**Quercetin Derivatives As Natural Inhibitors Of KRASG12D: An In Silico Strategy Against Pancreatic Cancer**

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**Background and aims.** Pancreatic cancer is a serious malignancy that develops from the exocrine or endocrine cells of the pancreas1. The five-year survival rate for pancreatic cancer continues to be low, standing at 13.5% 2. A new target for pancreatic cancer is the **KRAS G12D** mutation, which currently lacks effective marketed drugs. Recent strategies to inhibit the KRAS G12D mutation have shown limited success, emphasizing the urgent need for new therapeutic approaches. This study presents several Quercetin derivatives as potential inhibitors for this mutation.

**Methods.** We screened a library of approximately 374 natural compounds from the ChemDiv database. Using the LigPrep tool of Maestro Schrodinger software 2025-1 at pH 7.4, we prepared these compounds. The KRAS G12D protein, identified by PDB ID [7RPZ], was retrieved from the Protein Data Bank and minimized at pH 7.4. The protein and ligands were docked using ligand docking tools with HTVS, SP, and XP features. Among the compounds, Quercetin was selected for further analysis and underwent molecular dynamics simulations for 500 ns. We also derived 30 Quercetin derivatives using Ligand Designer and evaluated their ADMET properties alongside the standard drug MRTX-1133.

**Results.** Quercetin exhibited a promising docking score of -9.036 kcal/mol for KRAS G12D, retaining critical interactions with amino acids Arg68, His95, and Tyr64. This was superior to the standard drug MRTX-1133 dock score (-8.733 kcal/mol). Further, we derived 30 derivatives of quercetin using Ligand Designer. The best three Quercetin derivatives, based on their good docking scores, were identified for further molecular dynamics simulations, synthesis, and in vitro testing against pancreatic cancer cell lines (PANC-1).

**Conclusion/Discussion**

The best three Quercetin derivatives showed potential for inhibiting the KRAS G12D target and warrant further investigation through molecular simulations and in vitro assays. Integrating AI-based drug discovery aligns with ethical innovation and supports the development of personalized, plant-based oncology treatments.

**References:**

1.Two rare cancers of the exocrine pancreas: to treat or not to treat like ductal adenocarcinoma? *J Cancer Metastasis Treat*. 2023;9. doi:10.20517/2394-4722.2022.106

 2.Siegel RL, Kratzer TB, Giaquinto AN, Sung H, Jemal A. Cancer statistics, 2025. *CA Cancer J Clin*. 2025;75(1):10-45. doi:10.3322/caac.21871

 **Table 1.** Best Compounds name and dock score

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| **Compound Name** | **Dock scores(kcal/mol)** |
| **Derivative1** | **-10.935kcal/mol** |
| **Derivative 2** | **-10.656kcal/mol** |
| **Derivative 3** | **-10.558kcal/mol** |
| **Quercetin** | **-9.036kcal/mol** |
| **Standard MRTX-1133** | **-8.733kcal/mol** |