Docking study of selected citrus flavonoids towards exploring the potential anti estrogen activity

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Abstract

Breast cancer is one of the serious health issues for the women and it has been characterized with uncontrolled growth of cells in the breast tissue. An elevated level of expression of estrogen promotes survival to breast cancerous cells. The present study is focused on phytochemicals, to screen the inhibition of estrogen receptor activity. The selected phytochemicals are citrus flavonoids having anti-cancer, anti-oxidative, anti-proliferative, anti-angiogenic, anti-estrogenic and anti-inflammatory activities. The crystal structure of human estrogen receptor with PDB ID: 2IOG are retrieved from protein data bank (PDB) and citrus flavanoids from Pub Chem database. The drug behavior was studied using Lipinski's rule of five to screen the possible drug candidates. Further molecular docking is done to evaluate the anti estrogen activity. These flavonoids that have high binding affinities (values) with estrogen receptor and also good profile of ADMET properties were selected as a drug candidate. Based on the observed results it was inferred that the flavonoid Tangeritin can be a promising candidate for *in vitro* and *in vivo* testing to arrest the growth of breast cancer cells.

Keywords

Estrogen, flavonoids, Breast cancer, phytochemicals, Docking, Tangeritin

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1. Introduction

Breast cancer is one of the major leading cancers which affect adult women who are aged between 20 and 59 and the main causative agent for the highest mortality rate among females in India. It is one of the deadly cancers followed by lung cancer. Across the country highest rates were reported within women who are involved in household working where the illiteracy rates ranges from 8% to 46%. The reason includes lack of quality education, lifestyle habits and reproductive age [1,2]. The globalization is also a reason affecting the metropolitan cities such as Mumbai and New Delhi, and people getting exposed to UV rays, pollution, occupational hazards and junk food items in their daily lives [3]. Cancer is an uncontrolled cell division that can spread from one part to the other part of the body by metastasis. It is often noticed that 2 out of every 3 cases (70%) of breast cancers are found to be estrogen receptor positive (ER). The other receptor protein involved in breast cancer is human epidermal growth factor 2 (HER2) which occurs 1 in 7 cases (15%). If the aloft mentioned receptors are not involved then it is classified as triple negative breast cancer which occurs 1 in 5 cases of women (15–20%) [4–6]. Among all, estrogen receptor is the one which causes breast cancer in women at the age of 50 that means the estrogen hormone is supporting the growth of cancer cells like normal breast cells [7–9]. An elevated level of expression of estrogen is linked with breast cancer and regulating the biological effect of estrogen receptor by binding to it. The estrogen receptor exists as estrogen receptor alpha (ER α) and estrogen receptor beta (ER β) [10]. The biological effects are mainly mediated by ER α located in mammary gland, uterus and liver. The ER- α plays a key role as a transcription factor for nuclear DNA, which is necessary for mammary gland development. It also regulates cell proliferation and breast cancer signaling network [11–13]. Hence, the main approach for treating the breast cancer is the inhibition of estrogen receptor. Several estrogen receptor modulators and regulators used for breast cancer have shown various side effects. Therefore, it is important to devise alternative and traditional approaches which do not exhibit any side effects on normal cells. Many promising molecules were derived from natural sources such as plants, microbes and marine species which have developed activity against cancer and other diseases as

well [14]. Among all, plant secondary metabolites have been used for thousands of years in traditional medicine for curing various diseases. Flavonoids are the plant secondary metabolites having medicinal activity with anti cancer properties [15]. They regulate cell division and proliferation of cells. These compounds particularly regulate vascular endothelial growth factor (VEGF) in breast tumors [16]. In the current scenario, citrus flavonoids have emerged as one of the main families' of natural compounds with potent biological activity against breast cancer and other diseases. Flavonoids are the phenolic compounds of secondary metabolism of plants showing various health benefits such as antioxidant, anti carcinogenic, anti proliferative, anti inflammatory, anti antigenic and anti estrogenic properties [17]. Flavonoids are categorized into flavones, flavonols, flavonones and anthocyanins that occur in citrus plants. Some of the citrus flavonoid compounds have been demonstrated to inhibit proliferation in many cancerous cell lines [18]. This group of compounds has shown a number of *in-vitro* and *in-vivo* anti-inflammatory and anticancer actions [19]. The flavonoid compounds have good structural similarity and high binding affinity towards estrogen receptors and they could be a promising approach for breast cancer treatment. Therefore, *in-silico* docking method determines the drug likeliness of the flavonoids of the citrus family as a potential anti breast cancer drug against human estrogen receptor that has been attempted in the present study.

2. Methodology

2.1. Estrogen receptor protein preparation

The crystal structure of human estrogen receptor alpha (HER α) in complex with the ligand N- acetamide was selected from PDB (Fig. 1). The complex bound to the protein receptor molecule was removed [20]. Protein preparation wizard from Schrodinger module was used to prepare the structure of the target and the active site grid for docking was generated using Receptor grid generation application [21].

2.2. Ligand preparation

The citrus flavonoid class of ligands with various pharmacological and anticancer activities were identified from the Pub Med literature and included in the

Table 1

Chemical structures of citrus flavonoids and their activities.

S. No	Flavonoid compound & molecular formula	Pub chem. ID	Molecular mass (g/mol)	Structure	Activities	Reference
1	Hesperidin $C_{28}H_{34}O_{15}$	10,621	610.565 &		Anti hyper lipidemic, cardio protective, anti hypertensive and anti diabetic activities	[22]
2	Didymin	16,760,075	594.566 & $C_{28}H_{34}O_{14}$		Anti neo plastic effect	[23]
3	Eriocitrin	83,489	596.538 & $C_{27}H_{32}O_{15}$		Antioxidant activity	[24]
4	Narirutin	442,431	580.539 & $C_{27}H_{32}O_{14}$		anti-inflammatory	[25]
5	Diosmetin	5,281,612	300.266 & $C_{16}H_{12}O_6$		Anti oxidative, anti-inflammatory activity, and anti apoptotic activities	[26]
6	Neohesperidin	442,439	610.565 & $C_{28}H_{34}O_{15}$		antioxidant activity, anti diabetic and antibacterial activity	[27]
7	Quercetin	5,280,343	302.238 & $C_{15}H_{10}O_7$		anticancer activity	[28]

(continued on next page)

Table 1 (continued)

S. No	Flavonoid compound & molecular formula	Pub chem. ID	Molecular mass (g/mol)	Structure	Activities	Reference
8	Rutin	5,280,805	610.521 & C ₂₇ H ₃₀ O ₁₆		phenolic antioxidant	[29]
9	Tangeretin	68,077	372.373 & C ₂₀ H ₂₀ O ₇		Antioxidant, anti-inflammatory and neuro-protective effect	[30]
10	Diosmin	5,281,613	608.549 & C ₂₈ H ₃₂ O ₁₅		Antioxidant and anti diabetic activity	[31]
11	Apigenin	5,280,443	270.24 & C ₁₅ H ₁₀ O ₅		anti-cancer activity	[32]
12	Naringin	442,428	580.539 & C ₂₇ H ₃₂ O ₁₄		Anti oxidant, anti-inflammatory activities	[33]
13	Nobiletin	72,344	402.399 & C ₂₁ H ₂₂ O ₈		Cardiovascular dysfunction	[34]

study [22–34]. LigPrep modules is used to prepare 2D structure of the selected citrus flavonoid test compounds on assigning chiralities and are converted to 3D structures [35]. Ionization and tautomeric states were generated using OPLS_2005 force field. For each ligand, 32 stereoisomers were generated.

The selected 13 flavonoid compounds of citrus family having various biological activities were identified with their names and structures and are represented in Table 1.

2.3. Virtual screening docking and ADMET analysis

Initial screening of the citrus flavonoids was done using virtual screening workflow with default parameters using Glide program of Schrodinger [36]. The HTVS mode eliminates most of the stereoisomers and only a few of the isomers that passed after screening would be subjected to pass through SP and XP docking modes. Many of the false positives were eliminated in this critical screening step. The flavonoid ligands

Fig. 1. Human estrogen receptor alpha (HERα) with ligand.

Fig. 2. Ramachandran plot showing secondary structure backbone conformation of 98% of the amino acid residues of HERα protein are in favorable region which indicates the good protein structure to study the binding interactions with the ligand molecules.

Table 2

ADME properties predicted for citrus flavonoid ligand molecules using QikProp properties/descriptors. The stereo conformer per each ligand which showed the lowest energy with the receptor has been selected for ADMET analysis.

Pub chem. ID	Molecular weight	QPlogP o/w	QPlogS	QPPCaco	QPlogBB	PHOA	RO5	Docking score
Recommended values	(130.0–725.0)	–2.0–6.5	–6.5–0.5	<25 poor, >500 great	–3.0–1.2	>80% is high, <25% is poor	Maximum is 4	
68,077	372.374	–3.583	–4.07	4252.269	–0.109	100	0	–14.633
83,489	596.541	–1.965	2.202	2.567	–3.882	0	3	–14.471
442,428	580.541	–1.461	–3.33	2.683	–4.389	0	3	–13.608
442,431	580.541	1.423	–2.37	5.972	–3.46	0	3	–12.953
442,439	610.568	–1.507	3.067	3.085	–4.285	0	3	–12.248
5,280,343	302.24	0.362	–2.83	20	–2.352	52.348	0	–10.408
5,280,443	270.241	1.624	3.317	124.496	–1.411	73.955	0	–7.135
5,281,612	300.267	1.81	–3.51	153.748	–1.407	76.681	0	–6.997
5,281,613	608.552	–1.155	2.445	9.129	–3.411	0	3	–15.169
16,760,075	594.568	–0.669	–2.48	21.61	–2.897	8.039	3	–13.089
10,621	610.568	–1.324	2.704	5.693	–3.762	0	3	–8.981

Fig. 3. Glide docking pose of Tangeritin molecule in the active binding site of human estrogen receptor alpha (HER α).

Fig. 4. Ligand Tangeritin interactions with the binding active site of the human estrogen receptor alpha (HER α).

which show better affinity towards HER- α would be screened and subjected to find the different properties of the drug likeliness using Qikprop tool ADMET analysis. Finally, the interactions of selected ligand and protein docked complex were analyzed by pose viewer and ligand interaction tools and finally analyzed with Prime MM-GBSA application of Schrodinger [37] to get better negative binding free energy of the docked complex (see Fig. 1).

3. Results and discussion

Secondary structural quality analysis of HER α was done using ramachandran plot (Fig. 2) analysis using Schrodinger. All 296 conformations generated by Ligprep module were further evaluated for Virtual screening using Glide module. HTVS mode identifies active compounds for screening and 63 ligands were screened, followed by SP (Standard Precision), XP (Extra Precision) modes. The docking program produced the results for 61 ligands and Pubchem ID 72344 (Nobiletin) and Pubchem ID 5280805 (Rutin) were

eliminated by the docking mode HTVS. The reliable mode and strict docking gave result of 11 ligands.

The stereo conformer per each ligand which showed the lowest energy with the receptor has been selected and subjected to ADMET analysis. Diosmin (Pubchem. ID-5281613) have shown greatest binding affinity including good interactions with -15.169 docking score but was not considered as a lead because of the poor bioavailability values predicted from Qikprop (Table 2). The selected 11 ligands were undergone ADMET analysis and only one ligand stereoisomer was selected based on ADMET and with docking score of -14.633 was Pubchem ID 68077 (Tangeritin). The docked pose is considered as possible lead molecule (Fig. 3) and Glide provides the docking score. The MM/GBSA analysis of selected compound Pubchem ID 68077 has shown binding energy of 34.60. In recent study by Vishnuvarthan et al., 2017 reported that the *in silico* screening of flavonoids such as formononetin, tangeritin, myrecitin and kaempferol were used as targets against death receptors for prevention of cancer progression [38].

The Protein-ligand interactions of the stable docked HER alpha and tangeritin complex was visualized with ligand interaction diagram shown in Fig. 4. The 2D interaction showed the interacting residues are Met 343, Leu 346, Thr 347, Leu 349, Ala 350, Glu 353, Leu 384, Leu 387, Met 388, Leu 391, Arg, 394, Val 418, Glu 419, Gly 420, Met 421, Ile 424, Phe 425, Leu 428, Gly 521, His 524, Leu 525, Met 528, Cys, 530. In previous study by Dong et al., 2014 found that the tangeritin induces apoptosis in human gastric ACS cell lines through extrinsic and intrinsic signaling pathway [39]. In recent study by Fan et al., 2019 also reported the anticancer activity of tangeritin against drug resistant MDA-MB-231 breast cancer cell line and normal breast cancer cell line Hs841.T via cell apoptosis and activation of caspases [40].

4. Conclusion

After ADMET toxicity analysis, the PubChem drug candidate tangeritin, a flavonoid molecule was selected due to its good binding affinity for the active site human estrogen receptor alpha (HER α) and the interactions were analyzed. Identification of natural drugs like flavonoid compounds from the natural databases that have higher affinity to bind and regulate the human estrogen receptor is a noteworthy step for drug discovery to target the breast cancer and it will essentially help in the improvement of novel medications.

Declaration of Competing Interest

There is no conflict of interest.

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