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Original Article

Molecular docking of two cytotoxic compounds from *Calotropis gigantea* leaves against therapeutic molecular target of pancreatic cancer

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Abstract

The utilization of natural compounds as therapeutic agents to treat pancreatic cancer has recently focused on natural drug research. *Calotropis gigantea* has long been believed to be a medicinal plant that helps in treating various diseases. The bioactive compounds 9-metoxipinoresinol and isoliquiritigenin isolated from *C. gigantea* leaves are proven to act as therapeutic agents by inhibiting the cancer cell growth of Panc-1 cells. This study aimed to screen the potential molecular inhibition mechanisms of 9-metoxipinoresinol and isoliquiritigenin against pancreatic cancer development *in-silico*. We analyzed the activity of the aforementioned two compounds as inhibitors of several proteins that play a role in the growth of pancreatic cancer cells, such as GCNT3, GOT1, c-Met, PPARγ, BUB1, and NF-κβ, through molecular docking investigation. Our data suggested that 9-metoxipinoresinol and isoliquiritigenin were able to have well interaction with the target proteins, in which the predicted affinity energy ranged between -6.8 and 8.7 kcal/mol. The docking scores of 9-metoxipinoresinol and isoliquiritigenin were higher than the standard drug used (gemcitabine). Based on the binding affinity energy, GCNT3 and BUB1 are potentially to be used as target molecules for cancer therapy using 9-metoxipinoresinol and isoliquiritigenin, respectively.

Keywords: Panc-1 cells, *Calotropis gigantea*, GCNT3, BUB1, natural compound

Introduction

Calotropis gigantea is one of the herbs used for treatment of a variety of diseases. The bioactivity of various plant extracts has been presented to possess anticancer, antimalarial, antirheumatic, and antidiabetic potential associated with various secondary metabolites [1]. Natural compounds of 9-metoxipinoresinol and isoliquiritigenin, isolated from extract of *C. gigantea*, showed a potent cytotoxic activity against pancreatic cells[2]. Both compounds have an inhibition values (IC_{50}) below 5 μM against Panc-1 cells, which are lower than that of standard drug – gemcitabine (IC_{50}>25 μM) [2].

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Pancreatic cancer is one of the deadliest diseases and the percentage of deaths reaches 90% of the total cases [3]. The innovative treatment for this disease is continually being developed, where natural compounds have been considered as an alternative source to inhibit cancer cell growth by targeting its growth receptors. In this light, the Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation pathway mostly influences the cell growth of pancreatic cancer. Glucosaminyl (N-acetyl) transferase 3, mucin type (GCNT3) and nuclear factor kappa beta (NF-κβ) are proteins that play important roles in the KRAS pathway [4,5]. Other receptors such as glutamate oxaloacetate transaminase 1 (GOT1), tyrosine-protein kinase Met(c-Met), peroxisome proliferator-activated receptor (PPAR)γ, and budding uninhibited by benzimidazoles 1 (BUB1) are also cancer receptors used as therapeutic targets by suppressing the cell proliferation process [6–8]. Based on our previous research, the active compound in the *C. gigantea*, caloptropone, has a potent affinity energy in binding to the pancreatic cancer receptor, with the most active value of -9.1 kcal/mol (unpublished). The search for new target molecules of 9-metoxipinoresinol and isoliquiritigenin could be more efficiently conducted with the information from molecular docking simulation.

Molecular docking is a method of analyzing new drugs against their target proteins. The active compound works by binding to the target protein through different orientations. This docking method can provide the optimal orientation information by predicting the affinity energy and compound activity [9]. This method relies on the 3D structure information of a target and the electronics of the ligand to the target[10]. This article presents information about the affinity energy produced by 9-metoxipinoresinol and isoliquiritigenin through the molecular docking method. In comparison to the traditional *in-vitro* or *in-vivo* study, computational study using molecular docking could provide fast screening of probable molecular interaction. However, the results of computational studies should be confirmed using laboratory-based studies.

Methods

Hardware and software

Docking simulations were carried out on an Intel Celeron N3350 Acer computer, 1.00 GB memory processor (RAM), 32-bit operating system, Windows 10 pro. LigPlot +1.5.4, PyMOL 2.4 (Delano Scientific LLC, Italy), ChemDraw Ultra 12.0, Chem3D Pro 12.0, Gauss view, Discovery Studio Visualizer 4 and AutoDock Vina assisted by AutoDock Tools 5.6 were used during the simulations.

Ligand structure preparation

The structures of isoliquiritigenin (CID: 638278) and gemcitabine (CID: 60750) were obtained from the PubChem chemical structure database (www.pubchem.ncbi.nlm.nih.gov). The ligand structure was converted from the SDF format into PDB format using Pymol 2.4 software. The 9-metoxipinoresinol structure was created using ChemDraw Ultra 12.0, then converted to 3D with chem3D pro12.0. The structure of 9-metoxipinoresinol was optimized using Gaussian display and saved in PDB file format.

Proteins' preparation

Protein structures of GCNT3 (PDB ID: 2GAM), GOT1 (PDB ID: 3II0), c-Met (PDB ID: 6SD9), PPARγ (PDB ID: 3U9Q), BUB1 (PDB ID: 4QPM), NF-κβ (PDB ID: 1SVC), SOX2 (PDB ID: IGT0), and ADAM10 (GDP ID: 6BE6 were retrieved from the Protein Data Bank (PDB) (https://www.rscb/pdb.org). All protein data were stored in pdb format. Protein structures were prepared by removing molecules and ligands using Discovery Studio Visualizer 4.

Molecular docking

The 3D structure of the ligand and protein was added with polar hydrogen atoms and Gasteiger partial charge were carried out in the AutoDock Tools 1.5.6.rc3 and saved in pdbqt for further analysis. AutoDock Vina was used in the docking simulation with a predetermined grid box position and protein macromolecules remained rigid during the docking simulation[11]. Ten docking pose protein–ligand conformations were selected from Vina's AutoDock scoring function, and they were ranked according to their affinity energy. The conformation with the best

affinity energy was visualized using LigPLot +1.5.4 to show hydrogen bond interactions, hydrophobic interactions and bond distances, while the 3D interactions were visualized using PyMOL 3.1.

Results

Docking score

Affinity energy through ligand and protein binding is presented in **Table 1**. The 9-metoxipinoresinol and isoliquiritigenin bind to this target with high binding energies. Affinity energy produced was relatively high with best affinity energy for 9-metoxipinoresino against GCNT3 (-8.7 kcal/mol), whereas isoliquiritigenin had the best docking conformation with an affinity energy of -8.7 kcal/mol against BUB1. The affinity energies of 9-metoxipinoresinol and isoliquiritigenin also had better values than the reference drug (gemcitabine). Gemcitabine only produced the best affinity energy of 7.1 kcal/mol against GOT1.

Interaction of ligand and protein

The interaction formed between the ligand and protein affects the affinity energy. **Figure 1-3** show the polar hydrogen and hydrophobic interactions between the compound ligands and the target proteins. Gemcitabine has the best affinity energy in GOT1. This energy is generated from 2 hydrogen bonds (Ala191 (2.88 Å) and Asp200 (2.80 Å)) and 8 hydrophobic interactions (Asp237, Thr202, Arg236, He358, Pro201, Cys192, Ser231, Ala230) (**Figure 1**). The strongest hydrogen bond interaction occurred at Asp200 via hydrogen bonding to the gemcitabine atom with the oxygen atom (C terminal) of the Asp200.

The best affinity energy produced by isoliquiritigenin was in BUB1. Their interaction consists of three hydrogen bonds (Tyr869 (2.92 Å), Glu867 (3.18 Å), and Lys821 (3.14 Å)) and 13 hydrophobic interactions (Asp921, Asn922, Gly796, Glu795, Val801, Gly794, He945, Val819, Asp946, He924, Ala799, Met850, Leu868) (**Figure 2**). The strongest hydrogen bond occurred with the oxygen atom of the C-terminal at His144 with the hydrogen atom on isoliquiritigenin.

The 9-metoxipinoresinol had the most effective energy against GCNT3 and the interactions formed were two hydrogen bonds with Ala188 (2.78 Å) and Glu243 (2.78 Å) and eight hydrophobic interactions with Tyr187, Glu320, Arg109, Ala287, Lys288, Val254, Trp356 and Ser286 (**Figure 3**). The strongest polar hydrogen interaction occurred at hydrogen atom of 9-methoxypinoresinol with the oxygen atom of the side chain in Glu243.

Discussion

Our data suggest that two natural compounds derived from *C. gigantea*, 9-metoxipinoresinol and isoliquiritigenin, have a higher affinity energy than gemcitabine for each pancreatic cancer receptor, which may be better at inhibiting the growth of pancreatic cancer cell processes (**Table 1**). The value binding affinity informs the likelihood of interaction between the tested molecules, thus, might suggest the potential inhibition. Affinity energy greater than 5 kcal/mol indicates an effect on the receptor [12] and the resulting affinity energy guides us to the strength of the binding bond between the ligand and the receptor.

The 9-metoxipinoresinol has the best binding to the GCNT3. GCNT3 upregulates mucin biosynthesis and is associated to KRAS mutation [5,13]. The 9-metoxipinoresinol could be used as a new inhibitor to treat pancreatic cancer via the GCNT3 pathway, evidenced by the affinity energy that is similarly produced by talniflumate against the same protein[5]. The 9-metoxipinoresinol is a new compound and studies confirming its activity as an inhibitor against other cancer cells are still very rare. However, the parent compound of 9-metoxipinoresinol, pinoresinol, has been shown to inhibit the growth of several cancer cells. Pinoresinol attenuated LPS-induced phosphorylation of ERK1/2 MAPK and inhibit mutant p53 protein, which are targets for pancreatic cancer therapy [14–16]. Inhibition of c-Met decreased ERK 1/2 [17]. Meanwhile, inhibition of PPARG and BUB1 may have an impact on p53 activity, where PPARG

plays a role in activating the p53 gene and BUB1 involved in the p53 signaling pathway [18,19]. Pinoresinol is also reported to inhibit NF-κβand, therefore is important in reducing cancer cell activity[20].

Table 1. Affinity energy and molecular interaction of gemcitabine, isoliquiritigenin, and 9-metoxipinoresinol with proteins associated with pancreatic cancer cells

Protein	Ligand	Affinity energy (kcal/mol)	Interaction	Amino acids
GCNT3	Gamcitabine	-6.5	HI	Ser317, Ala188, Tyr187, Lys401, Cys217, Tyr288, Glu320
			PHI	Arg378, Asp319, Asn400
	Isoliquiritigenin	-7.8	HI	Glu243, Val354, Asn400, Tyr228, Val380, Ser286, Trp356, Glu320, Gly285
			PHI	Asp346, Arg378, Lys401
	9-metoxipinoresinol	-8.7	HI	Tyr187, Glu320, Arg109, Ala287, Lys288, Val254, Trp356, Ser286
			PHI	Ala188, Glu243
GOT1	Gamcitabine	-7.1	HI	Asp237, Thr202, Arg236, He358, Pro201, Cys192, Ser231, Ala230
			PHI	Ala191, Asp200
	Isoliquiritigenin	-7.9	HI	Gly108, Ser258, Phe19, tYr264, Lys259, Trp141, Tyr226, Asn195, Ala225, Thr110
			PHI	Arg267, Arg267, Arg267, Asp223
	9-metoxipinoresinol	-7.7	HI	Phe19, Tyr264, Thr110, Ser258, Trp141, Tyr226
			PHI	Arg267, Arg267, Lys259
c-Met	Gamcitabine	-6.3	HI	Ala1221, Phe1134, Met1131, Val1220, Leu1195, His1202, Phe1200, Gly1224
			PHI	Glu1127, Asp1222
	Isoliquiritigenin	-8.1	HI	Val1092, Phe1223, Lau1157, Ala1108, Gly1163, Met1211, He1084
			PHI	Asp1222, Lys1110
	9-metoxipinoresinol	-8.0	HI	Ala1108, Val1092, Phe1223, Glu1127, Ala1221, Phe1134, Met1131, Asp1222, Leu1140, Pro1158, Lys1110, Met1160, Leu1157
			PHI	-
PPARG	Gamcitabine	-6.4	HI	Lys457, Leu465, He456, Tyr473, Lys474
			PHI	Leu453, Asp475, Gln470
	Isoliquiritigenin	-7.6	HI	Leu353, Phe363, Cys285, Ser289, His323, Leu453, Tyr473, Leu469, His449, Phe282, Phe360, He281, Leu356
			PHI	Ala278
	9-metoxipinoresinol	-8.6	HI	He341, Arg288, He326, Leu3440, Leu333, Met364, ser289, Phe282, Cys285, Leu330, Tyr327
			PHI	His449, Ser342, Glu343, Ser342
BUB1	Gamcitabine	-6.8	HI	He945, He924, Leu793, Val801, Gly794, Gly796
			PHI	Asp946, Asn922, Asp921
	Isoliquiritigenin	-8.7	HI	Asp921, Asn922, Gly796, Glu795, Val801, Gly794, He945, Val819, Asp946, He924, Ala799, Met850, Leu868
			PHI	Tyr869, Glu867, Lys821
	9-metoxipinoresinol	-8.0	HI	Met850, Val801, Gly794, Thr873, Glu795, Leu875, Asp921, Asn876, He924, Leu793, Val819, He945, Leu868, Tyr869
			PHI	None
NF-κβ	Gamcitabine	-5.3	HI	Lys149, Leu143
			PHI	Glu152, Thr153, Arg157, Ser113
	Isoliquiritigenin	-6.8	HI	Val61, Tyr60, Val145, Lys149, Thr153, Ser113
			PHI	Ala62, His144, Thr146, Arg157
	9-metoxipinoresinol	-7.1	HI	Asp121, Leu143, Val145, Val61, Thr146, His144, Thr153
			PHI	Ser113, Arg157, Arg157, Lys149

HI: hydrophobic interaction, PHI: polar H interaction

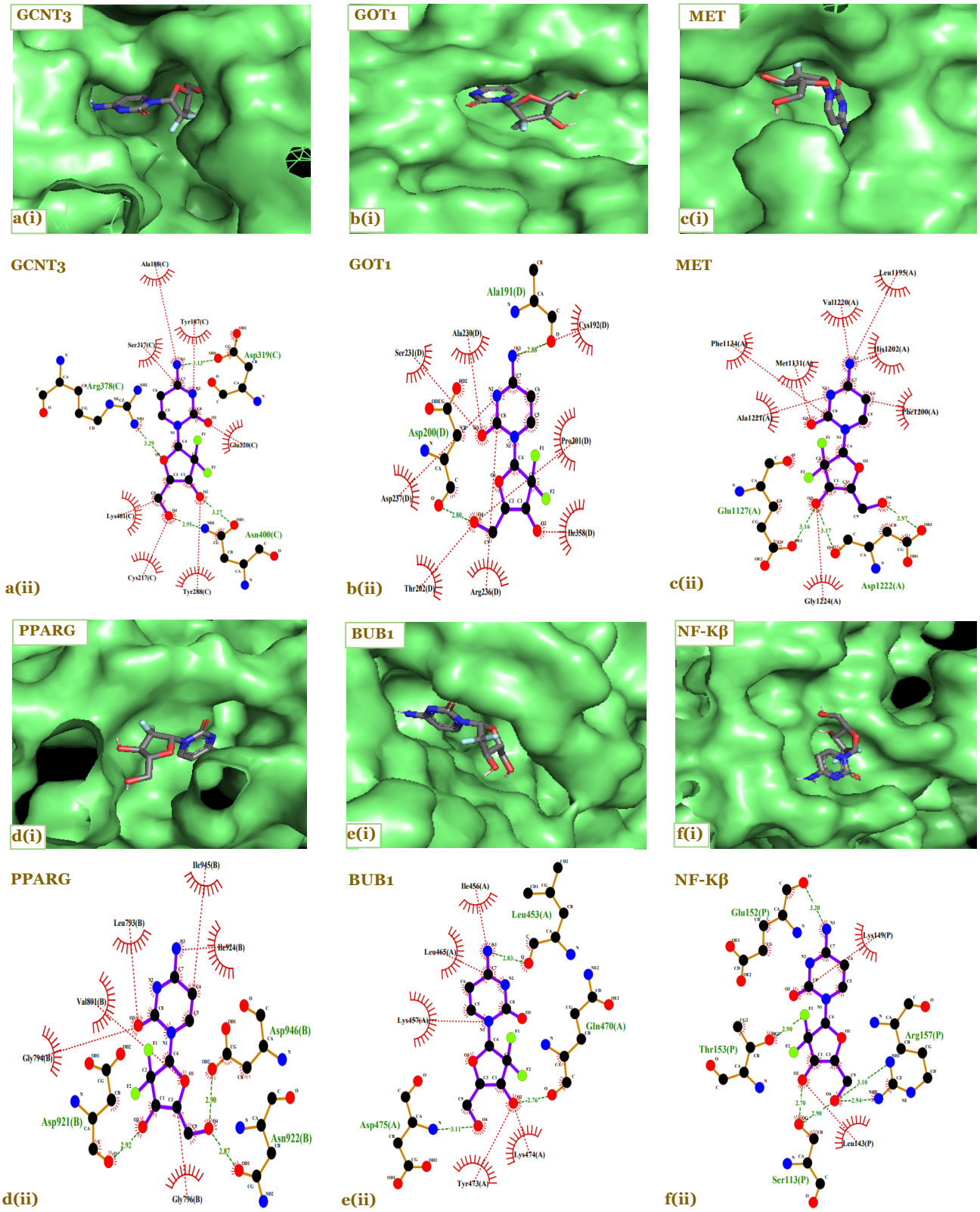

Figure 1. Interaction of gemcitabine with pancreas cancer proteins(a) GCNT3, (b) GOT1, (c) MET, (d) PPARG, (e) BUB1 and (f) NF-κβ. Panel is Showing 3D view of the interaction of gemcitabine with pancreas cancer proteins. Panel ii showing 2D view and overlay of gemcitabine in amino acids of the pancreas cancer proteins. GCNT3: glucosaminyl (N-Acetyl) transferase 3, GOT1: mucin type glutamate oxaloacetate transaminase 1, MET: metformin, PPARG: peroxisome proliferator-activated receptor, BUB1: budding uninhibited by benzimidazole 1 and NF-κβ: nuclear factor kappa beta.

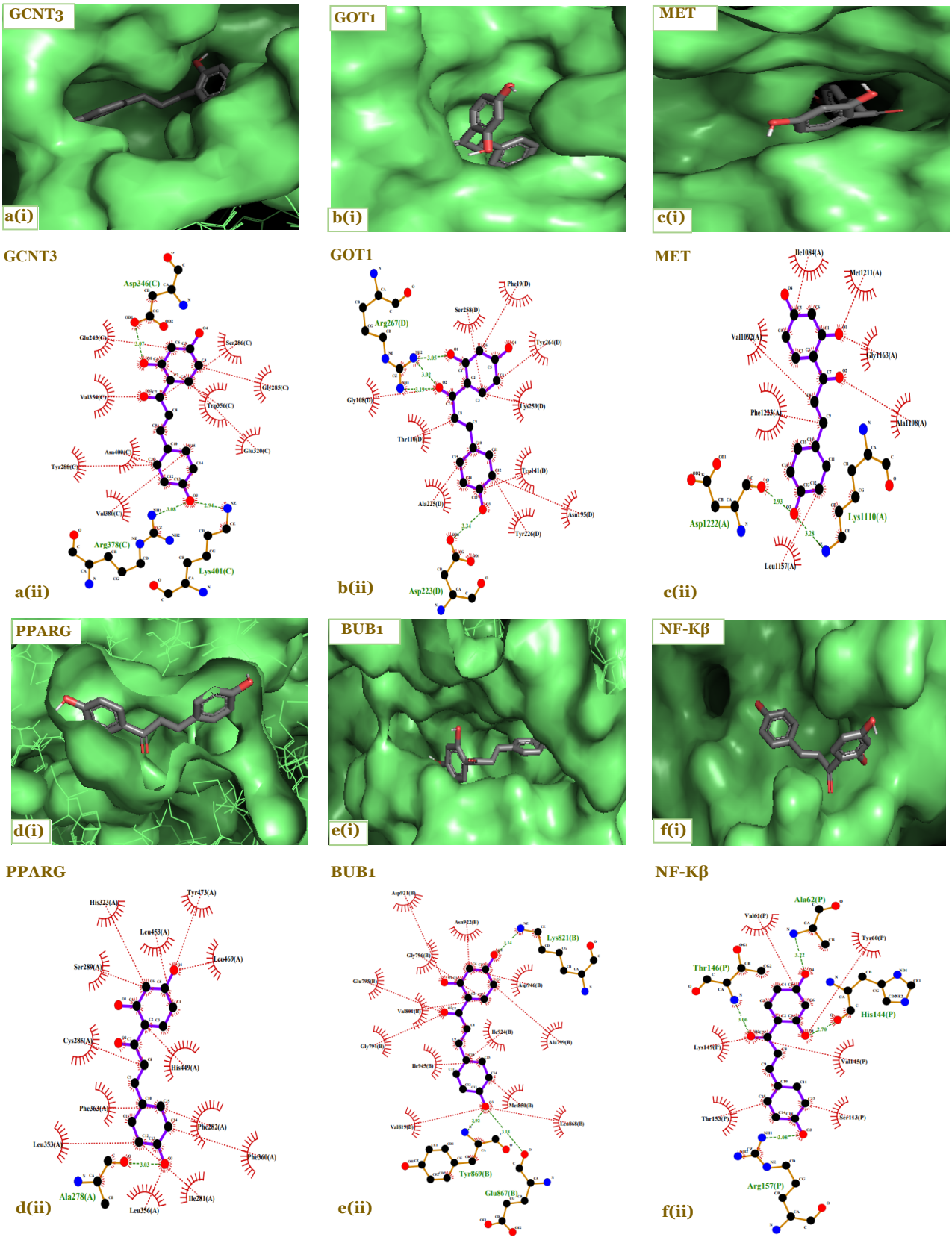

Figure 2. Interaction of isoliquiritigenin with pancreas cancer proteins (a) GCNT3, (b) GOT1, (c) MET, (d) PPARG, (e) BUB1 and (f) NF-κβ. Panel i showing 3D view of the interaction of gemcitabine with pancreas cancer proteins. Panel ii showing 2D view and overlay of gemcitabine in amino acids of the pancreas cancer proteins. GCNT3: glucosaminyl (N-Acetyl) transferase 3, GOT1: mucin type glutamate oxaloacetate transaminase 1, MET: metformin, PPARG: peroxisome proliferator-activated receptor, BUB1: budding uninhibited by benzimidazole 1 and NF-κβ: nuclear factor kappa beta.

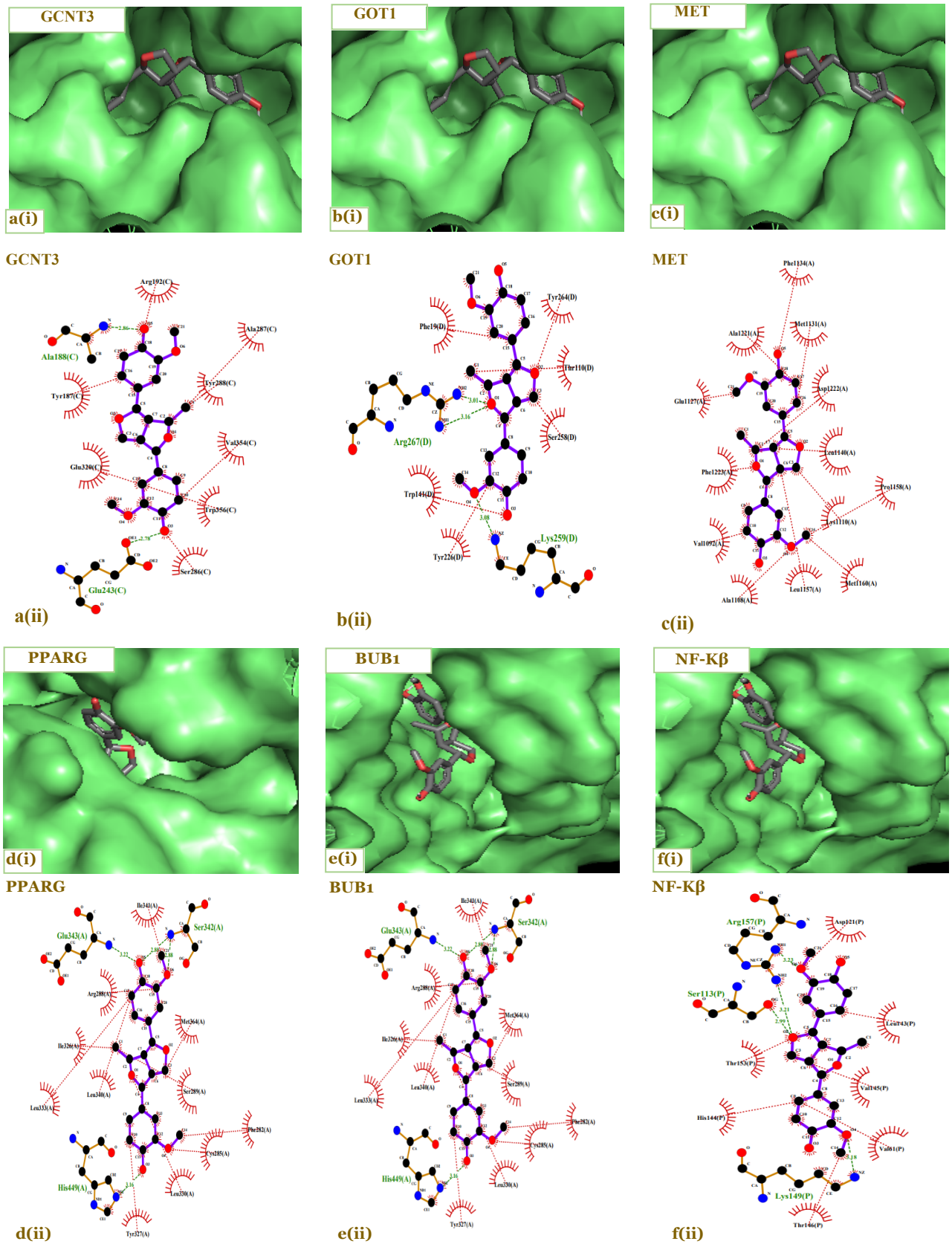

Figure 3. Interaction of 9-metoxipinoresinol with pancreas cancer proteins (a) GCNT3, (b) GOT1, (c) MET, (d) PPARG, (e) BUB1 and (f) NF-κβ. Panel i showing 3D view of the interaction of gemcitabine with pancreas cancer proteins. Panel ii showing 2D view and overlay of gemcitabine in amino acids of the pancreas cancer proteins. GCNT3: glucosaminyl (N-Acetyl) transferase 3, GOT1: mucin type glutamate oxaloacetate transaminase 1, MET: metformin, PPARG: peroxisome proliferator-activated receptor, BUB1: budding uninhibited by benzimidazole 1 and NF-κβ: nuclear factor kappa beta.

The isoliquiritigenin has the greatest affinity energy for the BUB1. BUB1 triggers the growth of pancreatic cancer cells and overexpression of BUB1 induces tumorigenesis and cell proliferation [21]. Significant expression of the mitotic kinase BUB1 also associates with various types of cancer and correlates with a poor clinical prognosis [22]. Isoliquiritigenin has been shown to reduce PI3K/AKT signaling pathways which is a developmental pathway for pancreatic cancer cells [14,23]. Inhibition of BUB1 and PPARG by isoliquiritigenin could consequently cause the reduction of PI3K/AKT signaling pathways owing to the abilities of BUB1 and PPARG to activate the PI3K/AKT via TGF-βupregulation [24,25]. In addition, c-Met is also critical in activation of PIK3/AKT [26] and isoliquiritigenin is able to directly inhibit the activity of NF-κβ [27].

The affinity energy of 9-metoxipinoresinol for GCNT3 occurs through hydrophobic and polar hydrogen interactions and the best interaction was shown in the amino acid of Glu243. This interaction can be used as a target inhibitor for GCNT3. A previous analysis found that the inhibitor for the DYRK1B receptor bound to Glu243 and exhibited great activity against protein inhibitor [28].

Conclusions

Our molecular docking data suggest that 9-metoxipinoresinol and isoliquiritigenin bind well to pancreatic cancer receptors, GCNT3, GOT1, c-Met, PPARγ, BUB1, and NF-κβ, with higher docking scores, compare to gemcitabine. The 9-metoxipinoresinol produces the best docking score on GCNT3 while soliquiritigenin on BUB1 with affinity energy of 8.7 kcal/mol. We suggest further investigation for *in-vitro* experiments to prove the mechanism of 9-metoxipinoresinol and isoliquiritigenin activities against pancreatic cancer receptors.

Declarations

Ethics approval

Not Applicable

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Conflict of interest

The authors declare that they have no competing interests.

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