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In silico Molecular Docking and Pharmacokinetic Study of Selected Phytochemicals With Estrogen and Progesterone Receptors as Anticancer Agent for Breast Cancer

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Abstract: Molecular docking and pharmacokinetic study were performed on 20 selected phytochemicals with estrogen and progesterone receptors and it was found that all the phytochemicals has strong binding energy and high number of interactions when docked with estrogen and progesterone receptors, Gabridin has the highest binding energy of -10.3 kcal/mol and 12 numbers of various interactions when docked with estrogen receptor, while Quercetin has the highest binding energy of -9.6 kcal/mol and about 14 numbers of various interactions when docked with progesterone receptor. Pharmacokinetic study carried out revealed that all the leading compounds (Gabridin and Quercetin) are in agreement with Lipinski rule of five without violating any of the conditions of bioavailability, this has shown that they will be readily bioavailable. With the high binding affinity of these compounds and good pharmacokinetic parameters, most of the phytochemicals used in this study can be used in designing a highly effective and readily bioavailable anti breast cancer drug.

Keywords: Phytochemicals, Estrogen, Progesterone, Gabridin, Quercetin.

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INTRODUCTION

Plants and their remedies have been used as herbal sources and other traditional beliefs to treat different kind of diseases among which cancer it belongs to, such plants and remedies include phytochemicals, bitter lemons, shikonin and others (1).

The word phytochemical is derived from Greek word "phyto" meaning plant, which constitutes the non-nutrient present in the plant diet (2). It has been used in the treatment and protection of chronic diseases such as cancers, hypertension, heart disease, and other diseases (2). A phytochemical is one of the compounds with history of anticancer activity and it has been used in the treatment of cancer due to its availability, and of less toxic and safe nature (3).

There is strong evidence suggesting that taking food and beverages that are rich in phytochemicals will help in preventing many diseases, but there is need of more research on specific phytochemicals and their contribution in prevention of many form of diseases (4).

Presently, cancer is one of the main cause of death as a result of diseases in the world and without more advances and screening in developing more drugs for the treatment of this ailment, its suggested to continue to be the leading cause of death due to diseases in the coming years (5). Breast cancer is the most fast growing cancer in women, apart from lung cancer, breast cancer cause more death of women than all the other type of cancers (6). The survival rate of the breast cancer has increased due to advances in screening and treatment, In United States (US), there are about 3.1 million survivors of breast cancer. 1 in every 37 or 3% of women are at the risk of dying from breast cancer (6). Awareness of the sign and symptoms and more advances in screening of drugs for the treatment of breast cancer are important ways of reducing the risk associated with the disease (6).

Presence of fluid through the nipple, change in the thickness of breast skin, formation of lumps, and enlargement are some of the sign and symptoms of breast cancer (7), when the disease advances there may be swollen lymph nodes, feeling pain especially in the bone and decrease in the breathing rate (8). Chemotherapy is commonly used in order to inhibit and stop the growth of the cancerous cells and the main advantage of chemotherapy is its ability to stop the growth of cancer cells that has spread to other places unlike surgery and radiation therapies that treat cancer cells that are limited within specified area (5).

This study aims at establishing the binding affinity, interactions, binding distances, and the important amino acid residues that participated in the binding between the selected phytochemicals with both estrogen and progesterone receptors as well as the pharmacokinetic parameters (bioavailability) of these phytochemicals. The study also aims at establishing weather these phytochemicals can be used in designing a therapeutic lead molecule for the treatment of breast cancer targeting not only estrogen but progesterone receptors. Both estrogen and progesterone receptors interact with breast cells (cancerous and normal), but most of the common drugs for the treatment of breast cancer are design and developed to target estrogen receptor only.

MATERIALS AND METHODS

Tools and Materials Used

The three-dimensional structure of both estrogen and progesterone receptor was obtained from the protein data bank (PDB ID 2IOK AND Ie3K) respectively, while the structure of all the selected phytochemicals in this study were retrieved from pubchem compound database and from literature (reference number 9). The tools used in this study include HP beatsaudio computer system (intel corei5, 12 GB RAM, windows 8.1 operating system), pubchem data base, protein data bank, chemdraw 3D pro 12.01v, spartan 14v1.1.4, pyrex, autodock tools in autodock 4.3 program, vina wizard, and discovery studio.

Methodology

Protein Preparation: The crystal structure of both estrogen and progesterone receptors was retrieved from protein data bank PDB ID (2I0K and Ie3K) respectively, the complexes bound to the receptor was removed using discovery studio, and the non-essential water molecule was removed and polar hydrogen was added and the already prepared receptor was saved in PDB format.

Ligand Preparation: Twenty phytochemicals were selected from pubchem and from literature (Reference no. 9) based on history of their interaction with estrogen and progesterone that is phytoestrogen and phytoprogesterone, their 3D structure was drawn using chemdraw 3D pro12.01v and their energy was optimized using spartan 14v1.1.4 and the optimized molecule was saved in PDB format.

Molecular Docking Simulation

Two goals involved in docking study are to determine the most likely binding mode of the lead compound and to measure its binding affinity for the target protein (10). Estimation of ligand protein affinity is one of the major and important step in drug discovery, only the potential molecules that demonstrate desirable binding affinity for the target receptor are taken up for further analysis. The molecules that strongly bind to the receptor will inhibit its function and thus can act as a drug (10). All the twenty phytochemicals are docked using pyrex software by selecting autodock as the docking engine to find the reasonable binding geometry and discover the protein ligand connections.

Interaction Studies

To study the mode of binding, docked conformation with minimum binding energy was selected, discovery studio was used to visualize and study the interaction between the different ligands and the receptor and all the various amino acid residues that participated in binding with the various distances.

RESULT AND DISCUSSION

Molecular docking studies was performed with autodock tools, all the twenty selected phytochemicals were docked with estrogen receptor PDB ID (2IOK) and progesterone receptor PDB ID (Ie3K), and it was found that all the phytochemicals have higher binding affinity to the receptors. The highest negative binding energy was selected and interaction study was performed using discovery studio, various amino acid interactions and the distance was ascertained.

After docking of the selected phytochemicals with estrogen receptor, it was found that of all the twenty phytochemicals, Gabridin has the highest binding energy of -10.3 kcal/mol and 12 numbers of various interactions, followed by Genestein and 4-methoxycoumesterol with binding energy of -9.8 kcal/mol and -9.7 kcal/mol and also 10 and 13 numbers of various interactions respectively, while Crocetin with -6.8kcal/mol has the least binding energy. From the result of interaction between the phytochemicals and estrogen receptor, Gabridin with highest binding energy and good number of interactions can be a lead compound in designing a therapeutic lead molecule for the treatment of breast cancer targeting estrogen receptor, while the amino acids Leu346, Ala350, Phe404, Leu387, Leu384, Leu525, and Glu353 are the most important residue for potential drug targeting estrogen receptor.

From the result of interaction between the phytochemicals and progesterone receptor, it was found that Quercetin has the highest binding energy of -9.6 kcal/mol and 14 numbers of various interactions, followed by 4-methoxycoumesterol and Diosgenin with -9.2 kcal/mol each and 10 and 11 numbers of various interactions respectively, while Indole-3-carbinol with -6.2 kcal/mol has the least binding energy. Quercetin with highest binding energy and good number of interactions can be a lead compound in designing a therapeutic lead molecule for the treatment of breast cancer targeting progesterone receptor, while the amino acids Arg766, Trp732, Pro696, Phe788, Glu695, Ile699, and Lys822 are the most important residues for the potential drug targeting progesterone receptor.

While only 5 of the 20 selected phytochemicals has additional type of interactions apart from hydrogen and hydrophobic when docked with estrogen receptor, 15 out of the 20 phytochemicals has additional type of interactions apart from hydrogen and hydrophobic interactions when docked with progesterone receptor. This shows that majority of the phytochemicals has additional type of interactions when docked with progesterone receptors.

Developing a potent drug of breast cancer targeting progesterone receptor will lead to a breakthrough in the treatment of breast cancer, even though both estrogen and progesterone receptors interact with breast cancer cells, most of the common drugs for the treatment of breast cancer are developed to target estrogen receptor only. About 80% of breast cancer cells are estrogen receptor-positive, out of this 80%, 65% are also progesterone receptor-positive, while 13% of the total breast cancer cells are estrogen receptor-positive and progesterone receptor-negative and about 2% are estrogen receptor-negative and progesterone receptor positive (11).

There is strong evidence suggesting that progesterone receptor plays an important role in the growth of breast cancer and that they might be potentially used in improving the success of endocrine treatment (12).

This study may be the subject of experimental validation and clinical trials to establish these phytochemicals as more potent drug for the treatment of breast cancer.

Table 2: Docking result of the selected phytochemicals with estrogen receptor.

Compounds	**Hydrogen bond**	**Hydrophobic interactions**	**Other interactions**	**Binding energy**	**Total number of interactions**
1)4-methoxy coumesterol	OH-Glu353(2.33), O-Gly521(3.35)	C-Leu387(3.80) C-Phe404(5.10) C- Phe404(5.49) C-Leu387(4.95) C-Ala350(5.33) C-Ala350(4.86) C-Leu391(5.23) C-Leu346(4.83) C-Leu384(5.01) C-Leu525(5.43) C-Ile424(5.30)	None	-9.7	13
2)Apigenin	OH-Glu353(2.57) OH-Arg394(1.35) OH-Thr347(1.96)	C-Leu346(3.98) C-Leu387(4.92) C-Leu346(4.43) C-Phe404(5.01) C-Ala350(5.07) C-Leu525(4.92) C-Ala350(5.35) C-Leu391(5.02) C-Ala350(5.25)	None	-9.1	13
3)Biochanin	OH-Arg394(3.98)	C-Phe404(5.55) C-Leu387(4.90) C-Met388(5.29) C-Phe404(5.27) C-Leu391(5.09) C-Leu387(4.20) C-Ala350(5.04) C-Ile424(4.80) C-Ile525(5.48)	None	-9.1	10
4) Coumesterol	O-Arg394(2.44) OH-Glu353(2.33)	C-Phe404(4.94) C-Phe404(5.42) C-Leu391(4.98) C-Leu387(5.50) C-Ala350(5.37) C-Ala350(5.16) C-Leu346(4.71) C-Leu346(4.80) C-Leu346(5.11) C-Leu525(4.68) C-Leu384(5.47) C-Leu387(4.34)	None	-9.6	14

5) Crocetin	OH-Glu1353(2.10) O-Arg1394(2.72) OH-Glu1423(2.00) O-Gly1420(3.46) O-His1524(3.74)	C-Leu1525(4.34) C-Leu1384(4.79) C-Leu1525(4.60)	None	-8.1	8
6) Curcumin	OH-Leu387(2.71)	C-Leu387(3.87) C-Leu391(5.34) C-Leu525(5.13) C-Phe404(5.01) C-Ala350(4.71) C-Trp383(4.39)	None	-7.3	7
7) Daidzein	O-His524(3.64) OH-Gly525(4.39)	C-Leu387(3.92) C-Leu387(5.33) C-Phe404(5.70) C-Phe404(5.05) C-Leu384(5.40) C-Leu384(5.42) C-Ala350(5.12) C-Leu391(5.09) C-Leu525(5.39) C-Met388(5.12) C-Ile424(4.73)	None	-9.0	13
8)Diosgenin	None	C-Ile1326(4.42) C-Ile1326(5.26) C-Ile1326(4.70) C-Ile1326(4.41) C-Arg1394(5.02) C-Arg1394(3.87) C-Arg1394(4.35) C-Pro1406(5.03) C-Pro1324(4.18) C-Leu1403(5.30) C-Trp1393(5.42)	None	-9.6	11
9)Formononetin	O-Arg1394(2.37) OH-Leu1387(2.78)	C-Phe1404(5.00) C-Leu1384(5.41) C-Leu1391(4.83) C-Leu1387(4.44) C-Met1388(4.96) C-Met1421(5.22) C-Ile1424(4.42)	None	-8.9	9
10)Gabridin	None	C-Phe1404(5.00) C-Ile1424(5.27) C-Ile1424(4.57) C-Ile1424(3.81) C-Leu1391(4.51) C-Leu1387(4.42) C-Leu1384(5.16) C-Leu1384(5.15) C-Leu1525(4.99) C-Met1421(3.78) C-Met1421(4.12) C-His1524(5.08)	None	-10.3	12
11)Genestein	O-Glu353(1.65)	C-Leu525(5.48) C-Leu387(5.31) C-Leu387(4.21) C-Leu391(5.09) C-Ile425(4.78) C-Ala350(5.05) C-Phe404(5.67) C-Phe404(4.90) C-Met388(5.28)	None	-9.8	10

12)Hesperetin	OH-Met1437(2.98) O-His476(2.88) O-His476(2.12) OH-Lys472(1.38)	C-Met1437(3.88) C-Met1437(3.94) C-Lys472(3.11) C-Leu469(5.02)	C-Met1437(3.41)	-7.8	9
13)Indole-3-cabinol	O-Arg1394(2.56) NH-Phe1404(2.69) NH-Leu1327(2.62) H-Leu1327(3.04) H-Leu1327(2.51)	C-Ile1326(3.84) C-Ile1326(5.48) C-Pro1406(5.25)	C-Arg1394(3.63) C-Arg1394(3.99)	-6.2	10
14)Kaempferol	O-Leu1327(2.33) OH-Pro1325(2.96)	C-Ile1326(3.76) C-Ile1326(4.80) C-Arg1394(4.31) C-Pro1324(3.84)	C-Arg1394(3.38) C-Glu1353(3.31)	-8.5	8
15)Lignan	None	C-Phe404(4.88) C-Leu346(4.80) C-Leu346(4.95) C-Leu346(5.19) C-Leu387(5.05) C-Leu525(4.60) C-Ala350(4.77) C-Met343(5.90)	None	-7.3	8
16)Luteolin	O-His524(3.48)	C-Phe404(4.86) C-Leu384(5.46) C-Met388(5.45) C-Leu384(5.45) C-Leu346(5.25) C-Leu387(4.69) C-Leu525(5.21) C-Ala350(4.50) C-Ile424(4.77)	None	-8.9	10
17)Lycopene	O-Phe461(2.60) O-Lys472(1.88) O-Ser463(1.71) OH-Thr460(2.21) O-Phe461(2.69)	C-Leu462(4.43) C-Ala1430(4.99) C-Leu462(5.29)	None	-7.1	8
18)Naringenin	OH-Met528(2.97)	C-Thr347(4.77) C-Leu525(3.86) C-Ala350(4.31) C-Leu525(5.29)	C-Met528(5.87) C-Met343(5.19)	-7.9	7
19)Quercetin	O-Leu1327(2.32) OH-Glu1353(2.12) O-Leu1327(2.19) OH-Glu1353(2.22)	C-Ile1326(3.80) C-Arg1394(4.79) C-Arg1394(4.23) C-Pro1324(3.86)	C-Arg1394(3.37) C-Glu1353(2.26)	-8.7	10

20) Resveratrol	OH-Glu1353(2.61) OH-Leu1346(1.84)	C-Phe1404(5.06) C-Ile1424(5.42) C-Leu1387(5.26) C-Met1388(5.46) C-Leu1346(5.37) C-Ala1350(4.62) C-Phe1404(4.70) C-Leu1384(5.28) C-Ile1424(4.85) C-Met1388(5.41)	None	-8.8	12

Table 2 above shows the various interactions (hydrogen, hydrophobic, and other interactions), binding energies and the total number of interactions of the studied phytochemicals when docked with estrogen receptor. It can be seen that while Gabridin has the highest binding energy of -10.3 kcal/mol and 12 numbers of various interactions, 4-methoxycoumesterol with binding energy of -9.7 kcal/mol and 13 number of interactions has the highest number of interactions. It can also be seen that five of the selected phytochemicals (Hesperatin, Indole-3-carbinol, Kaempferol, Naringenin and Quercetin) has additional type of interaction in addition to hydrogen and hydrophobic interactions.

Table 3. Docking result for selected phytochemicals with Progesterone receptor.

Compounds	**Hydrogen bond**	**Hydrophobic interactions**	**Other interactions**	**Binding energy**	**Total number of interactions**
1)4-methoxy coumesterol	OH-Gln(2.25)	C-Phe778(4.70) C-Phe778(5.21) C-Leu763(5.43) C-Leu718(4.38) C-Leu718(4.93) C-Met759(5.32 C-Leu718(4.93) C-Leu715(5.28)	C-Met759(4.24)	-9.2	10
2)Apigenin	OH-Leu758(2.69) O-Gln725(2.87)	C-Arg766(5.27) C-Pro696(4.86) C-Arg766(4.38)	C-Arg766(3.49) C-Arg766(4.46) C-Glu695(3.69)	-7.8	8
3)Biochanin	OH-Leu718(2.65) OH-Gln725(2.79) OH-Met759(2.54)	C-Phe778(4.92) C-Phe778(5.25) C-Leu763(5.48) C-Met759(4.89) C-Cys891(4.71)	C-Met759(4.09) C-Met756(5.45) C-Leu763(3.91)	-8.9	11
4)Coumesterol	O-Ile699(2.25) O-Gln725(3.48) O-Arg766(3.95)	C-Arg766(5.05) C-Gln725(5.21)	C-Arg766(3.31)	-9.0	6
5)Crocetin	O-Leu876(3.80)	C-Leu799(3.80)	None	-6.6	2
6) Curcumin	OH-Asn879(2.03) OH-Lys875(2.52) OH-Lys875(2.41)	C-Thr829(3.96) C-Val925(5.20) C-Ile920(4.98)	None	-7.5	8

	O-His931(3.33) O-Ser757(3.39)				
7) Daidzein	O-Gly762(3.31)	C-Pro696(5.07) C-Arg766(4.57)	C-Arg766(4.22) C-Glu695(3.44) C-Glu695(4.07)	-7.5	6
8)Diosgenin	None	C-Pro696(5.04) C-Pro696(3.90) C-Pro696(4.47) C-Val698(5.16) C-Met692(4.75) C-His776(4.95) C-Trp765(4.74) C-Lys769(4.56) C-Arg766(4.45) C-Arg766(4.71) C-Arg766(4.51)	None	-9.2	11
9)Formononetin	O-Gly762(3.36) O-Gln725(4.05)	C-Pro696(4.59) C-Arg766(5.12)	C-Glu695(3.35) C-lu695(4.14) C-Gln725(3.2	-7.9	7
10)Gabridin	O-His770(3.67)	C-Val729(4.69) C-Val729(4.85) C-Val698(4.93) C-Lys822(5.48) C-Pro696(4.90) C-Pro696(4.70) C-Leu758(4.51) C-Arg766(4.6	C-Glu695(3.49) C-Arg766(3.58)	-8.9	11
11)Genestein	OH-Met759(2.53) OH-Gln725(2.71) OH-Arg766(2.17)	C-Phe778(4.89) C-Phe778(5.24) C-Leu718(5.04) C-Met759(5.04	C-Cys891(5.14) C-Met759(4.08)	-8.8	9
12)Hesperatin	OH-Glu695(2.18) NH-Gln815(2.92)	C-Pro696(4.75)	C-Arg766(3.99)	-7.0	4
13)Indole-3-carbinol	NH-Gln725(2.61) OH-Leu763(3.10) OH-Leu758(3.27)	C-Ile699(5.19) C-Pro696(4.80)	None	-6.8	5
14)Kaempferol	OH-Glu695(1.91)	C-Trp732(5.80) C-Val698(5.46) C-Ile699(5.12) C-Leu758(5.37) C-Lys822(6.82) C-Ile699(3.20) C-Ile699(4.30)	C-Arg766(3.59) C-Arg766(4.01) C-Lys822(3.37)	-9.0	11
15)Lignan	OH-Lys822(2.38) OH-Arg766(2.31)	C-Ile699(4.46) C-Pro696(4.96) C-Phe818(5.55) C-Val729(3.30)	None	-7.8	6
16)Luteolin	OH-Gln725(2.22) OH-Ser728(3.37) OH-Gly762(3.18) OH-Gly762(1.67)	C-Arg766(3.51) C-Pro696(4.89) C-Pro696(4.34)	C-Arg766(3.59) C-Arg766(4.44) C-Glu695(3.66)	-8.2	10

17)Lycopene	OH-Gly762(3.20)	C-Pro696(4.64)	C-Glu695(4.10) C-Glu695(4.50)	-7.9	4
18)Naringenin	OH-Arg766(2.91) OH-Pro696(2.08) NH-Val698(3.46)	C-Pro696(4.42)	C-Glu695(4.29)	-8.2	5
19)Quercetin	OH-Phe778(2.66) OH-Glu695(1.95) O-Ile699(3.33)	C-Trp732(6.99) C-Pro696(5.44) C-Arg766(5.24) C-Val698(5.28) C-Ile699(5.09) C-Trp732(5.75) C-Lys822(5.21)	C-Arg766(3.94 C-Arg695(4.12 Arg695(4.37) C-Arg766(3.62)	-9.6	14
20)Resveratrol	OH-Phe778(3.08) OH-Glu695(2.17)	C-Leu758(5.32) C-Val729(5.37) C-Pro696(5.40) C-Pro696(5.16) C-Ile699(5.10) C-Trp732(5.56) C-Trp732(5.32) C-Lys822(5.09)	C-Arg766(4.29) C-Arg766(3.68) C-Lys822(3.93)	-9.1	13

Table 3 above shows the various interactions (hydrogen, hydrophobic, and other interactions), binding energies and the total number of interactions of the studied phytochemicals when docked with progesterone receptor. It can be seen that Quercetin with binding energy of -9.6 kcal/mol and 14 numbers of various interaction has highest of both binding energy and number of interactions. It can also be seen that only 5 of the 20 selected phytochemicals (Crocetin, Curcumin, Diosgenin, Indole-3-carbinol and Lignan) has only hydrogen and hydrophobic interactions while all the remaining 15 has other type of interactions in addition to hydrogen and hydrophobic intrecations.

Pharmacokinetic Study

The process of screening, design and development of a drug is a very huge and peculiar task that needs high investment in research. This is not only limited to the cost which may engulf hundreds of millions to billions of dollars but also a long period of time between 10 to 25 years in order for a drug to reach its final (clinical) phase (13). Apart from cost and time, it also need a lot of multidisciplinary human resource. In order to avoid waste of time and resources, modern technique that utilize cost and reduce the time and manpower needed during the development of drug are mostly employed recently this include QSAR, docking and pharmacokinetic studies (14).

Some of the drugs failed at the last stage of clinical trials after spending huge amount of money and time, in order to avoid this, pharmacokinetic study is mostly carried out at the initial stage of development in order to select promising compounds that will not fail at the last stage of the development. Absorption, distribution, metabolism and excretion are the four steps of pharmacokinetic phase of drug development (ADME), with inclusion of toxicological study more recently it is abbreviated as (ADMET) study (15, 16).

There is strong correlation between some chemical descriptors and the ADMET properties, such as oral absorption that depends on low molecular weight, PSA which is the determinant of fractional absorption, the penetration of the lipid membrane by passive diffusion requires the breaking down of hydrogen bond as such needs low number of hydrogen bond and the excretion of the residue of these compounds from the body depends on low molecular weight and log P(17)

Lipinski's Rule of five: This is the most important concept in drug discovery at the preclinical stage in the last decade (18). The rule was proposed by Chris Lipinski and his teammates in 1997 as a result of their attempt to have an insight as to what properties of molecules will reduce or hinder the absorption and permeability of molecules. This rule stated that if a compound violate 2 or more of the following conditions, the compound will be poorly absorbed or it will be impermeable:

Molecular weight < 500
Number of hydrogen bond donors ≤ 5
Number of hydrogen bond acceptors ≤ 10
Calculated Log p ≤ 5
Polar surface area (PSA) <140 Å^2

With the use of specific softwares, these criteria can be used in removing outlier compound very easily at initial stage of drug development. Some classes of drugs that act as substrate for intestinal transporters and intravenously administered drugs are exception to Lipinski's rule of five because they do not undergo absorption (19).

In this study, these parameters was calculated using ADMET descriptors in Discovery Studio 3.5 and the descriptors from Spartan software during the optimization process as shown in Tables 4 and 5.

Table 4. Compliance of selected phytochemicals docked with estrogen receptor to Lipinki's rule of five.

Phytochemicals	**Molecular weight <500**	**H-bond donors ≤5**	**H-bond acceptors ≤10**	**LogP ≤5**	**PSA <140**	**Number of Lipinski's rule violation**
4-methoxycoumesterol	282.25	2	2	-3.03	55.35	0
Apigenin	270.24	3	3	-2.83	72.94	0
Biochanin	284.27	1	1	-1.92	59.86	0
Coumesterol	282.25	2	2	-3.03	55.35	0
Crocetin	328.41	5	5	3.78	66.52	0
Curcumin	368.39	1	1	-1.26	76.29	0
Daidzein	254.24	2	2	-0.95	58.85	0
Diosgenin	414.63	0	0	5.17	32.99	1
Formononetin	268.27	2	2	-0.84	46.13	0
Gabridin	324.38	0	0	-1.26	49.53	0
Genestein	284.27	1	1	-1.92	59.86	0
Hesperatin	302.28	4	4	-3.12	79.08	0
Indole-3-carbinol	147.18	5	3	-0.74	32.36	0
Kaempferol	286.24	2	2	-3.46	88.14	0
Lignan	302.37	0	0	0.01	76.98	0
Luteolin	286.24	1	1	-3.46	90.62	0
Lycopene	536.89	5	5	11.11	15.02	2
Naringenin	272.26	1	1	-2.15	74.62	0
Quercetin	302.24	4	4	-4.54	105.68	0
Resveratrol	228.25	3	2	-0.62	58.94	0

Source: Lipinski CA (Reference no. 19).

From Table 4 shown above, it can be seen that the pharmacokinetic study of the selected phytochemicals when docked with estrogen receptor readily complied with Lipinski's rule of five or does not violate any of the rule of bioavailability with exception of Diosgenin which violates one rule having logP > 5.0 and Lycopene that violates two rules of molecular weight > 500 and logP > 5. Violation of only one rule will not hinder the bioavailability of the compound such as Diosgenin which can be readily bioavailable while Lycopene with violation of two rules, its bioavailability cannot be confirmed according to the rule.

Table 5. Compliance of selected phytochemicals docked with progesterone receptor to Lipinski's rule of five.

Phytochemicals	**Molecular weight <500**	**H-bond donors ≤5**	**H-bond acceptors ≤10**	**LogP ≤5**	**PSA <140**	**Number of lipinski's rule violation**
4-methoxycoumesterol	282.25	1	1	-3.03	55.35	0
Apigenin	270.24	2	2	-2.83	72.94	0
Biochanin	284.27	4	4	-1.92	59.86	0
Coumesterol	282.25	3	2	-3.03	55.35	0
Crocetin	328.41	1	1	3.78	66.52	0
Curcumin	368.39	5	5	-1.26	76.29	0
Daidzein	254.24	1	1	-0.95	58.85	0
Diosgenin	414.63	0	0	5.17	32.99	1
Formononetin	268.27	3	3	-0.84	46.13	0
Gabridin	324.38	1	1	-1.26	49.53	0
Genestein	284.27	3	3	-1.92	59.86	0
Hesperatin	302.28	2	2	-3.12	79.08	0
Indole-3-carbinol	147.18	1	1	-0.74	32.36	0
Kaempferol	286.24	1	1	-3.46	88.14	0
Lignan	302.37	2	2	0.01	76.98	0
Luteolin	286.24	4	4	-3.46	90.62	0
Lycopene	536.89	1	1	11.11	15.02	2
Naringenin	272.26	3	3	-2.15	74.62	0

Quercetin	302.24	3	2	-4.54	105.68	0
Resveratrol	228.25	2	2	-0.62	58.94	0

Source: Lipinski CA (Reference no. 19).

Also from Table 5 shown above, it can be seen that the pharmacokinetic study of the selected phytochemicals when docked with progesterone receptor readily complied with Lipinski's rule of five as it does not violate any of the rule of bioavailability with exception of Diosgenin which violate one rule having logP > 5.0 and Lycopene that violate two rules of molecular weight > 500 and logP > 5. Violation of only one rule will not hinder the bioavailability of the compound as such Diosgenin can be readily bioavailable while Lycopene with violation of two rules, its bioavailability cannot be confirmed from the Lipinski's rule.

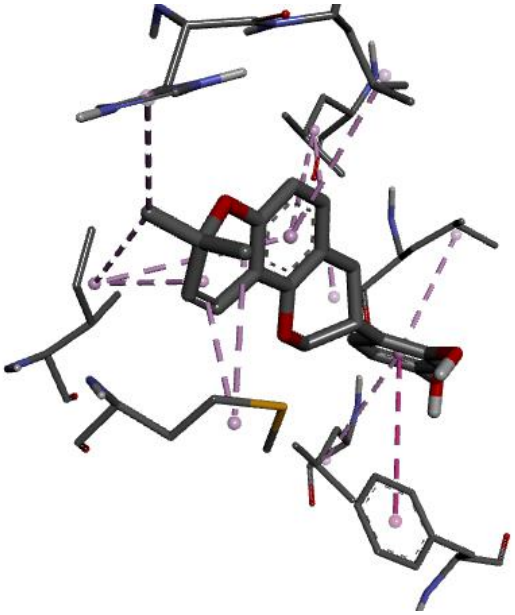

Figure 1. 3D ligand-receptor interaction between Gabridin and Estrogen receptor.

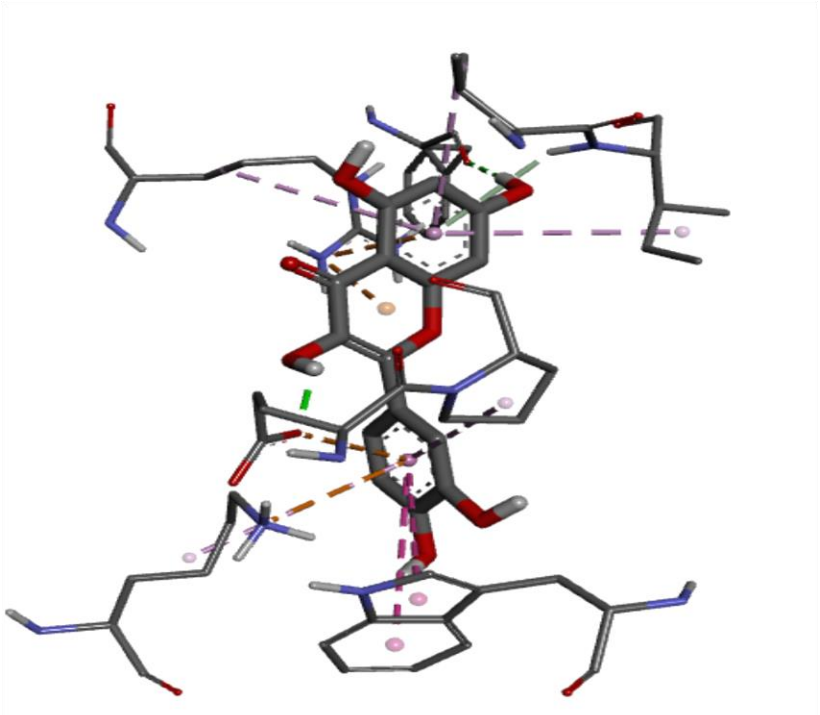

Figure 2. 3D Ligand-Receptor interaction between Quercetin and Progesterone receptor.

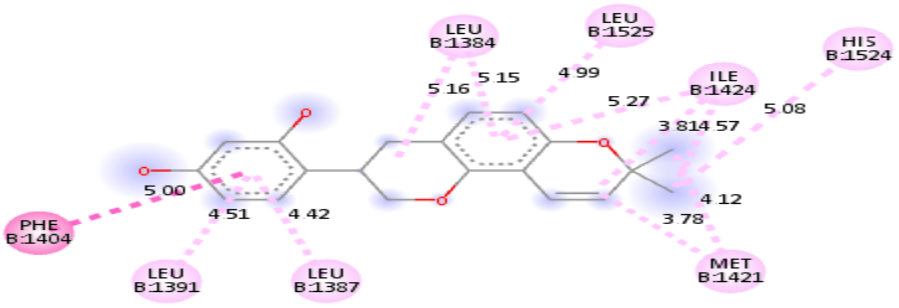

Figure 3.2D Structure showing interaction between Gabridin and Estrogen receptor.

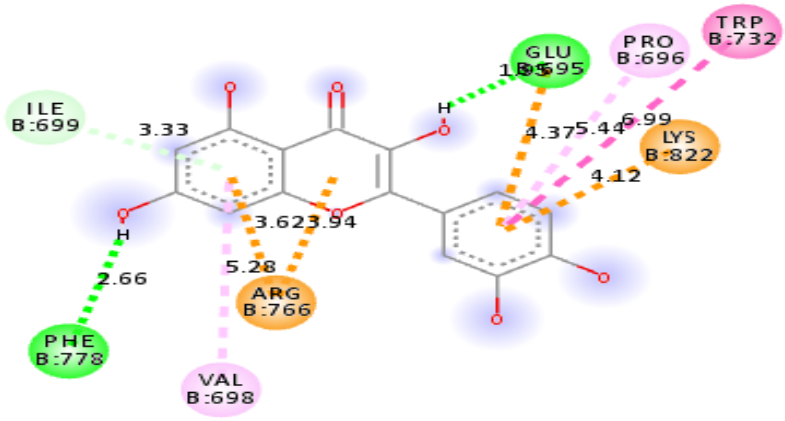

Figure 4.2D Structure showing interaction between Quercetin and Progesterone receptor.

CONCLUSION

Breast cells, both carcinogenic and normal, have receptors for binding with both estrogen and progesterone to stimulate growth response, in the present study both estrogen and progesterone receptors was docked with selected phytochemicals, Gabridin with a binding energy of about -10.3 kcal/mol and 12 numbers of various interactions can be used as a potential lead compound for the design of novel drug for the treatment of breast cancer targeting estrogen receptor. Most of the drugs for the treatment of breast cancer are developed to target estrogen receptor only, in this study it was found that Quercetin with a binding energy of about -9.6 kcal/mol and about 14 numbers of various interactions when docked with progesterone receptor can be used as a potential lead compound for the design of a novel drug candidate for the treatment of breast cancer targeting progesterone receptor.

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