protein and its downstream signalling cascades active all of the time, aiding in carcinogenesis. KRAS has an accuracy of activating in lung (30%), colorectal (44%), and pancreatic (97 %).[8] Drug development uses different *in silico* methods that use it as an effective tool (Schrodinger Suite 2021- 4 software) to better interpret protein-ligand interactions. With the use of these techniques, interactions at the molecular level between ligands and their protein target may be predicted and investigated, revealing details about their binding affinities and possible therapeutic effects.[9] *In silico* studies can clarify the molecular processes underlying the interaction of KRAS quadruple for anti-cancer activity.

This computational work attempts to provide molecular insights into the function of flavourless targeting KRAS.[10] This research illustrates the the binding interactions between flavonoids and ligands using in silico approaches, molecular dynamics simulations, and looking into other structural factors like the binding affinity, MMGBA, and ADMET screening that lead to signaling pathways PI3K- PDK1-AKT, RAF-MEK-ERK, RALGDS involved in the anti-cancer activity processes. The results of this study may provide insight into the processes by which flavonoids regulate the KRAS pathway towards cancer.[11]

**Docking of KRAS G-Quadruplex Protein with Ligands (folic acid, quercetin, and hesperidin) with the Release of Amino Acids for Effective Anti-Cancer Activity**

To illustrate the efficiency of protein binding with the drug, 3D modeling of the desired receptor of KRAS-G Quadruplex will be studied. KRAS is a member of the RAS family of small GTPases, which are switch proteins between GTP-bound and inactive GDP states. KRAS largely affects cellular activities like cell proliferation, differentiation, and cell death survival through signaling of RAF/MeK/ErK, Pi3/Pdk1/Akt, and RALGDS pathways.[12] Activating mutations in the KRAS gene prevent GTP hydrolysis, making the protein and its downstream signaling cascades active all of the time, aiding carcinogenesis. From this study, we will illustrate the in silico docking mechanism of K-RAS- G Quadruple with the drug and other protein compounds like Folic acid, Quercetin, and Hesperidin.[13]

## EXPERIMENTAL

**Materials and Methods**

The desired protein structures for the pathways were computed to be PDB IDs 1LFD, 1VWH, and 6X7B at binding energies of 2.10 Å, 1.48 Å, and 1.95 Å, respectively, and were used for further investigation. In general, protein structures were structured based on bond order, charges, missing hydrogen atoms, different amide groups, surface chemistry, and so on.[14] Water molecules 5 Å of the hetero atom was

removed. The ionisation states of hetero atoms present in the protein structure were docked, and the most stable state was chosen. Finally, using the OPLS2005 force field software, a desired reduction of the protein was performed to realign side-chain hydroxide groups. Root Mean Square Deviation (RMSD) tolerance of 0.3 Å constraints were used to reduce the attach with protein binding sites. The ligands were structured in CID format using the program ChemDraw version 8.0. These ligands were translated to mol-2 format, and the program was run in Maestro's Lig-prep Schrodinger suite 2021. Compounds were minimised in the ultimate step of Lig-prep using the Optimised Potentials for Liquid Simulations (OPLS3) force field in the Schrodinger Impact program. For minimisation, the steepest descent algorithm was utilised, followed by the conjugate gradient technique. A single low-energy ring conformation was created for each ligand, and the optimised ligands were employed in docking studies. The ligand was preserved in the crystal structure of the obtained and prepared protein, which was used to build the receptor grid. The receptor grid dimensions were set to 14 Å × 14 Å × 14 Å for all three proteins.[15]

**Validation of the Docking Program**

The docking process was assessed by determining the interaction of co-crystallised ligands bearing the lowest-energy pose predicted parameters like: ligand-protein scoring function, Glide score, and binding affinity of the targets by X-ray crystallography structural illustration. By removing the co-crystallized ligand from the protein's binding site and re-docking the ligand with its binding site, the extra-precise Glide docking approach was confirmed. For analysis, the hydrogen bonding interactions and the root mean square deviation (RMSD) between the anticipated and observed X-ray crystallographic conformations were employed. The prepared ligands were docked in the catalytic pockets of 1LFD, 1VWH, and 6X7B using the Glide module's enhanced precision XP mode. The Glide module's XP visualize mode was utilized for post-docking analysis of active ligands with substantial G-scores. The G-score of the desired ligand was activated by the hydrophilic interactions, hydrogen bonding interactions, and electrostatic forces of attraction, which in turn are the parameters for increasing the binding affinity of the ligand with protein targets.[16]

**Mm-Gabs Binding Free Energy Calculation**

The free energy of binding of the ligand was docked using the Schrödinger Suite's Prime MM-GB/SA module, with the generalized-Born/surface area (GB/SA) method using the continuum VSGB 2.0 solvent model; the external OPLS3 force field was used for the reduction in energy required for the post-docking process of the ligated-receptor molecule.[17]

**ADMET Screening**

The suggested compounds' in silico ADMET characteristics were assessed using Qik Prop of the Schrödinger Suite 2021.[18]

**MD Simulation**

The stability of the Hesperidin was performed at 100 NS MD simulation. The complex that was subjected to the solvent system with an external OPLS3 force field was examined by the Desmond module in Schrödinger 2021. The molecular system was prepared with crystallographic water consisting of TIP3P molecules under ortho-structured rhomboid periodic boundary conditions at a 10 Å buffer site. The constant temperature of 300 K was maintained by a Nose-Hoover thermostat chamber and barostat equipment, and a pressure of 1 bar on structured systems was established, respectively.[19]

## RESULTS AND DISCUSSION

**Molecular Docking**

The molecular docking procedures for the ligands with the targeted receptors selected for the desired pathway was performed to depict the active sites by the Glide module Maestro-12.3 version, resulting in different binding affinities at the different active pockets shown in Fig.-1 and docking results are summarized in Table-1a, Fig.-2, Table-1b, Fig.-3 and Table-1c, Fig.-4. The ligands were structured by computed method and further docked with 1LFD, 1VWH, and 6X7B, illustrating the RAF/MEK, PI3/AKT and RALGDS pathways. The results illustrated in Table-1a, it was suggested that the compounds Folic acid, Hesperidin, and quercetin, with 1LFD with better G- score lies between -6.39 to -

14.92. The results showed the affinity of ligands to 1LFD that targets lipophilic binding pockets with protein-ligand interaction due to heterocyclic ring formation and hydrogen bonding interactions between different substrates, as all compounds have interacted with receptors within a similar binding pocket. The interactions of Folic acid were activated with some amino acid residues such as Lys 216 and Asp 233 at the dynamic site. The docked pockets for Folic acid, Hesperidin, and Quercetin with high G-score were subjected to screening.

Table-1a: Docking Results for Folic Acid (FA), Hesperidin, and Quercetin with PDB ID: 1LFD

| Compounds | Glide score | Lipophilic EvdW | H Bond | Glide score | Glide Energy | Glide model |
|---|---|---|---|---|---|---|
| Quercetin | -14.9 | -30.7 | -3.4 | -42.5 | -73.2 | -118.7 |
| Hesperidin | -6.4 | -29.7 | -5.1 | -29.5 | -59.2 | -63.7 |
| Folic Acid | -11.8 | -33.3 | -3.4 | -24.3 | -57.5 | -88.1 |
| 1LFD - 2-preprocessed | -17.8 | -40.2 | -6.7 | -102.0 | -142.2 | -242.8 |

Table-1b: Docking Results for Folic Acid (FA), Hesperidin, and Quercetin with PDB ID: 1VWH

| Compounds | Glide score | Lipophilic EvdW | H Bond | Glide score | Glide Energy | Glide model |
|---|---|---|---|---|---|---|
| Quercetin | -4.5 | -32.3 | -1.4 | -9.4 | -41.6 | -55.5 |
| Hesperidin | -11.1 | -42.1 | -6.2 | -12.5 | -54.6 | -73.3 |
| Folic Acid | -7.8 | -25.4 | -4.0 | -8.5 | -33.9 | -48.8 |

Table-1c: Docking Results for Folic Acid (FA), Hesperidin, and Quercetin with PDB ID: 6X7B

| Compounds | Glide score | Lipophilic EvdW | H Bond | Glide score | Glide Energy | Glide model |
|---|---|---|---|---|---|---|
| Quercetin | -3.98 | -34.76 | -1.53 | -9.80 | -44.56 | -65.77 |
| Hesperidin | -7.28 | -32.83 | -3.04 | -14.97 | -47.80 | -63.45 |
| Folic Acid | -9.74 | -19.85 | -4.28 | -11.15 | -31.01 | -45.97 |

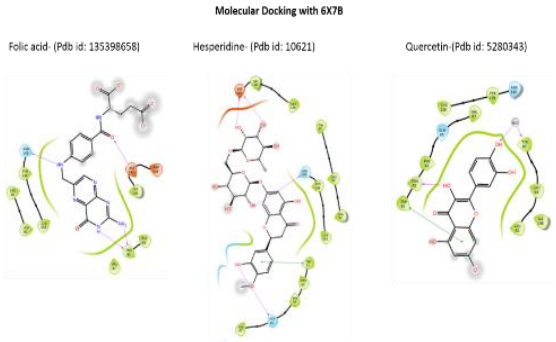



Fig.-1: Molecular Docking of 1LFD: (1a) Folid Acid, (1b) Hesperidine, (1c) Quercetin (1LFD)

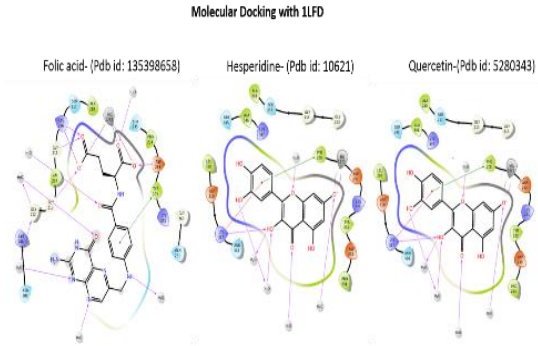



Fig.-2: Molecular Docking of 1VWH (2a) Folid Acid, (2b) Hesperidine, (2c) Quercetin

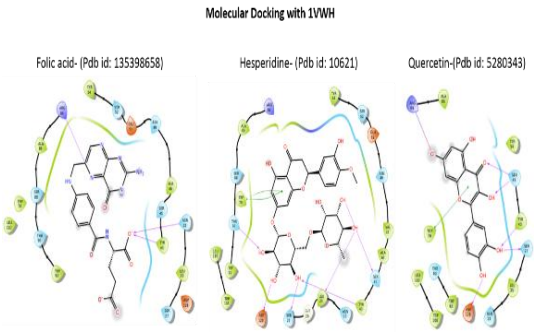



Fig.-3: Molecular Docking of 6X7B: (3a) Folid Acid, (3b) Hesperidine, (3c) Quercetin (6X7B)

## MMGBSA AND ADMET

The stability of the binding power between the ligands and genes was performed by the module mm-gb/sa Schrodinger suite 2021. The OPLS3 field delivered forces that were used to decrease the energy at the XP active site of the docked ligand-receptor complex with gb/sa continuous vsgb 2.0 solvent model. The outcomes are summarised in Table 2. From the results of MM-GBSA binding energy calculations, the stability of docking with 1LFD, 1VWH, and 6X7B was more significant. The results obtained were the dG bind values in the range -50.69 (4n) and -115.80 Kcal/mol (4m), dG C values, dG vdw values with dG lipophilic values are undoubtedly contributed for it's overall complex structure strength. The G-score and MM-GBSA play an important role in the structural elucidation of the docked molecule. The ADMET assay as depicted in Table-2, followed by ADMET assay as depicted in Table-3 were performed.

Table-2: Prime /MMGBSA Free Energy Calculation for Folic Acid (FA), Hesperidin, and Quercetin with PDB id: 1LFD, 1VWH, 6X7B

| Compound code | PDB ids | ΔGbind (Kcal/mol) | ΔGbind Coulomb | ΔGbind covalent | ΔGbind HBond | ΔGbind Lipophilic | ΔGbind-Vander |
|---|---|---|---|---|---|---|---|
| Quercetin | 1LFD | -50.7 | -8.5 | -10.3 | 2.9 | -13.2 | -66.5 |
| Hesperidin | | -21.1 | 15.7 | -2.4 | 2.4 | -9.6 | -52.1 |
| Folic Acid | | -56.3 | -49.9 | -6.9 | 0.5 | -9.6 | -58.9 |
| Co ligand | | -115.8 | -196.4 | 4.9 | -10.8 | -7.7 | -65.4 |
| Quercetin | 1VWH | -25.5 | -1.7 | 1.9 | -4.6 | -15.5 | -27.5 |
| Hesperidin | | -89.1 | -54.0 | 12.6 | -5.6 | -25.2 | -49.9 |
| Folic Acid | | -45.8 | -68.8 | 10.6 | -3.3 | -17.3 | -20.4 |
| Co ligand | | -71.8 | -40.4 | 26.0 | -4.3 | -21.9 | -72.4 |
| Quercetin | 6X7B | -52.1 | 54.4 | 1.6 | -4.1 | -10.7 | -39.5 |
| Hesperidin | | -46.6 | -40.1 | 8.0 | -3.7 | -14.6 | -29.7 |
| Folic Acid | | -30.0 | -16.2 | 2.9 | -0.7 | -12.3 | -22.9 |
| Co-ligand ZVP | | -81.27 | -45.67 | 0.02 | -0.74 | -30.09 | -40.50 |

Table-3: ADMET Screening for the Compounds

| Compound | dipole | Donor HB | Accept HB | logP o/w | No. of metabolite | QPlog Khsa | Rule of Five |
|---|---|---|---|---|---|---|---|
| Coligand_ZVP | 4.52 | 2 | 10 | 3.2 | 4 | 0.50 | 1 |
| Quercetin | 15.38 | 6.25 | 12.75 | -0.38 | 6 | -1.06 | 2 |
| Hesperidin | 4.14 | 7 | 20.05 | -1.38 | 11 | -1.21 | 3 |
| Folic Acid | 6.03 | 4 | 5.25 | 0.36 | 5 | -0.34 | 0 |
| Recommended values | 1- 12.5 | 0– 6 | 2-20 | -2-6.5 | 1 – 8 | –1.5 – 1.5 | max 4 |

## MD Simulation

A 100-ns molecular dynamics simulation was performed to understand the molecular insights involved in the binding of Hesperidine in the active pocket of 1VWH. The 2D-trajectory interaction figure showing

hydrogen bonding with amino acids like Asp128, Tyr-54, Ser- 52, Thr-90 is preserved in the molecular docking site targeting pockets. The RMSF value obtained for the desired ligand was 0.5 Å. Other ligand properties such as gyration radius, surface area of the molecular structures, surface area of solvents and ligands were in the range of 4.9-6.2 Å, 500.15–520.5 Å2, 290.75–410 Å2 and 410–430 Å2, respectively.
The analyzed results showed protein RMSD values in the range between 1.9–3 Å and 2.3–3 Å. The Ca atoms lie in the range 2.4-4.7 Å and finally stabilized at 60ns of simulation at a 3 Å RMSD value. RMSD Fluctuations up to 3.7 Å were observed between 55-60 ns. During the MD simulation running time, stable hydrophobic interactions were linked with Asp-128. The stability of the ligand-protein complex was determined by RMSD, with a moderate fluctuation of the yj6j ligand-protein complex at 1.72 Å. Ligand-protein interactions led to the release of amino acids like Asp-128, Tyr-54, Ser- 52, Thr-90 that rendered their specific glide score, binding energies and affinity towards each other. It depicted that the ligand formed a stabilized molecule by hydrophobic interactions at 5%–90% of MD simulation time, with released residues like Trp-79, Arg-84, Trp-108. It also formed H2 interaction bonds with Asp128, Tyr-54, Ser- 52, Thr-90 over the course of 80% of the simulation trajectory. The MD simulation of Hesperidine with 1VWH contacts is outlined in Fig.-4.

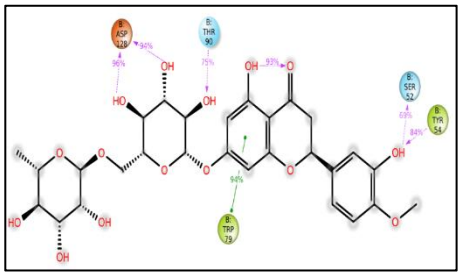
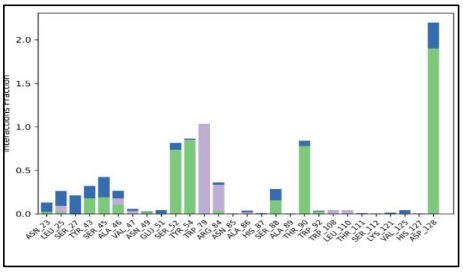
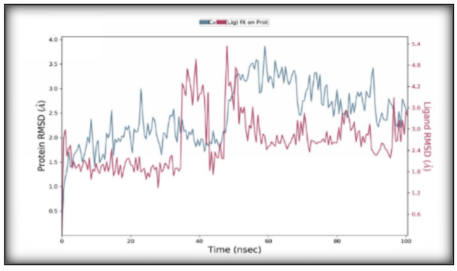


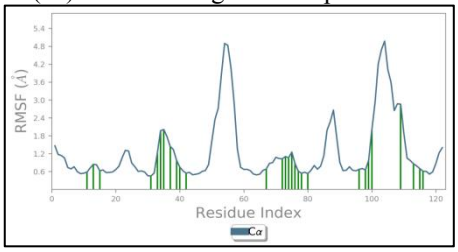
Fig.-4: 100ns MD Simulation for Hesperidine 1VWH (10621)(4a): 2D Interaction of Hesperidin



(4b): Protein Interaction Images of Hesperidin with Ligand



(4c): RMSD images of Hesperidin



(4d): RMSF images of Hesperidin

**Dipole-interaction of the Molecule**

**DonorHB:** hydrogen bonds estimation replaced by the solute to water molecules in water medium

**Accept HB:** Hydrogen bonds estimation by the quantity of the solute in water molecules

**QPlogPo/w:** Estimation of octanol: water partition efficiency.

**#metab:** Quantity of metabolic reactions.

**QPlogKhsa:** Human serum albumin linkage estimation

**Rule of Five:** Lipinski's rule of five violations.[20]

The K-RAS gene belongs to the RAS family that plays an important role in the activation of the K-RAS protein by the regulation of the MAPK pathway that, in turn, activates RAF-MEK, PI3-AKT and RALGDS pathways. As a result, the K-RAS gene can work as a switch on/off activator tool by sending signals to the genes and cellular nucleus responsible for upregulation and downregulation mechanisms for tumor progression. This isoform spreads cancer, for which targeted biological systems and treatments are required to be illustrated for downregulation of K-RAS protein for effective anti-cancer activity.

Anti-cancer agents in coordination with targeting agents like flavonoids (Hesperidin, Quercetin, Folic Acid). In this study, 3 flavonoids were chosen, of which Hesperidin gave the best molecular docking results with the 3 pathways chosen in the study, that is, RAF/MEK, PI3/AKT and RALGDs pathway binding with the ligand for showing good affinity results of the molecules. To investigate the pharmacokinetic and toxicity assessment of the genes and ligands, the ADMET programme was performed using Quick Prop Schrodinger Suite 2024. Molecular docking of Hesperidin, Quercetin and Folic Acid with the ligands IVWH, ILFD and 6X7B.

This process was performed to analyze the docking sites of the receptor pockets with the binding affinities of the desired pathways chosen. The results of G score were -6.39 to -14.92 when binding with 1VWH, Lys-216 and Asp-233 was released. MMGBSA was performed to understand the stability of the binding capacity of the ligated receptor using prime-GB/SA module Schrodinger site 2021. Stable protein interactions with ligands were found to be in the range -50.69 (4n) and -115.80 Kcal (4m), that was obtained by the DFT/MEP analysis of the electronic nature and electronic distribution between the genes and ligands. Hesperidine with 1VWH gave the best docking results; as a result, an MD simulation was carried out using the RAF/MEK pathway with the release of Thr-90, Tyr-54, Ser-52, and Asp-128, with a RMSF value that gave 80% simulation trajectory by hydrophobic interactions.

## CONCLUSION

From the docking study of Hesperidin, Quercetin, Folic acid, and co-ligand depicted better arrangement at dynamic pocket sites. The present study identified the lead molecule Hesperidin with interactions of IVWH, ILFD and 6X7B, illustrating the RAF? MEK, PI3/AKT, and RALGDs pathways for further evaluation of proteins with ligands. From the results obtained, the compound Quercetin with PDBI ID: 6X7B can be used using the PI3K-PDK1- AKT pathway, Hesperidin PDBI ID: IVWH showed the best release in the RAF-MEK-ERK pathway and Folic Acid PDBI ID: ILFD is preferred to inhibit anti-cancer activity using the RALGDS pathway. Folic acid and co-ligand have significant anti-colon cancer activity and are helpful; further development of these compounds will be illustrated by in-vitro studies that are yet to be done.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## AUTHOR CONTRIBUTIONS

The present work is related to *SDG-3: Good Health and Well-being*. All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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