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DFT and Molecular Docking Investigation of Potential Anticancer Properties of some Flavonoids

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ABSTRACT

There is a continuous need to discover and obtain more efficient drug-like molecule to suppress cancer in humans. Recently researchers are using molecular docking technique to improve the understanding of the interaction between drug and receptor, in other to obtain novel drugs for more efficient usage. Anticancer activities of some selected flavonoids were studied using Density Functional Theory (DFT) and molecular docking approach. These Flavonoids were docked against breast cancer cell line (3s7s). Autodock tool was used to locate the binding site of the protein, AutoDockVina was used for the docking simulation and Biovia Discovery Studio 2017 was used for post-docking analysis. The binding affinity obtained was used to correlate the inhibitory activity of these flavonoids with their calculated molecular descriptors. The obtained binding energy showed that quercetin has the highest inhibition efficiency hence it has the highest ability to inhibit 3s7s than other studied compounds. It was observed that some molecular descriptor such as energy gap, dipole moment, logP and E_{HOMO}, were significant to the inhibiting ability of quercetin in the active site of the protein.

Keyword: molecular docking, DFT, antitumor, novel drugs, flavonoids.

INTRODUCTION

Cancer is one of the major diseases that is posing serious threat to human life and has been reported as the leading disease-related to the cause of death in the world [1]. The use of radiation therapy and surgery as methods of cancer treatment is only effective when the cancer is discovered early. Review on new chemical entities reported that over 70% of anti-cancer drugs are from natural products or from synthesized compounds that are structurally related to natural products, also the modification of these drug molecules can further enhance their efficacy and reduce adverse effects [2]. Recent studies suggest that the consumption of different fruits and vegetables has the ability to fight against cancer and reduce the cancer risk level at least by 20% [3]. This has made more researchers to focus on the use of plant-derived compounds to combat cancer. Naturally occurring compounds have been used for the prevention and treatment of cancer and are more beneficial than synthetic compounds due to less toxicity, more accessibility and being less expensive [4].

Flavonoids are secondary plant metabolites characterized by two or more aromatic rings and are found in fruits, vegetables, grains, bark, roots, stems, flowers, tea, beer, cocoa and wine [5]. Flavonoids are categorized into flavonols, flavones, anthocyanidins, and isoflavones on the basis of the direction of the phenyl ring, degree of unsaturation and state of substitution [6]. Research has shown that flavonoids possesses several biological activities

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such as antiviral, anti-allergic antioxidative, antiinflammatory, antibacterial, and anticancer activities [7-9].

Great advancements in computational methods have made it possible for the development of novel drugs with more efficacies. Molecular docking analysis between various ligands and the receptor protein of interest is gaining huge interest nowadays. In docking study, the binding energy of docked compound helps to determine the strength of interactions between the ligand and a protein which allows a prediction of potential application of the compound [10, 11]. Density functional theory (DFT) with its different levels of calculations has been found effective and reliable in successfully predicting the properties of various compounds. It has been used to obtain some fundamental properties of compounds which could not be easily derived from laboratory procedures [12-15].

The search for more anticancer drugs with high potency and low side effect on human has prompted us to conduct a DFT and docking studies on the anticancer activities of some selected flavonoids from literature [16], namely luteolin, apigenin, chrysin, quercetin, galangin, hesperetin, naringenin, taxifolin, daidzein, kaempferol, and genistein. The objectives of the study are; to calculate molecular descriptors of the studied flavonoids using quantum chemical method through DFT, to investigate the ligand-protein intermolecular interactions between the flavonoids and receptor proteins through docking approach, and finally to observe the correlation between the calculated descriptors and the binding affinities of the ligands.

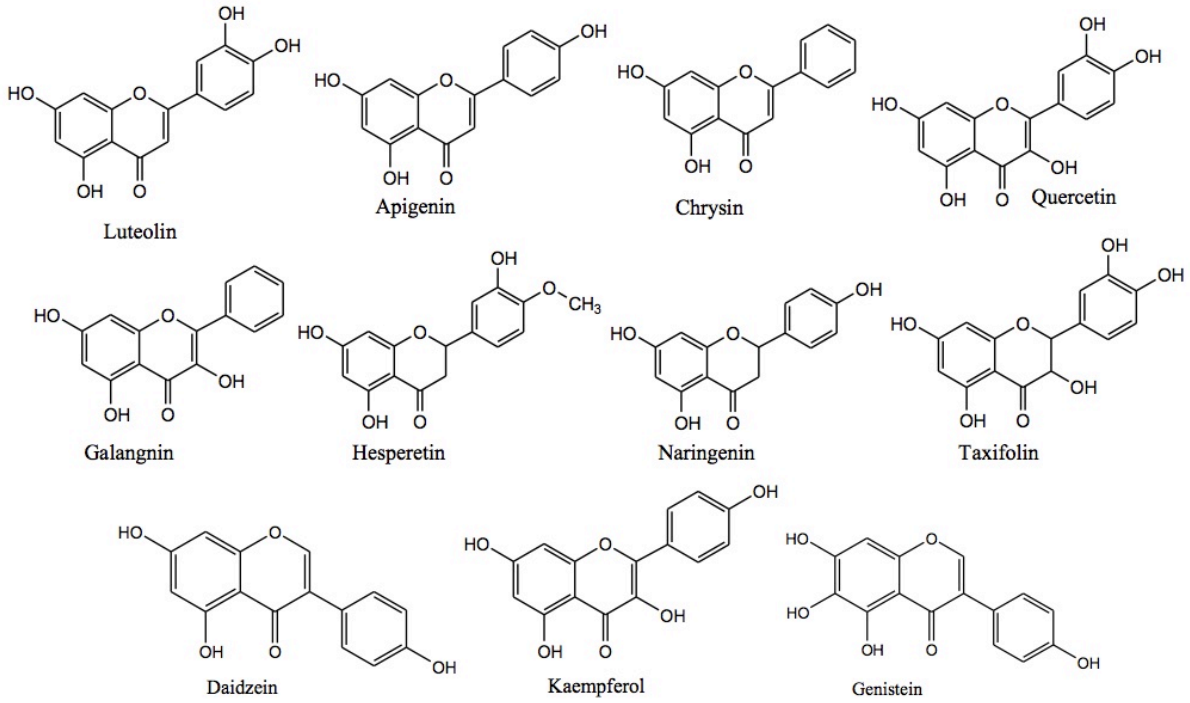

Figure 1. The Schematic structures of the studied flavonoids

EXPERIMENT

Quantum Chemical Methods

Eleven flavonoids as shown in Figure 1 were obtained from literature [16]. The geometry optimized structures were generated using Spartan'14 (Wavefunction, Inc) [17]. DFT

calculations were carried out using the Becke's gradient exchange correction [18] with the Lee–Yang–Parr correlation functional (B3LYP) [19], together with the 6-31G* basic set.

Molecular Docking Study

All compounds were docked to catalytic binding sites of breast cancer cell lines (PDB: 3s7s) [20] downloaded from protein data bank to predict their binding modes and approximate binding free energies. The receptor protein was prepared using Discovery Studio 4.1 visualizer. Autodock tool was used to locate the binding site of the protein. Docking simulation was done with the AutoDockVina. BioviaDiscovery Studio 2017 was used to analyze the output of the docking process. The lowest energy conformation was identified and binding energies were evaluated.

RESULT AND DISCUSSION

Correlation between molecular descriptors and the binding affinities of the flavonoids

Calculated molecular descriptors namely; E_{HOMO} (highest occupied molecular orbital energy), E_{LUMO} (lowest unoccupied molecular orbital energy), Energy gap, dipole moment (DM), Chemical potential (CP), molecular weight (MW), Area (A), volume (V), polarizability (POL), partition coefficient (logP), polar surface area (PSA), hydrogen bond donor (HBD) and hydrogen bond acceptor (HBA) for the studied flavoniods are shown in Table 1. The binding affinity/ binding energy for each complex formed by the flovoniods (ligand) with the protein (3s7s) are also shown in Table 1. From the study, the values obtained for the binding affinity ranges from -8.2 Kcal/mol for quercetin to -6.2 Kcal/mol for chrysin. The low value of binding energy revealed that all the studied flavonoids have good tendency to inhibit the receptor. From the result, quercetin requires the smallest binding energy to inhibit the active site of the protein (3s7s), this shows that it will have the highest ability to inhibit the protein and form the most stable complex with the protein. While chrysin with the highest binding energy showed that it has the least tendency to inhibit the active site of the protein.

Table 1. Molecular Descriptors Calculated using DFT

Molecule	E_{HOMO} (eV)	E_{LUMO} (eV)	Energy Gap (eV)	DM (Deby)	CP	MW (amu)	Area (A^2)	Volume (A^3)	POL	PSA ($Å^2$)	LogP	HBD	HBA	Affinity (kcal/mol)
Luteolin	-5.85	-1.64	4.21	7.55	-3.75	286.24	273.50	259.20	61.40	92.64	1.01	4	6	-7.9
Apigenin	-6.06	-1.60	4.46	5.76	-3.83	270.24	266.06	252.40	60.79	74.86	1.40	3	5	-6.5
Chrysin	-6.18	-1.70	4.48	4.29	-3.94	254.24	257.33	245.38	60.22	55.22	1.79	2	4	6.2
Quercetin	-5.69	-1.72	3.97	1.89	-3.71	302.24	280.81	266.42	62.05	109.98	-0.07	5	7	-8.2
Galangin	-5.94	-1.77	4.17	2.40	-3.86	270.24	264.74	252.60	60.88	72.62	0.71	3	5	-7.5
Hesperetin	-5.71	-1.44	4.27	5.05	-3.56	302.28	299.23	283.43	63.36	79.99	1.50	3	6	-7.6
Naringenin	-6.00	-1.44	4.46	2.99	-3.72	272.26	270.80	256.56	61.11	75.02	1.63	3	5	-6.9
Taxifolin	-5.74	-1.65	4.09	2.51	-3.70	304.25	286.49	271.06	62.39	110.92	0.58	4	7	-7.2
Daidzein	-5.86	-1.46	4.4	3.17	-3.66	254.24	259.71	246.31	60.31	59.87	2.13	2	4	-6.3
Kaempferol	-5.80	-1.69	4.11	2.16	-3.75	286.24	273.45	259.61	61.46	92.25	0.32	4	6	-6.3
Genistein	-5.85	-1.50	4.35	2.05	-3.68	270.24	264.66	252.23	60.81	74.35	1.74	3	5	-6.7

The calculated E_{HOMO} values are -5.85, -6.06, -6.18, -5.69, -5.94, -5.71, -6.00, -5.74, -5.86, -5.80, and -5.85 eV from luteolin to genistein respectively as shown in Table 1. Frontier

molecular orbital theory, indicate that E_{HOMO} and E_{LUMO} are determining factor for the estimation of the cytotoxicity and general bioactivity of molecular compounds [21, 22]. The higher the E_{HOMO} value the higher the ability to donate electrons to neighboring molecule. Quercetin has the highest E_{HOMO} value (-5.69 eV), which suggest that it has the highest tendency to donate electron, hence this may contribute to it having greatest ability to inhibit breast cancer cell line (3s7s) as shown by its lowest binding energy of 8.2 kcal/mol. Chrysin on the other hand with the lowest E_{HOMO} value (-6.18 eV), has the lowest tendency of donating electrons and in turn it has the least ability to inhibit the studied protein.

Energy gap is a significant descriptor that measures the reactivity of the drug-like molecule towards the receptor [23]. Smaller/lower energy gap signifies greater reactivity towards the receptor [24, 25]. The calculated values of energy gap in this study as shown in Table 1 ranges from 3.97 eV in quercetin to 4.48 eV in chrysin. This confirms quercetin to be the most reactive among the studied compounds and also shows why it has the highest inhibiting tendency and best interaction with the receptor. Chrysin which has the lowest bandgap value is the least reactive and also has the least inhibiting efficiency.

Dipole moment is the product of the magnitude of the charge and the distance of separation between the charges. The lowest value of the calculated dipole moment in the studied molecules was found in quercetin (1.89 Debye) and it also has the highest ability to inhibit the protein, this may suggest that lower dipole moment signifies better/higher inhibiting ability.

LogP is the total estimation of lipophilicity of a compound that affects its behavior in range of biological membranes [26]. From the obtained result it was observed that quercetin with lowest binding energy (-8.2 Kcal/mol) also turned out to have the lowest log P value of -0.07. The low log P value has influenced its interaction with the receptor by increasing its ability to inhibit well than other studied molecule. Chrysin which has the least ability to inhibit the protein has a much higher value of LogP (1.79) though not the highest value among the studied compounds. LogP, Molecular weight, HBD and HBA are globally associated with solubility and permeability of a molecule, For a drug to have good absorption or permeation the drug must have molecular weight value ≤ 500, HBD ≤ 5, HBA ≤ 10 and Log P ≤ 5 [27]. All the studied flavonoids have these properties.

Almi *et al.,* [28] reported that polarizability of a molecule is higher for larger molecules in which electrons are far from the positively charged nucleus than in smaller molecules and such molecules have stronger attractions with other molecules. In this study, daidzein and chrysin both have the smallest molecular weight (254.241amu), they are the least polarizable with polarizability value of 60.31 for daidzein and 60.22 for chrysin. As a result, they have weaker interaction with the protein reducing their inhibiting strength which translated into higher binding energy value.

Polar surface area (PSA) is a sum of surfaces of polar atoms in a molecule [29]. PSA is an indicator of the ligand hydrophilicity. It strongly reflects hydrogen bonding capacity and polarity and measure the ability of a drug to permeate/penetrate cells. It plays an important role in shaping the protein-ligand interaction by affecting the non-bonded contribution to the binding energy. Drug-like molecule that are carried by trans-cellular route and are administered orally should not have PSA value greater than 120 $Å^2$ [30]. The PSA value for studied flavonoids ranges form (55.216 $Å^2$-110.920 $Å^2$), hence they can all be absorbed orally. However, chyrsin has the lowest value of PSA, this may also contribute to its low inhibiting ability.

Interaction between flavonoids (ligand) and receptor (3s7s)

The interactions between the ligand and the receptor are shown in Table 2. The interaction between quercetin and the protein is shown in Figure 1. Hydrogen bonding with some of the residues in the binding site of the protein was observed in all of the complexes formed. Van der waal forces of interaction were also observed in all the complexes.

Table 2. Interactions between ligands and receptor (3s7s)

Ligands	Interactions between ligands and receptor (3s7s)
Luteolin	(i) GLN-472 (ii) HIS-475, LIG: O (iii) LEU-479, LIG: O (iv) PRO-368 (v) ASN-75, LIG: O (vi) ARG-400 (vii) GLY-399 (viii) ARG-365 (ix) TYR-366, LIG: O (x) ARG-403, LIG: O (xi) GLN-367, LIG: O (xii) LYS-473, LIG: H.
Apigenin	(i) ARG-400, LIG: O (ii) ARG-79 (iii) ASN-75 (iv) HIS-475 (v) LEU-479 (vi) SER-72 (vii) LYS-473, LIG: H (viii) PRO-368 (ix) GLY-399 (x) ARG-403, LIG: O
Chrysin	(i) ASN-136 (ii) LYS-376, LIG: O (iii) GLU-92 (iv) PHE-116 (v) ASN-393 (vi) ILE-229 (vii) ILE-89 (viii) SER-90 (ix) SER-118 (x) LYS-119, LIG: O (xi) GLY-117
Quercetin	(i) ILE-474 (ii) PRO-368 (iii) LEU-479 (iv) ASP-371(v) ASN-75, LIG: O, H (vi) ARG-400 (vii)GLY-399 (viii) HIS-475 (ix) ARG-403, LIG: O, O (x) TYR-366, LIG:H (xi) GLN-367, LIG: O, O (xii) LYS-473, LIG: H.
Galangin	(i)THR-94 (ii) GLU-92 (iii) PHE-116 (iv) GLY-117 (v) LYS-376, LIG: O (vi) ARG-115 (vii) ASN-136 (viii) SER-114 (ix) LYS-119, LIG: O (x) SER-90, LIG: H (xi) SER-118, LIG: O (xii) ILE-89 (xiii) ASN-393, LIG: H
Hesperetin	(i) ILE-474 (ii) HIS-475 (iii) LEU-479 (iv) ASN-75, LIG:O (v)ASP-371 (vi)) ASN-397 (vii) ARG-400 (viii) GLY-399 (ix)ARG-403, LIG: H, O (x) PRO-368 (xi) TYR-366 (xii) GLN-367, LIG: O (xiii) LYS-473 (xiv) GLN-472
Naringenin	(i) GLY-117 (ii) LYS-119 (iii) GLU-92 (iv) LEU-120 (v) ASP-232, LIG: H (vi) SER-118 (vii) SER-90, LIG: O (viii) ILE-89 (ix) PHE-116 (x) LYS-376 (xi) ASN-393 (xii) ARG-115 (xiii) ASN-136 (xiv)) SER-114
Taxifolin	(i) LYS-376, LIG: O (ii) GLY-117 (iii) PHE-116 (iv) GLU-92 (v) ASN-393 (vi) ILE-89, LIG: H (vii) ILE-229 (viii) SER-90, LIG: O (ix) SER-118 (x) LYS-119, LIG: O (xi) ASN-136, LIG: H (xii) SER-114
Daidzein	(i) SER-72 (ii) HIS-475 (iii) ASN-75 (iv)TYR-366 (v) ARG-403, LIG: H (vi) ARG-365 (vii) GLY-399 (viii) PRO-368 (ix) ASP-371 (x) LEU-479 (xi) LYS-473
Kaempferol	(i) ARG-403, LIG: O (ii) PRO-368 (iii) ASN-75 (iv) HIS-475 (v) ARG-79, LIG: O (vi) TRY-76 (vii) SER-72 (viii) LEU-479 (ix) LYS-473 (x) ASP-371 (xi) GLY-399 (xii) ARG-365 (xiii) TYR-366
Genistein	(i) SER-72 (ii) HIS-475 (iii) ASN-75 (iv) ASP-371(v) GLY-399 (vi) PRO-368 (vii) ARG-365 (viii) ARG-403, LIG: H (ix) TRY-366 (x) LEU-479 (xi) LYS-473 LIG: O

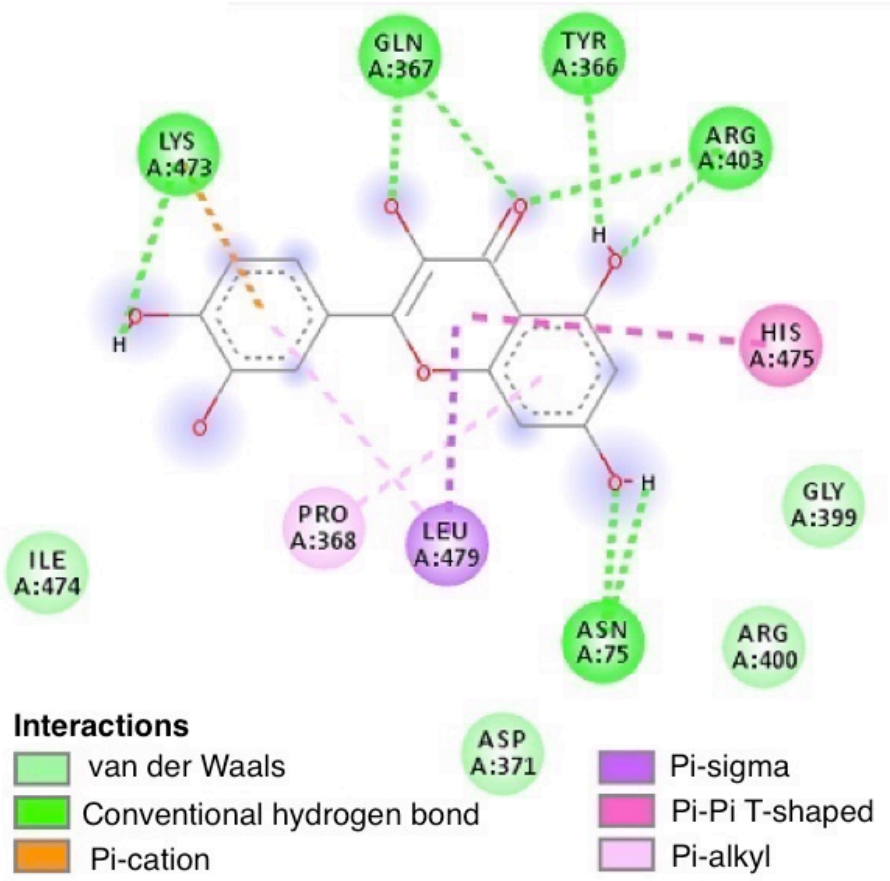

Figure 1. Interactions between quercetin (ligand) and receptor (3s7s)

CONCLUSION

Eleven flavonoids were optimized and their molecular parameters were obtained by Density functional theory calculation. The compounds were docked to catalytic binding sites of 3s7s (MCF-7 receptor protein) and binding affinity values of the studied compounds were obtained. It was observed that quercetin has the highest ability to inhibit 3s7s than other studied flavonoid. The correlation between calculated descriptors and calculated values of binding affinity showed that lower energy gap value, lower dipole moment, lower logP and high value of E_{HOMO} enhanced the inhibiting strength of the ligands. On the other hand, an increase in molecular weight, area, volume, PSA and polarizibility may enhance the inhibiting strength of the ligands.

CONFLICT OF INTEREST

Authors declare the submitted manuscript have no any conflict of interest.

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