Naturally Occurring Rhamnopyranose Esters as Anticancer Agents: Molecular Docking and ADMET Study

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Abstract

*After heart disease, cancer continues to be the second most prevalent cause of death in the USA. Several chemotherapeutic treatments (drugs) are available for cancer that use powerful chemicals to kill the body's rapidly proliferating cells. However, recent research disclosed that many clinically viable anticancer drugs have been developed with the help of chemicals originating from plants. A number of phytochemicals isolated from plants possess rhamnopyranoses and some of them are acyl rhamnopyranoses. Encouragingly, such compounds were reported for their cell proliferation and migration inhibition activities against invasive human triple-negative breast cancer cells. In this study, four naturally occurring rhamnopyranose esters were checked against three cancer-related proteins (PDB IDs: 3TJM, 4OAR, and 5FGK) via molecular docking. Rhamnose compounds **3**-**6** showed better binding energy compared to the related standard drugs in use in the hospitals. Compound **6** was found highly potential against all the proteins (-8.5 to -11.3 kcal/mol). ADMET studies have also been discussed in this respect. This study indicated that natural rhamnopyranose esters could be used to stop the spreading of cancer cells like other reported sugar fatty acid esters (SFAEs).*

Keywords: *Anticancer drugs, Cancer, Molecular docking, Natural products, Phytochemicals, Sugar esters, Sugar fatty acid esters (SFAEs).*

1. Introduction

Cancer is a condition marked by abnormal cell growth. It is regarded as one of the world's deadliest diseases. Men are more likely to develop prostate, lung, stomach, colorectal, and liver cancers than women, who are more likely to develop colorectal, breast, lung, thyroid, and cervical cancers [1]. In fact, according to the WHO, cancer is a broad category of disease that can begin in virtually every organ or tissue of the body when aberrant cells grow out of control [1]. By altering or eliminating significant risk factors and putting into practice currently recommended evidence-based preventative methods, between 30% and 50% of cancer-related fatalities could be avoided. However, once a person is affected by uncontrolled cell growth medication/therapeutic treatment is essential. Standard chemotherapy does not always stop cell motility; instead, it generally causes programmed cell death in cancer cells that divide quickly through mechanisms such as suppression of cell division

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and interruption of deoxyribonucleic acid/ribonucleic acid (DNA/RNA) synthesis [2]. Therefore, searching for novel therapeutic agents is essential.

There is a growing tendency to use natural compounds as drugs and some of them play an important role in the discovery of anticancer antioxidants [3,4]. For instance, medications used in clinical settings such as taxanes, doxorubicin, epothilones, vincristine, and camptothecin are either derived from natural products or were discovered from parent natural product compounds [5,6]. Carbohydrates are abundant in phytochemicals and sugar esters (SEs) are also present in them. Sugar fatty acid esters (SFAEs) are biodegradable, non-ionic surfactants with amphiphilic properties of interest to prepare many biologically active and household products [7]. They have broad uses in the food, pharmaceutical, detergent, agricultural, fine chemical, and personal care sectors because of their effective stabilizing and conditioning qualities [8-13]. SFAEs can be created through the esterification of non-polar fatty acids with sugar/sugar alcohols [14-20]. Their properties vary with the degree of substitution (DS) and hence, they have attracted a lot of scientific attention. Moreover, having numerous stereocenters and functionality, carbohydrates provide synthetic chemists a convenient way to obtain chiral intermediates at low cost for application in the synthesis of natural products [21,22].

Among the monosaccharides, L-rhamnopyranose is a widely distributed natural sugar that is present in a wide variety of natural carbohydrates [23,24]. For instance, the actinomycete *Norcardia brasiliensis* IFM0406 broth included brasilicardin A (**1**, Figure 1), which has two rhamnopyranosyl moieties. The immunosuppressive properties are brought on by the addition of 3-hydroxybenzoate esters in the 3- and 4-positions of its rhamnose unit(s) [25]. Against glutamate-induced neurotoxicity, 2-*O*-acetyl-3,4-di-*O*-(*E*)-pmethoxycinnamoyl-L-rhamnopyranoside from *S. buergeriana* showed significant protective benefits [26]. The enzyme 3-hydroxysteroiddehydrogenase, which is a useful target in the search for antiphlogistic and antitumor drugs, has been reported to be inhibited by a number of rhamnopyranoside derivatives that have been isolated and discovered from several species of *Streptomyces* [27,28]. In our Organic laboratory, several rhamnose esters (**2a-e**) were synthesized and found to show antimicrobial potentiality [29-33].

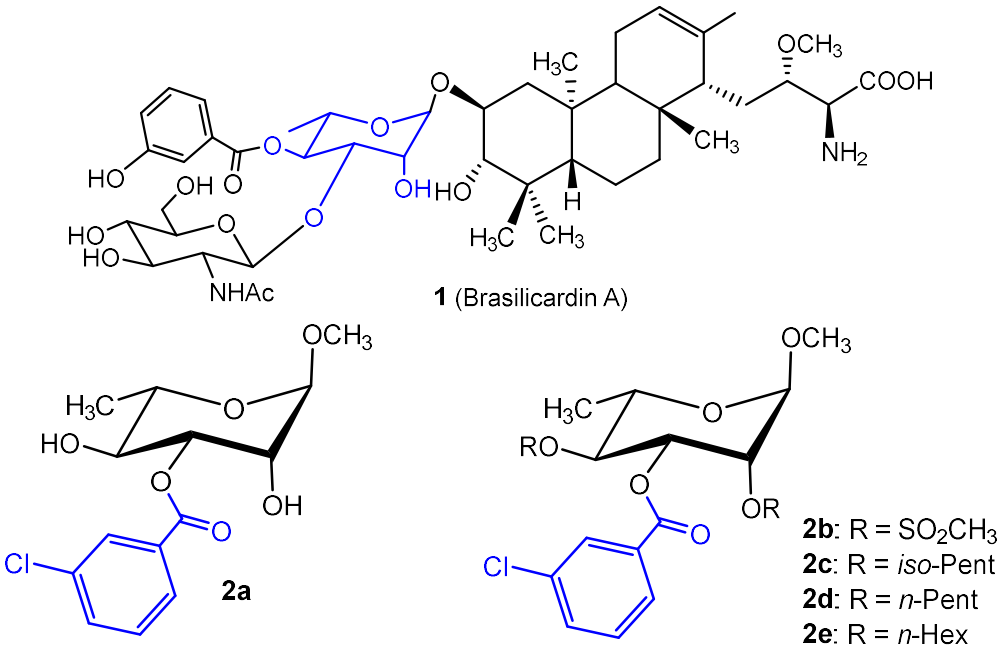

Figure 1. Natural and synthetic rhamnose compounds of biological interest.

There is a long tradition of using medicinal herbs to treat various disorders, including cancer. Several clinically viable anticancer drugs have been developed with the help of chemicals originating

from plants. In this context, some compounds (quercitin, quercitrin, and salanin, etc.) from the leaves of *Azadirachta indica* were performed docking studies with yeast Cdk protein and showed good interaction with the cdc28 protein [34]. Recently (2022), ethyl acetate and chloroform extracts of *Ifloga spicata* were found highly active against HepG-2 cell line (MTT assay, IC_{50} values 5.54 and 6.52 µg/mL, respectively) [35]. According to Snoch et al. [36], altering the hydrophobic chains of sugar fatty acid esters (SFAEs) can change how hazardous they are to human skin melanoma and prostate cancer cell lines. The synthesized SFAEs showed potential metastatic properties with IC_{50} values 63.3–1737.6 µM.

As a continuation of our research work on bioactive molecules [37-41], we were interested to check their anticancer potentiality. Thus, four natural rhamnopyranoside esters are considered for their anticancer properties *via* molecular docking and ADMET (absorption, distribution, metabolism, excretion, and toxicity) studies.

2. Materials and methods

2.1. Natural rhamnose-based SFAEs

As mentioned earlier, rhamnose-based esters are available in natural products [42,43]. Compound **3** was isolated and identified from the *Streptomyces* sp. strain TN58 found in Tunisian soil [44]. In 2020, Elmaidomy and co-workers [45] successfully isolated several phytochemicals from the stems of *Premna odorata* B. Among them, three rhamnopyranose-based esters **4**-**6** were characterized by spectral methods. Tests for antioxidant and cell proliferation inhibition activities (using human triple-negative breast cancer cells) were conducted. The results were unambiguously positive and showed enhanced biological potentiality of the separated compounds [45]. These compounds **3**-**6** are used in the present study.

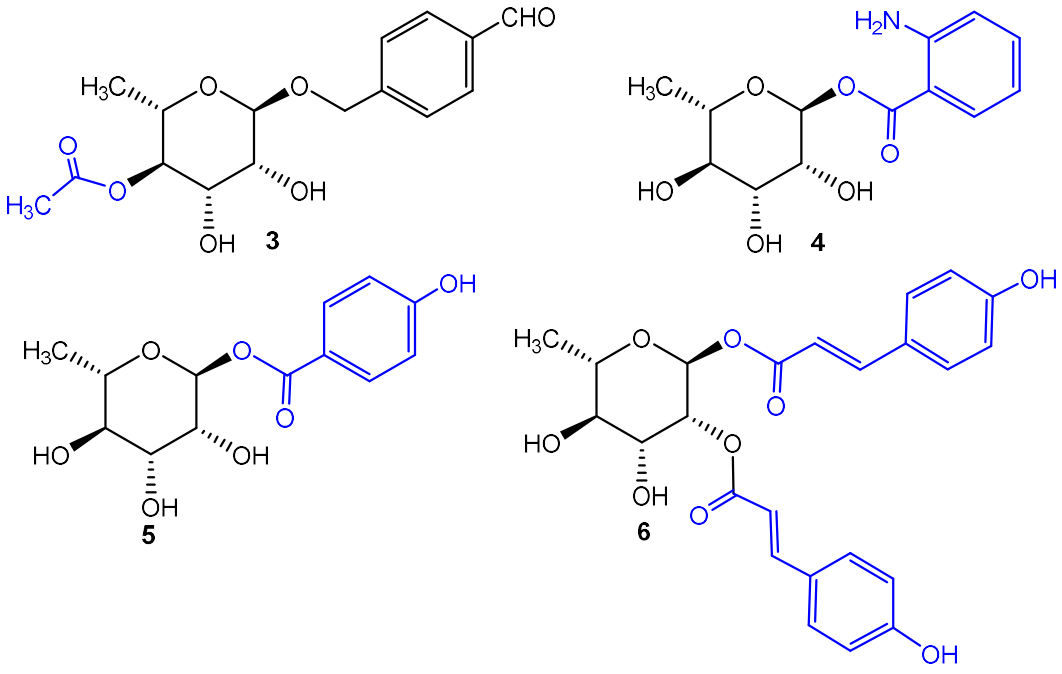

Figure 2. Structures of natural rhmnaose-based SEs 3-6 for anticancer study.

2.2. Methods used for molecular docking

Computer-aided drug design typically makes use of molecular docking (CADD). It can be used

at many stages of the drug design process to: (i) anticipate the binding mode of already known ligands; (ii) find novel and potent ligands; and (iii) as a tool to forecast binding affinity [46,47]. In our study, we used molecular docking of compounds **3**-**6** employing freely available PyRx (AutoDock) software [48,49].

Ligand preparation: Firstly correct structures of all the natural rhamnoses **3**-**6** are drawn in ChemDraw 18.0 and saved as MOL file. These are opened in Chem3D and minimized with MM-2 followed by saving as SDF formats and used for docking in the next step.

Protein preparation: Three cancer-related proteins such as (i) human fatty acid synthase thioesterase (PDB: 3TJM), (ii) progesterone receptor peptide (PDB: 4OAR), and (iii) cyclin-dependent kinase (CDK8) (PDB: 5FGK) were retrieved from the popular RCSB Protein Data Bank [50,51]. After opening these in Discovery Studio, these are dried and unnecessary atoms are removed. These are further opened in Swisspdb software, conducted energy minimization, and saved as pdbqt format.

Docking: In the PyRx software (AutoDock), proteins are loaded followed by the import of ligands. The ligands **3**-**6** are further subjected for energy minimization with PyRx-associated software. At this stage, ligands are selected and proceed to the next step where maximum box sizes were used. Docked complexes were duly saved, and opened in the Discovery Studio and necessary data has been collected [52,53].

2.3. ADMET calculation

Chemical absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiling aids in reducing potential dangers throughout clinical development [54]. Scientists are aware that ADMET profiling is required to identify whether or not a molecule is suitable to advance to the clinical stage because drug development failures might be caused by efficacy or safety difficulties [55,56]. Utilizing the pkCSM tool (http://biosig.unimelb.edu.au), *in silico* ADMET was calculated for the current experiment [57]. For the calculation of pkCSM-pharmacokinetics, the appropriate stereochemical structures of the SEs **3**–**6** were translated to the respective SMILES (simplified molecular-input line-entry system) and SD file formats. Using SwissADME's free web tools (http://www.swissadme.ch), the comparable SMILES and SD file formats were also employed to predict drug-likeness features [58].

3. Results and discussion

3.1. Molecular docking: Binding energy with cancer causing protein 3TJM

Mixed, targeted, and customized therapy is being employed to treat cancer increasingly frequently these days. The most promising treatments target tumor cells in a host body using inspiration from nature. Synthetic and highly effective therapies sometimes look insufficient as well as costly. Attention was made to get natural therapeutic agents like sugar fatty acids esters (SFAEs) and related research started in 1970 [59]. Experimental results explicit SFAEs' ability to inhibit excessive proliferation of cells in the bone marrow. Thus, in the present study, four natural SFAEs 3-6 are considered and checked for their ability to anti-proliferation of cells against three cancer-related proteins.

Firstly, we considered human fatty acid synthase (hFAS) (PDB: 3TJM) as it catalyzes a variety of fatty acid synthesis in the body and causes several diseases including cancers. Hence, hFAS is a target for anti-cancer drug development [60]. Molecular docking binding affinities of **3**-**6** with 3TJM are shown in Table 1. Binding affinities of the natural SFAEs (-6.3 to -11.3 kcal/mol) are comparable to the standard anticancer drug topotecan (-7.4 kcal/mol). Unsaturated acyl rhamnopyranose ester **6** showed the highest binding affinity (-11.3 kcal/mol) followed by 3-*O*-acetyl-rhamnose **3** (-7.7

kcal/mol). Rhamnopyranose-based SFAEs **3**-**6** showed several interactions with amino acid (AA) residues of the enzyme 3TJM like standard topotecan (Table 2). For better visualization, interactions between SFAEs and enzymes are also presented in Figure 3.

Table 1. Molecular docking score (binding affinity) with 3TJM.

Ligand/ Drug	Binding affinity (kcal/mol)	No. of H bond	No. of Hydrophobic bond	No. of van der Waal/ES bond[a]	Total bonds
3	-7.7	2	5	0	7
4	-6.3	0	6	0	6
5	-6.5	0	6	0	6
6	-11.3	0	8	0	8
Topotecan (TPT)	-7.4	3	5	2	10
[a]ES = electrostatic; so far -6.0 kcal/mol is standard docking score					

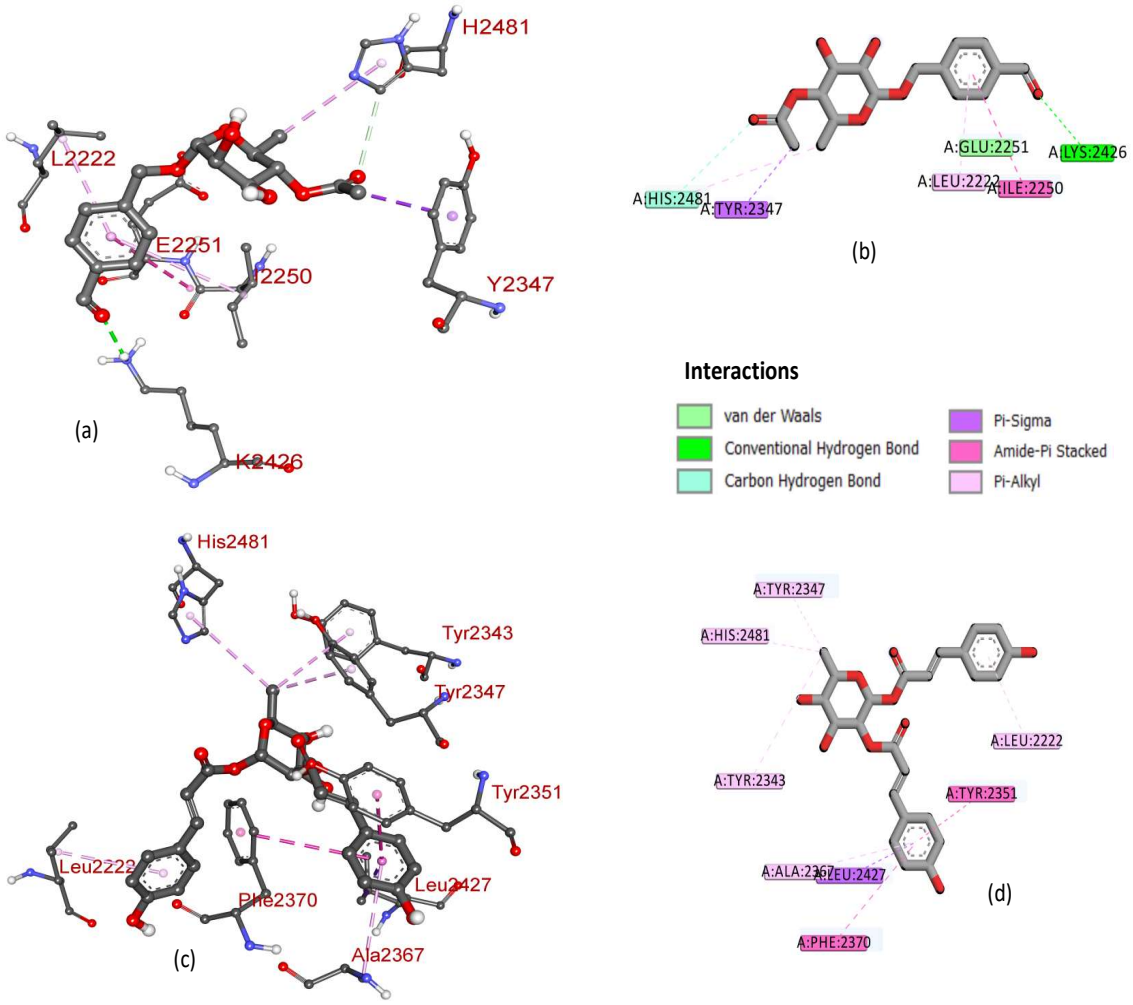

Figure 3. 3D and 2D non-bond interactions of 3TJM with ligands - (*a*), (*b*) **3**; and (*c*), (*d*) **6**.

Table 2. Interaction of compounds with amino acid (AA) residues in compounds-3TJM complex.

Drug	Hydrogen bond		Hydrophobic bond		Van der Waals bond	
	Interacting residue of amino acid	Distance (Å)	Interacting residue of amino acid	Distance (Å)	Interacting residue of amino acid	Distance (Å)
3	LYS2426 HIS2481	2.30659 3.60039	TYR2347 ILE2250 HIS2481 LEU2222 ILE2250	3.77739 4.81434 4.87778 4.68179 5.37677	Absent	
4			TYR2347 ILE2250 PHE2370 PHE2423 ILE2250 VAL2344	4.44896 4.46877 5.47883 4.42897 4.70364 5.15332	Absent	
5			TYR2347 ILE2250 PHE2370 PHE2423 ILE2250 VAL2344	4.44896 4.46877 5.47883 4.42897 4.70364 5.15332	Absent	
6			LEU2427 TYR2351 PHE2370 TYR2343 TYR2347 HIS2481 LEU2222 ALA2367	3.89325 4.10401 5.72170 5.31378 4.18470 4.94343 4.63617 4.96877	Absent	
Topotecan (TPT)	SER2221 GLU2251 TYR2307	2.59638 2.91400 3.14200	ALA2482 HIS2481 VAL2256 ALA2482 ILE2250	4.63781 5.17995 5.37410 4.67044 5.18481	GLU2251 GLU2251	3.51756 4.07741

Note: TRP = Tryptophan, ASP = Aspartic acid, GLU = Glutamic acid, LEU = Leucine, THR = Threonine, ASN = Asparagine, GLN = Glutamine, PHE = Phenylalanine, ILE = Isoleucine, ARG = Arginine, VAL = Valine, SER = Serine, PRO = Proline, GLY = Glycine, HIS = Histidine, LYS = Lysine, TRP = TRPosine, CYS = Cysteine, MET = Methionine.

3.2. Molecular docking: Binding energy with cancer causing protein 4OAR

Our next target enzyme was the human progesterone receptor (PR) related protein (PDB: 4OAR). Most breast cancer drugs are targeting human PR [61]. For example, a highly selective PR antagonist is ulipristal acetate (UPA) is available in the market. Thus, 4OAR was adopted for molecular docking with rhamnose-based SEs **3**-**6**. Docking results are presented in Table 3.

It is clear from Table 3 that SEs **3**-**6** have a higher binding affinity (BA) (-7.7 to 8.9 kcal/mol) compared to the standard ulipristal acetate (-6.9 kcal/mol). Rhamnose ester **6** showed the maximum BA (-8.9 kcal/mol) followed by acetate **3** (-8.5 kcal/mol). All the compounds have a variety of bonding and non-bonding interactions compared to the ulipristal acetate (Table 4 and Figure 4). Both ulipristal acetate and compound **6** interact with CYS891 in chain A. Additionally, rhamnose esters several hydrogen bonds with the amino acid residues of chain A (Table 4). These H-bonds are

probably responsible for their higher binding affinities.

Table 3. Molecular docking score (binding energy) with 4OAR.

Ligand/ Drug	Binding energy (kcal/mol)	No. of H bond	No. of Hydrophobic bond	No. of van der Waal/ES[a] bond	Total bonds
3	-8.5	3	4	1	8
4	-7.8	6	6	1	13
5	-7.7	4	6	1	11
6	-8.9	3	7	0	10
Ulipristal acetate	-6.9	0	2	0	2
[a]ES = electrostatic; so far -6.0 kcal/mol is standard docking score					

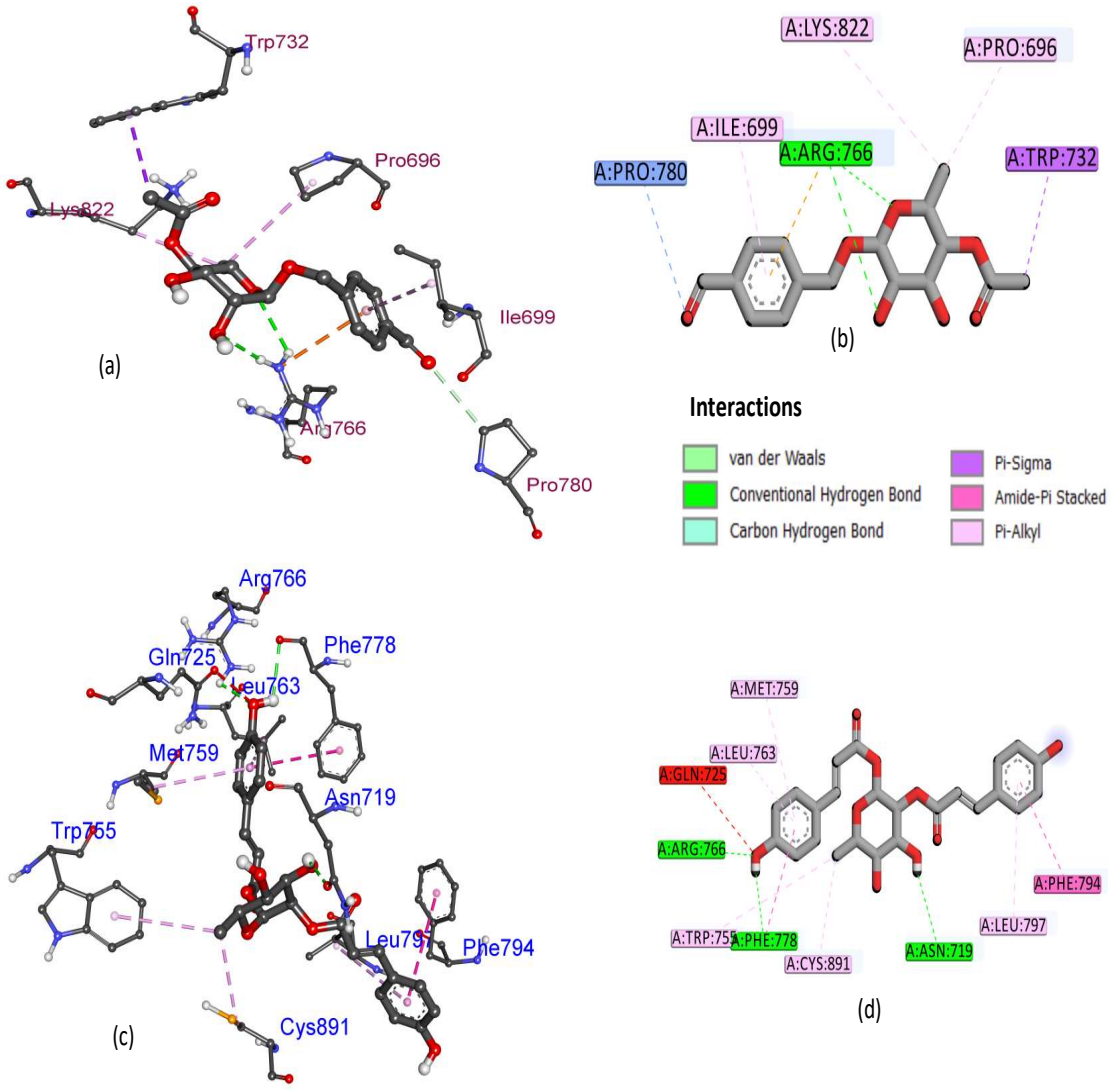

Figure 4. 3D and 2D non-bond interactions of 4OAR with ligands - (*a*), (*b*) **3**; and (*c*), (*d*) **6**.

Table 4. Interaction of compounds with amino acid (AA) residues in compounds-4OAR complex.

Drug	Hydrogen bond		Hydrophobic bond		Van der Waals /ES bond	
	Interacting residue of amino acid	Distance (Å)	Interacting residue of amino acid	Distance (Å)	Interacting residue of amino acid	Distance (Å)
3	ARG766 ARG766 PRO780	2.71903 2.94511 3.50793	TRP732 PRO696 LYS822 ILE699	3.98838 4.95069 5.23245 4.58957	ARG766	4.02901
4	ARG766 ILE699 PHE778 GLN725 UNK1 ILE699	2.20714 2.88715 2.57122 2.19084 2.34771 2.63355	VAL698 ASP697; VAL698 PRO696 LYS822 PHE818 ILE699	3.87101 4.64534 4.97147 5.17104 5.24640 5.27371	ARG766	4.21398
5	SER728 ARG766 PRO696 LYS822	2.83544 2.04286 2.41457 3.24195	VAL729 TRP732 TRP732 ILE699 PRO696 LEU758	3.60331 5.57146 5.52667 4.24415 4.83511 5.30345	LYS822	3.24195
6	ARG766 PHE778 ASN719	2.49600 2.64071 2.36963	PHE794 PHE778 CYS891 TRP755 MET759 LEU763 LEU797	5.12810 4.99925 4.10214 5.01043 5.15711 5.10761 5.41374	Absent	
Ulipristal acetate			MET759 CYS891	4.60149 4.87029	Absent	

Note: TRP = Tryptophan, ASP = Aspartic acid, GLU = Glutamic acid, LEU = Leucine, THR = Threonine, ASN = Asparagine, GLN = Glutamine, PHE = Phenylalanine, ILE = Isoleucine, ARG = Arginine, VAL = Valine, SER = Serine, PRO = Proline, GLY = Glycine, HIS = Histidine, LYS = Lysine, TRP = TRPosine, CYS = Cysteine, MET = Methionine.

3.3. Molecular docking: Binding energy with cancer causing protein 5FGK

With good molecular BAs of rhamnopyranose SEs **3**-**6** in the previous sections, we employed another cancer-related enzyme cyclin-dependent kinase (CDK8; PDB: 5FGK). In colon and stomach malignancies, the expression of the CDK8 gene is correlated with the activation of -catenin, a crucial transcriptional regulator of canonical WNT signaling [62]. Molecular docking BAs of **3**-**6** with 5FGK are presented in Table 5. In this case also, compound **3** and **6** showed excellent binding affinities. For validation, docking scores are compared with standard drug named ribociclib. Ribociclib (KISQALI®) is a pill that is referred to as a targeted treatment because it interferes with or blocks chemicals that are involved in the proliferation of cancer cells. It is not chemotherapy. With respect to ribociclib (-8.9 kcal/mol) rhamnose esters shoed slightly lower binding affinities (-8.5 to -7.5 kcal/mol). For better understanding, related interactions are presented in Figure 5 and Table 6 including standard drug.

Table 5. Molecular docking score (binding energy) with 5FGK.

Ligand/ Drug	Binding energy (kcal/mol)	No. of H bond	No. of Hydrophobic bond	No. of van der Waal/ES[a] bond	Total bonds
3	-7.7	3	5	0	8
4	-7.6	5	5	0	10
5	-7.5	4	4	0	8
6	-8.5	4	8	0	12
Ribociclib	-8.9	2	5	0	7
[a]ES = electrostatic; so far -6.0 kcal/mol is standard docking score					

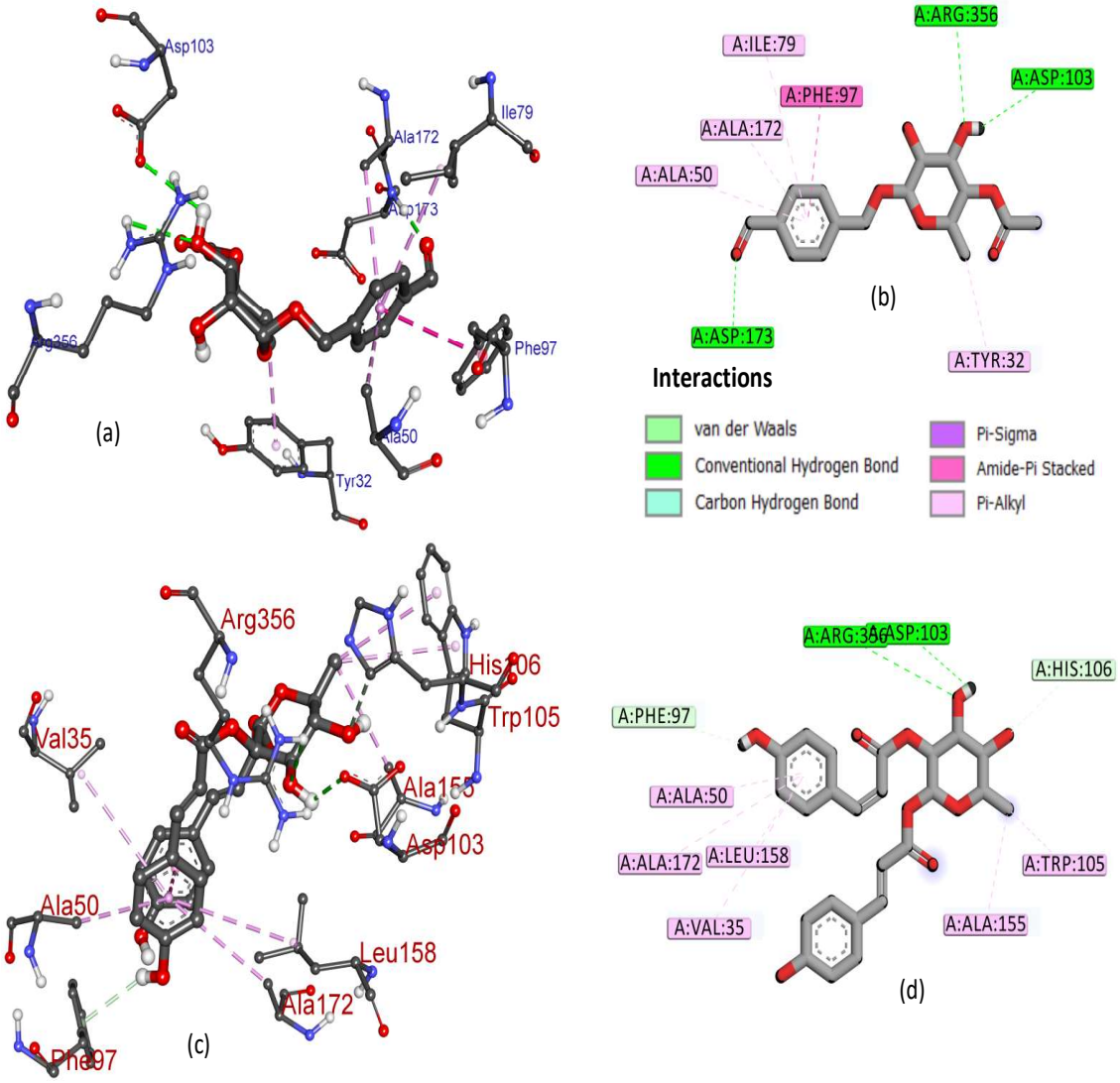

Figure 5. 3D and 2D non-bond interactions of 5FGK with ligands - (*a*), (*b*) **3**; and (*c*), (*d*) **6**.

Table 6. Interaction of compounds with amino acid (AA) residues in compounds-5FGK complex.

Drug	Hydrogen bond		Hydrophobic bond		Van der Waals /ES bond	
	Interacting residue of amino acid	Distance (Å)	Interacting residue of amino acid	Distance (Å)	Interacting residue of amino acid	Distance (Å)
3	ASP173 ARG356 ASP103	1.95773 2.96779 2.87197	PHE97 TYR32 ALA50 ILE79 ALA172	4.11637 4.01255 5.30722 5.07992 4.75260	Absent	
4	ALA100 ARG356 UNK1 ASP98 TYR99	2.79575 3.01603 2.78748 2.52265 3.30698	TYR32 ALA172 ILE79 LEU158 PHE97	3.74731 4.47971 3.96125 5.18217 4.56786	Absent	
5	ARG356 ARG356 ALA100 ASP98	2.96723 2.33521 2.35948 2.84600	TYR32 ALA172 LEU158 VAL35	3.69290 3.72080 4.69089 4.94948	Absent	
6	ARG356 ASP103 HIS106 PHE97	2.85220 2.39185 3.74545 2.91772	UNK1 ALA155 TRP105 TRP105 VAL35 ALA50 LEU158 ALA172	3.68384 4.39449 4.81519 4.72126 5.22754 4.67866 5.40142 5.25045	Absent	
Ribociclib	LYS52 GLU357	2.27737 2.59651	TYR32 VAL35 ALA50 LYS52 TYR32	3.90735 3.89390 5.29917 4.69478 5.27449	Absent	

Note: TRP = Tryptophan, ASP = Aspartic acid, GLU = Glutamic acid, LEU = Leucine, THR = Threonine, ASN = Asparagine, GLN = Glutamine, PHE = Phenylalanine, ILE = Isoleucine, ARG = Arginine, VAL = Valine, SER = Serine, PRO = Proline, GLY = Glycine, HIS = Histidine, LYS = Lysine, TRP = TRPosine, CYS = Cysteine, MET = Methionine.

3.4. ADMET results of rhamnopyranose esters 3-6

Having good molecular binding affinities rhamnopyranose SEs **3**-**6** are placed for ADMET calculations. For validity, three standard anticancer drugs are also used for ADMET prediction. As shown in Table 7, human intestinal absorption (HIA) and p-glycoprotein inhibition (P-gpi) of the SEs are comparable to the standard anticancer drugs (topotecan, ribocicilib). All the compounds can pass through the blood-brain barrier (BBB) and central nervous system. However, they are non-substrate of CYP3A4 (except **3**). Their excretion in terms of total renal clearance is comparable to the standard drugs (Table 7). Encouragingly, these compounds **3**-**6** are non-inhibitor of hERG and hence these SEs are safe. These ADME data are in accord with previously reported articles [63.64].

Table 7. ADMET properties of rhamnose compounds **3**-**6** with standard drugs.

Drug	Absorption			Distribution		Metabolism	Excretion	Toxicity	
	C2P	HIA (%)	P-gpI	BBB (permeability)	CNS (permeability)	CYP3A4 substrate	Total clearance (mL/min/kg)	hERG inhibitor	Acute LD_{50} (mol/kg)
3	1.323	95.751	Yes	-1.234	-3.237	Yes	0.698	No	2.585
4	0.210	56.289	No	-0.807	-3.632	No	0.221	No	1.616
5	0.255	53.035	No	-0.972	-3.179	No	0.629	No	1.960
6	-0.243	58.757	Yes	-1.343	-3.392	No	0.219	No	3.036
Topotecan	0.926	76.772	No	-1.005	-3.823	Yes	1.144	No	3.061
Ulipristal acetate	0.706	98.895	Yes	-0.038	-1.684	Yes	0.249	No	2.706
Ribociclib	1.323	95.751	Yes	-1.234	-3.237	Yes	0.698	No	2.585

4. Conclusion

Natural phytochemicals serve as vital resources for developing new medications and are also used in the treatment of cancer. Here, 4 natural rhamnopyranose esters **3**-**6** are successfully docked with cancer-causing three enzymes, namely human fatty acid synthase (3TJM), human progesterone receptor (4OAR), and cyclin-dependent kinase (5FGK). The results are found to be encouraging and are in conformity with some *in vitro* results. Especially, 2-*O*-(*p*-hydroxycinnamoyl)-rhamnose ester **6** and 4-*O*-ehanoylrhamnose ester **3** bearded excellent binding affinities with all three types of cancer target proteins with a good number of hydrogen bonds. These observations will hopefully pave a way for the establishment of anticancer agents from the biodegradable rhamnopyranose scaffold.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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