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Exploring Inhibition of ASK1 by Phytochemicals from *Momordica charantia* (Linn.) for Pancreatic Cancer: An *in silico* Investigation

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Abstract: The utilization of *Momordica charantia* (Linn.) for diverse human ailments has been well-documented, with a range of biological activities attributed to it. This study aims to identify potential anti-cancer compounds from *M. charantia* targeting ASK-1. A library of 77 compounds sourced from the PubChem database underwent molecular docking analysis using the Schrödinger Maestro tool. Predictions of drug-like characteristics were achieved through the QikProp module and the AdmetSAR web server. This study reveals that the phytoconstituents from *M. charantia* exhibit better binding affinity and a comparable MM-GBSA score to the reference drug, CAMPTOSAR. Moreover, advanced ADMET predictions affirm the non-carcinogenic nature of these compounds, as well as their alignment with Lipinski's rule. This study proposes these identified substances as prospective anti-cancer agents. Nevertheless, preclinical and clinical evaluations are imperative to gauge their efficacy in addressing pancreatic cancer.

Keywords: molecular docking; ASK-1; MM-GBSA; pancreatic cancer; ADMET.

1. Introduction

Pancreatic cancer affects the pancreas in the digestive tract and is asymptomatic. The rate of its death is as high as its cases, and it affects more men than women, with it being the 7th deadliest type of cancer. There is a higher prevalence of pancreatic cancer in developed countries than in developing countries [1-3]. Although promising, the survival rate of patients with pancreatic cancer is low despite yearly survival improvement. According to the American

Cancer Society, the survival rate in the USA is 12% as of January 2023, which is just a 1-point increase from the previous year [3]. The causes of pancreatic cancer are unknown, and early diagnosis is difficult. The risk of infection is linked to smoking and alcohol abuse as significant causes. Obesity and diabetes are also considered to be contributing factors to the high risk of disease, and personal genetic makeup is a predisposing factor for its development [2]. Similar to other deadly cancers, pancreatic cancer is currently being treated with surgery and an antimetabolite known as gemcitabine. However, high resistance and frequent recurrence after surgery make cures difficult [3].

ASK1, also known as MEKK5, is a member of the MAP3K family and serves as an upstream kinase in the MKK3/6-p38 and MKK4/7-JNK pathways. It becomes activated in response to various cellular stress conditions, including oxidative stress and endoplasmic reticulum stress, playing crucial roles in intracellular stress and apoptotic signaling pathways [4]. Previous research has demonstrated that ASK1 activation induces apoptosis in breast, liver, lung, colon, and osteosarcoma cells. However, contrasting findings have emerged in certain cancer types, such as gastric, ovarian, and pancreatic cancers, where ASK1 promotes cell proliferation and contributes to tumor growth [4]. This dual role of ASK1 underscores the complexity of its regulatory mechanisms and underscores its potential as a therapeutic target in specific cancer contexts [5, 6]. The multifaceted nature of ASK1 and its activation by diverse cellular stress conditions emphasize its importance in cellular stress responses. ASK1-mediated signaling pathways are intricately involved in coordinating intracellular stress responses and apoptotic pathways. Understanding the mechanisms underlying ASK1-mediated signaling and its context-specific effects on cancer cell fate is crucial. Exploring the intricate interplay between ASK1 and specific cancer microenvironments will provide valuable insights for developing tailored therapeutic interventions. Given the dual role of ASK1 in cancer, the development of selective ASK1 modulators that can promote cancer cell apoptosis or inhibit cell proliferation in a tumor-specific manner holds promise for precision medicine approaches. Targeting ASK1 in a context-dependent manner may offer novel strategies for combating cancer and improving patient outcomes [7].

Momordica charantia (Linn.), commonly known as bitter melon, bitter gourd, balsam pear, or karela, belongs to the Cucurbitaceae family and is extensively cultivated in Asia, Africa, and South America. Its historical use for treating various ailments like toothache, diarrhea, furuncles, and diabetes has been documented [8]. Bitter melon's therapeutic attributes, sourced from its crude extracts and isolated compounds, encompass a spectrum of benefits, including diabetes and lipid level reduction, as well as activities against bacterial, fungal, and HIV infections [8, 9, 10]. Recent investigations, both in vitro and in vivo, have revealed the promising anticancer potential of bitter melon [9-13].

This study aims to employ computational techniques to predict the inhibitory effects of phyto-compounds sourced from *Momordica charantia* (Linn.) with a focus on utilizing molecular docking, pharmacokinetic profiling, and evaluation of drug-likeness properties to comprehensively analyze the pharmacological attributes of these *Momordica charantia* (Linn.) compounds to identify potential drug candidates from M. charantia that hold promise in combating Pancreatic cancer.

2. Materials and Methods

The computational tools employed in this study are built within the Schrodinger Suites software (2021 version) running on Windows 11.

2.1. Ligand preparation.

For this study, a compilation of 77 phytochemicals of M. charantia from diverse literature sources was gathered and downloaded in a ".SDF" format from the PubChem website (https://pubchem.ncbi.nlm.nih.gov/) [14-16]. Ligand preparation was carried out under pH 7.0 conditions, utilizing the LigPrep module with the OPLS3 force field [17, 18]. Tautomer generation was omitted, and stereoisomer calculation was limited to one per ligand. The output was formatted in the Maestro output format. Additionally, a reference ligand, CAMPTOSAR, was identified and retrieved from PubChem. Similar preparation procedures were applied to this reference ligand, and it was subsequently employed as a benchmark drug for comparison.

2.2. Protein preparation.

The protein ASK1, identified by its PDB ID: 4BHN, was acquired from the RCSB database (http://www.rcsb.org/pdb). The downloaded protein structures underwent preparation using the protein preparation module within the Schrodinger suite. During the preprocessing of the protein, bond orders were assigned, water molecules were excluded, and heteroatoms were set to approximate a pH of 7.0. Furthermore, optimization and minimization processes were applied to refine the protein structure.

2.3. Receptor grid generation.

In the context of protein-ligand docking, the creation of a receptor grid plays a pivotal role in establishing the binding orientation and dimensions of the active site. Employing the receptor grid generation module, the axes for the ASK1 binding pocket were calculated using the position of the co-crystallized ligand. The specific coordinates for the x, y, and z grids were determined as follows: 0.68 for x, 5.34 for y, and -29.63 for z.

2.4. Generation of E-pharmacophore model.

In the context of virtual screening, a pharmacophore hypothesis was generated based on the interactions observed between the co-crystallized ligand and the target protein. This hypothesis was constructed using the Phase module. During the process of hypothesis generation, features responsible for interactions with the protein were automatically generated using the "AUTO" option within the Protein-ligand complex type of pharmacophore [19]. Subsequently, the prepared ligands underwent screening to ensure that they exhibited a minimum of 2 out of the 4 features specified by the pharmacophore model (Figure 1).

2.5. ADMET-based virtual screening.

Subsequently, the compounds identified as hits in the initial pharmacophore screening underwent a secondary screening process based on Lipinski's Rule of Five criteria. The QikProp module was employed to calculate these properties, and any compound found to violate less than one of the criteria was retained, while ligands with more than one violation were excluded from further consideration.

2.6. Molecular docking.

Using the Glide tool, docking was performed via the Extra Precision (XP) scoring function. Within this framework, the Lipinski-filtered compounds were subjected to screening

within the active site of the protein, previously delineated by the generated grid. The objective was to identify molecules exhibiting the most favorable docking scores. During the docking experiment, the protein was treated as a rigid entity, while the ligand's rotatable bonds were allowed to move freely [19].

2.7. Estimation of binding-free energy.

The MM-GBSA technique for calculating binding energy uses the energy characteristics of the free ligand, free receptor, and receptor-ligand complex to compute binding affinity [20].

The MM-GBSA estimation was performed on the docked complexes using the formula:

$$\Delta G^{bind} = G^{complex}X - (G^{protein} + G^{Ligand}) \quad (1)$$

Where ΔG binds is the protein-ligand complex's binding free energy. Gcomplex is the free energy of the complex, Gprotein is the free energy of the protein in the absence of the ligand, and Gligand is the free energy of the ligand in the absence of the protein.

2.8. ADMET prediction.

The QikProp module and admetSAR webserver (http://lmmd.ecust.edu.cn/admetsar2/) were employed to assess the pharmacokinetic profile, drug-likeness, and toxicity of the top 5 compounds, which also included the reference ligand. The predictions were subsequently visualized using R Studio [21-24].

3. Results and Discussion

The application of in-silico screening of natural compounds for drug development has proven to be more efficient compared to the laborious, costly, and often inefficient laboratory screening methods. Computational studies have significantly reduced the risk of late-stage drug failures [25]. Bitter melon, with its historical use in traditional medicine, boasts a wealth of bioactive constituents, including triterpenoids, triterpene glycosides, phenolic acids, flavonoids, lectins, sterols, and proteins [26-28]. These compounds hold potential as anticancer agents, offering the advantage of minimal side effects.

This study delves into the in-silico exploration of the impact of phytochemicals from *Momordica charantia* (Linn.) on ASK-1. By docking the protein ASK-1 with a library of substances generated for this purpose, the molecular interactions, inhibitory potential, and binding orientations of these compounds against ASK-1 were evaluated. The findings notably highlight the ASK-1 inhibitory capabilities of the top five compounds: Myricetin, Quercetin, Luteolin, Kaempferol, and Epigallocatechin (Table 1).

Table 1. Docking Score and Druglikeness of the top compounds from *Momordica charantia* (Linn.) and the standard Gefitinib.

Entry Name	XP GScore	MMGBSA dG Bind	Rule of five violation(s)
Myricetin	-10.616	-54.45	1
Quercetin	-10.162	-45.21	0
Luteolin	-9.636	-43.87	0
Kaempferol	-9.031	-43.61	0
Epigallocatechin	-8.955	-41.29	1
CAMPTOSAR	-3.973	-56.26	1

3.1. Pharmacophore-based virtual screening.

A pharmacophore, a term denoting essential features within a ligand or molecule, is imperative for facilitating optimal interactions with a specific biological target and eliciting its desired biological response [28, 29]. In this study, the pharmacophore model was constructed by drawing insights from the interaction of the co-crystallized ligand with our target, ASK-1 (Figure 1). Subsequently, this model served as a filtering tool to narrow down our extensive list of phytochemicals derived from M. charantia.

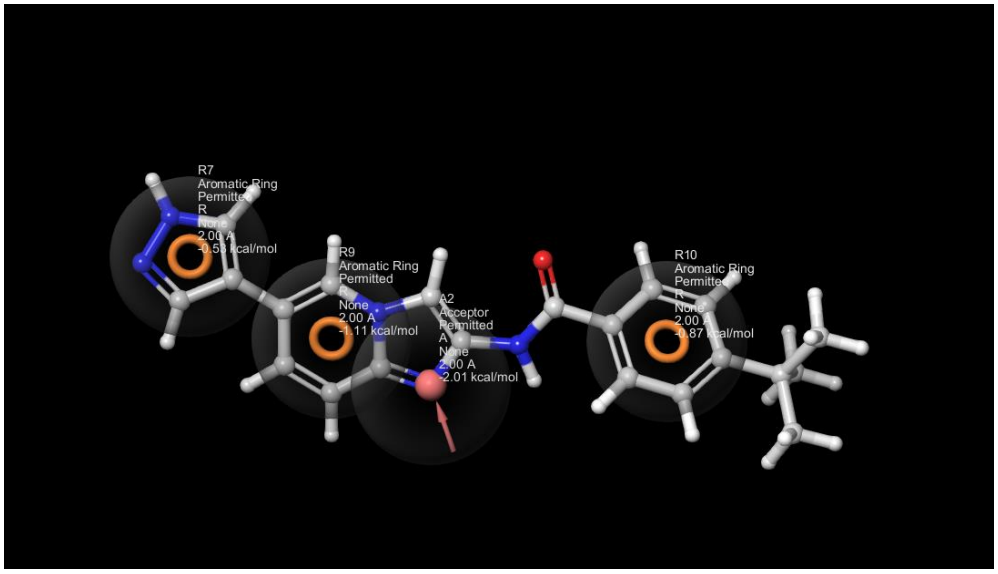

Figure 1. Pharmacophore hypothesis for this study.

3.2. Docking/MMGBSA.

The graphical representation depicting the docking scores and MM/GBSA screening outcomes for the identified hit compounds is illustrated in Figure 2, accompanied by the corresponding numerical data available in Table 1. Figures 3 and 4 offer an insightful analysis of the post-docking results in both 2D and 3D formats. This analysis focuses on discerning the binding orientations and interactions that transpire between the hit compounds and the specific amino acid residues situated within the active site of the protein ASK-1, with a particular emphasis on the key amino acid residues implicated in these interactions.

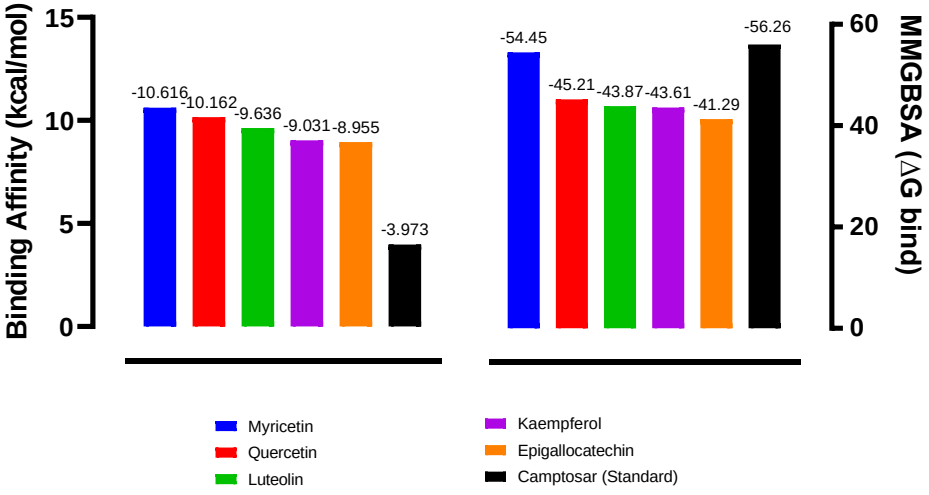

Figure 2. Graphical Representation of the Docking and MM-GBSA scores of the top-ranked compounds and the standard CAMPTOSAR.

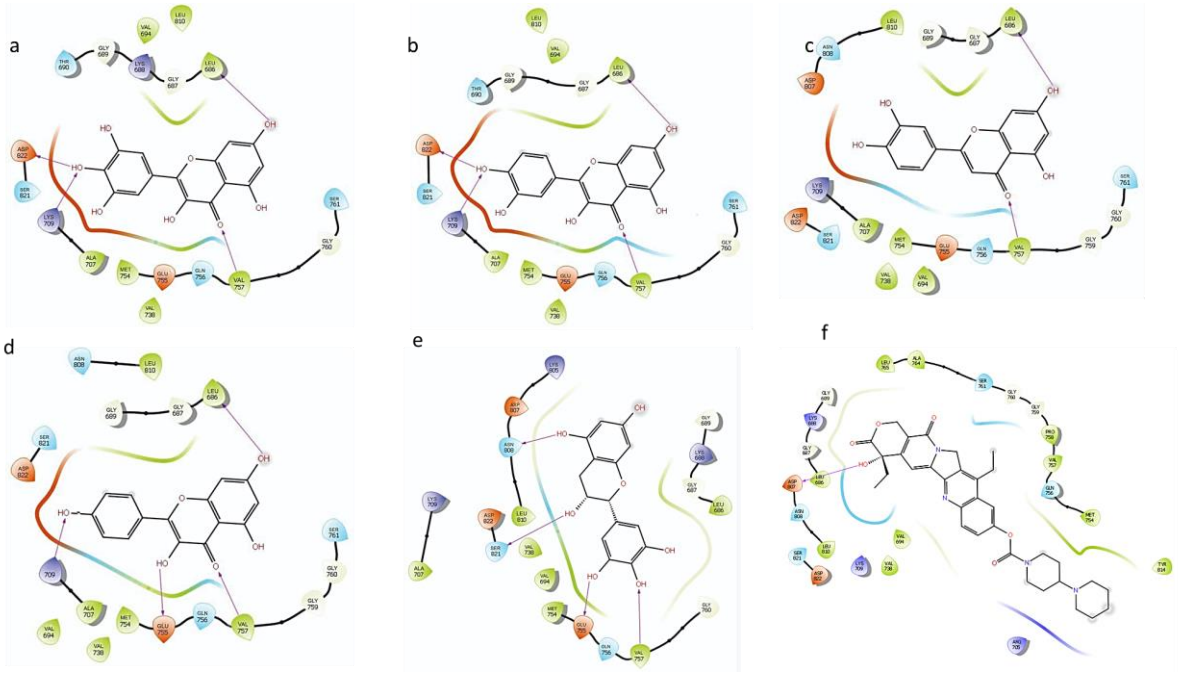

Figure 3. 2D interactions of the top compounds and CAMPTOSAR (Standard Drug) in the active site of FGFR2. **(a)** Myricetin; **(b)** Quercetin; **(c)** Luteolin; **(d)** Kaempferol; **(e)** Epigallocatechin; **(f)** CAMPTOSAR.

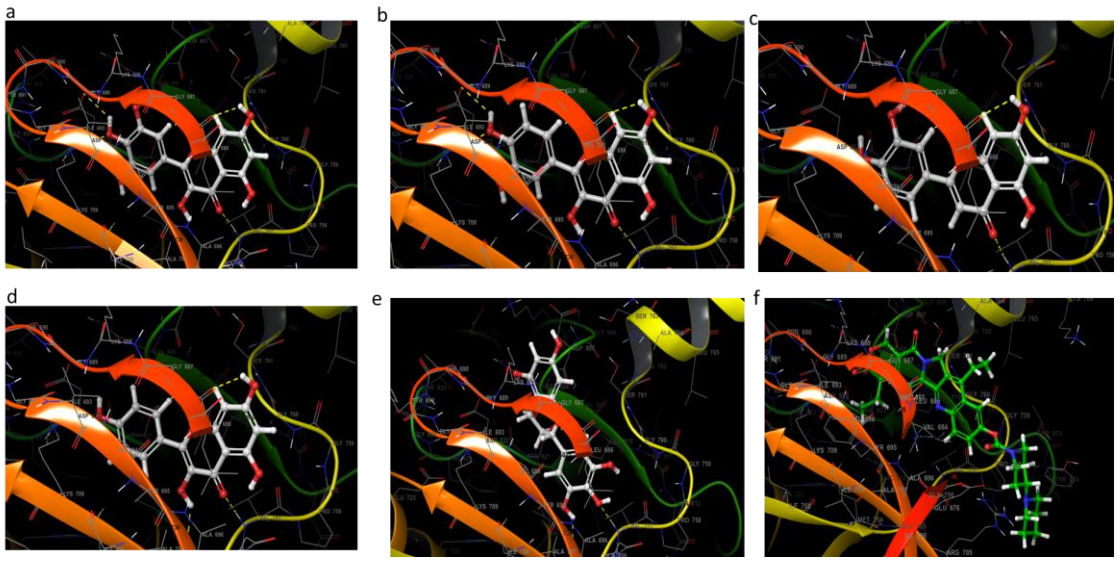

Figure 4. 3D interactions of the top compounds and CAMPTOSAR(Standard Drug) in the active site of FGFR2 **(a)** Myricetin; **(b)** Quercetin; **(c)** Luteolin; **(d)** Kaempferol; **(e)** Epigallocatechin; **(f)** CAMPTOSAR.

According to the data presented in Table 1, the docking scores for the top five ligands exhibited varying degrees of difference in comparison to the reference compound, CAMPTOSAR. Among these, Myricetin displayed the highest binding energy, measuring at -10.616 kcal/mol, along with a competitive MM-GBSA score of -54.45, in comparison to the standard drug CAMPTOSAR (-56.26). In stark contrast, Epigallocatechin had a docking score of -8.955 and an MM-GBSA score of -41.29.

Further delving into specific interactions, Myricetin demonstrated a notably high binding energy of -10.616 kcal/mol in contrast to the binding energy of -3.973 kcal/mol exhibited by the standard drug, CAMPTOSAR. This increased binding energy is attributed to a substantial array of hydrophobic interactions involving amino acids such as VAL 694, LEU 810, LEU 686, ALA 707, MET 754, VAL 738, and VAL 754, in addition to hydrogen bonds observed at LEU 686, VAL 757, LYS 709, and ASP 822.

Quercetin and Luteolin, while displaying differing binding affinities within the binding pocket, both shared a common set of amino acids: ALA 707, MET 754, VAL 738, VAL 694, VAL 757, LEU 810, and LEU 686 contributing to their hydrophobic interactions within the ASK-1 binding pocket. On the other hand, Kaempferol engaged in hydrogen bond interactions with amino acids LEU 686, VAL 757, GLU 755, and LYS 709, along with hydrophobic interactions involving amino acids LEU 810, LEU 686, VAL 694, ALA 707, VAL 738, MET 754, and VAL 757 (Table 2; Figure 3).

Table 2. Interacting amino acids at the active site with the lead compounds and standard drug.

Compound name	Docking score (Kcal/ mol)	H-Bond	Hydrophobic interacting amino acids	Other interactions
Myricetin	-10.616	LEU 686, VAL 757, LYS 709, ASP 822	VAL 694, LEU 810, LEU 686, ALA 707, MET 754, VAL 738, VAL 757	NONE
Quercetin	-10.162	ASP 822, LYS 709, VAL 757, LEU 686	LEU 810, VAL 694, LEU 686, ALA 707, MET 754, VAL 738, VAL 757	NONE
Luteolin	-9.636	LEU 686, VAL 757	ALA 707, MET 754, VAL 738, VAL 694, VAL 757, LEU 810, LEU 686	NONE
Kaempferol	-9.031	LEU 686, VAL 757, GLU 755, LYS 709	LEU 810, LEU 686, VAL 694, ALA 707, VAL 738, MET 754, VAL 757	NONE
Epigallocatechin	-8.955	ASN 808, SER 821, GLU 755, VAL 757	ALA 707, LEU 810, VAL 738, VAL 694, MET 754, VAL 757, LEU 686	NONE
CAMPTOSAR	-3.973	ASP 807	LEU 686, LEU 810, VAL 694, VAL 738, PRO 758, VAL 757, MET 754, MET 754, TRY 814, LEU 765, ALA 764	NONE

In the proximity of the ASK-1 binding site, Epigallocatechin established hydrogen bonds with amino acids: ASN 808, SER 821, GLU 755, and VAL 757 while simultaneously forming hydrophobic bonds with amino acids: ALA 707, LEU 810, VAL 738, VAL 694, MET 754, VAL 757, and LEU 686. Epigallocatechin had a docking score -8.955kcal/mol.

The findings of this study align with the results of earlier studies. A study corroborated the presence of the same amino acids at the active site that was identified in this study [30]. Additionally, another independent study underscored the pivotal role of LEU 686 as a key amino acid at the active site, further validating its significance in ligand binding [31]. Interestingly, the top ligands identified in this study demonstrated their modulatory capabilities by forming H-bonds and hydrophobic interactions with LEU 686.

Hydrogen bonds are significant because they contribute to the specificity and stability of the ligand-protein interaction. In this study, Myricetin forms hydrogen bonds with key amino acids like LEU 686, VAL 757, LYS 709, and ASP 822, which enhance its binding stability in the active site. The more stable and specific the binding, the more likely the ligand will effectively inhibit the target protein's activity. Hydrophobic interactions with residues such as VAL 694, LEU 810, ALA 707, and MET 754 are crucial for strengthening the binding of the ligand in a non-aqueous environment within the protein's active site. These interactions contribute to a higher binding affinity by minimizing the free energy of binding and promoting a better connection between the ligand and the protein. The combination of these interactions (hydrogen bonding and hydrophobic) determines the overall strength of the ligand's binding affinity, which is reflected in the docking scores and MM-GBSA values. A stronger binding affinity suggests that the compound may be a more effective inhibitor, making it a promising candidate for drug development.

3.3. Drug likeness and ADME analysis.

The assessment of ADMET properties played a pivotal role in elucidating the compounds' *in vitro* pharmacokinetic and toxicological behaviors [32]. Initial screening for adherence to Lipinski's rule of five, a well-accepted guideline for drug-like characteristics, was carried out. The QikProp software facilitated property calculation, while the admetSAR web tool conducted more detailed ADMET profiling (Figure 5). Except for Myricetin, Epigallocatechin, and CAMPTOSAR, violating just one criterion, all of the top bioactive compounds successfully complied with Lipinski's rule, a fundamental criterion for orally administered drugs. This conformance signifies that these compounds possess drug-like attributes, rendering them suitable candidates for oral administration [33]. Orally administered drugs must align with Lipinski's rule of thumb, encompassing specific criteria: a molecular weight below 500 g/mol, no more than ten hydrogen bond acceptors, five or fewer hydrogen bond donors, and a log P value less than five [33]. Deviation from these parameters could lead to inadequate absorption or limited bioavailability, rendering a molecule unsuitable for oral drug administration [25].

Figure 5. ADMET profile of top-ranked compounds and CAMPTOSAR.

Human Intestinal Absorption (HIA), the capacity of drugs to be absorbed through the human gut, holds paramount importance within the ADMET framework [34]. HIA significantly influences the transportation of drugs to their intended targets. Enhanced HIA correlates with superior absorption within the intestinal tract. Notably, all top-ranked compounds, including the standard CAMPTOSAR, are anticipated to exhibit favorable HIA. However, the standard drug, CAMPTOSAR, is predicted to effectively traverse the Blood Brain Barrier (BBB).

Regarding P-glycoprotein-mediated efflux, all leading compounds are identified as non-inhibitors and non-substrates of P-glycoprotein, except for the standard drug. The standard's P-glycoprotein inhibitory role indicates its potential to heighten bioavailability by impeding cellular efflux [35]. Conversely, non-inhibitor status suggests efflux via P-glycoprotein, potentially limiting bioavailability and promoting drug elimination via bile and urine.

Concerning metabolism, Quercetin, Kaempferol, and CAMPTOSAR are identified as substrates of CYP 3A4, a prominent isoform of the cytochrome P450 family. On the other hand, all compounds, excluding Epigallocatechin, are forecasted to inhibit CYP3A4. Non-inhibitory status signifies an absence of interference with the metabolic biotransformation process governed by the isoform. The cytochrome P450 enzymes play a pivotal role in drug elimination through metabolic processes. Inhibiting these enzymes poses a heightened risk of pharmacokinetic interactions, potentially leading to undesirable side effects due to altered drug clearance and accumulation. Figure 5 illustrates that all compounds, including the standard, exhibit non-inhibitory and non-substrate traits for both CYP2D6 and CYP2C9, highlighting their compatibility in terms of these cytochrome P450 isoforms.

In our ADMET analysis, we mainly focused on the inhibitory effects of the compounds on key CYP450 isoforms, including CYP3A4, CYP2D6, and CYP2C9, as these enzymes play critical roles in drug metabolism and can lead to significant drug-drug interactions when inhibited. However, compounds may not only inhibit but also induce CYP450 enzymes, potentially altering the metabolism of other co-administered drugs. CYP450 induction is an important consideration as it can accelerate the metabolism of substrates, reducing their therapeutic efficacy or leading to the formation of toxic metabolites. Inducers of CYP450 enzymes can increase the metabolic clearance of drugs, resulting in lower plasma concentrations and potentially compromising the intended therapeutic effect.

The compounds underwent rigorous scrutiny for hepatotoxicity, carcinogenicity, mutational potential, and eye irritation. Encouragingly, none of the compounds, including the standard, are predicted to be carcinogenic. The Salmonella typhimurium reverse mutation assay (AMES) serves as a preliminary toxicity assessment, determining whether a substance induces mutations in bacteria [36]. Notably, all compounds, except Epigallocatechin and CAMPTOSAR, exhibited AMES positivity.

4. Conclusions

In this in silico study, we explored Apoptosis signal-regulating kinase 1 (ASK-1) inhibition, employing a comprehensive dataset of 77 phytochemicals sourced from *Momordica charantia* (Linn.). Among these, the top five compounds emerged as promising candidates, exhibiting robust binding affinities through molecular docking in comparison to the reference drug, CAMPTOSAR. Notably, the binding energies for these compounds ranged from −10.616 kcal/mol to −8.955 kcal/mol, surpassing the docking score attributed to CAMPTOSAR(-3.973 kcal/mol).To augment our understanding, we subjected the leading compounds and CAMPTOSAR to thorough ADMET analysis, unraveling their potential in terms of absorption, distribution, metabolism, and toxicity. These findings collectively underline the prospective role of these compounds as potential ASK-1 inhibitors, however further in vitro and in vivo, to confirm the true efficacy of these compounds against Pancreatic cancer.

Author Contributions

Conceptualization, D.S.B. and A.P.A.; methodology, D.S.B.; software, D.S.B. and S.C.I.; validation, D.S.B., A.P.A., and J.A.K.; formal analysis, D.S.B. and I.H.A.; investigation, D.S.B., J.A.K., and I.M.A.; resources, D.S.B., F.A.A., and Z.A.A.; data curation, D.S.B. and S.O.S.; writing—original draft preparation, D.S.B.; writing—review and editing, D.S.B., D.A.O., and C.B.I.; visualization, D.S.B. and S.C.I.; supervision, D.S.B. and D.A.O.; project administration, D.S.B.; All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

Not applicable.

Data Availability Statement

Data supporting the findings of this study are available upon reasonable request from the corresponding author.

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Conflicts of Interest

The authors declare no conflict of interest.

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