Exploring the Potential of Chemical Constituents of *Datura metel*in Breast Cancer from Molecular Docking Studies

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Abstract. Breast cancer remains a pervasive health challenge worldwide, prompting the exploration of novel therapeutic prospects. *Datura metel* has long been recognized for its pharmacological properties, particularly in containing various bioactive compounds like alkaloids, flavonoids, and terpenoids. This review focuses on the potential of chemical constituents sourced from *Datura metel*, a traditional medicinal plant, in combating breast cancer, primarily through molecular docking studies. The review meticulously scrutinizes the chemical composition of *Datura metel*, emphasizing the identified compounds known for their therapeutic attributes. Through an extensive analysis of molecular docking studies, the interactions between these *Datura metel* constituents and crucial molecular targets associated with breast cancer are elucidated. The phytoconstituents (compound 1-13) were found to be more potent as compare to Tomoxifen citrate as standard anticancer drug. The findings presented herein beckon for further exploration, highlighting a promising avenue in the pursuit of effective and targeted treatments for breast cancer. In conclusion, this review emphasizes the synergistic integration of computational approaches with traditional knowledge, accelerating the discovery and development of innovative breast cancer therapies.

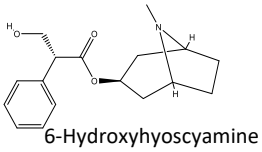
1 Introduction

Breast cancer is the most common cancer in women, with approximately 2.3 million cases reported each year. Over the past three decades, there has been a notable increase in its occurrence and mortality rates. This rise can be attributed to advancements in cancer detection, better recording of cancer cases, and changes in risk factor profiles. A combination of modifiable and non-modifiable risk factors significantly contributes to the overall array of risk factors associated with breast cancer [1]. As per WHO, they released a framework to achieve the goal of preserving 2.5 million lives from cancer by the year 2040 [2].
The breast contains glands responsible for producing milk, situated in front of the chest wall. Positioned on the pectoralis major muscle, the breast is supported and connected to the chest wall by ligaments. Comprising 15 to 20 lobes arranged in a circular pattern, the size and shape of the breast are regulated by the surrounding fat. Eachlobe is composed of lobules housing glands that respond to hormone stimulation by producing milk Breast cancer typically progresses silently, with most individuals discovering the condition through routine screenings. Alternatively, some may notice a breast lump incidentally, experience changes in breast size or shape, or observe nipple discharge [3].
The medicinal plants have been consistently utilized as remedies for diverse illnesses. Most of the people residing in developed nations are reported to rely on traditionalmedicine practices [4].The global increase in the use of medicinal plants can be attributed to their demonstrated efficacy in treating specific diseases and assertions about their safety for consumption [5]. The promising outcomes have been observed with natural plant derived product in serving as effective agents against tumors and cancer. These plant products not only demonstrate efficacy but also exhibit reduced toxicity in their application [6].
*Datura metel*L. is a perennial herbaceous plant of Solanaceae family that can grow up to the height of 1.5 meters. Its leaves are simple, alternate, dark green, broadly ovate, shallowly lobed and smooth. The large, solitary, trumpet- shaped flowers emit a sweet fragrance, and display diverse range of colors from white to yellow and light to purple dark. These flowers are pollinated by insects, and the resulting fruits takes the form of capsules covered with spines. *D. metel* is rich in various phytochemicals, including alkaloids, phenols, tannins, saponins and sterols [7]. The plant is employed for addressing conditions like diarrheaand skin diseases. It is also used in managing epilepsy, insanity, hysteria, rheumatic pain, hemorrhoids, painful menstruation, skin ulcers and wound healing. Its use is in burns, aids in soothing coughs [8].

The molecular modeling with docking stimulations involves examining the interaction between a ligand and macromolecular targets. Analyzing the preferred alignment can then be utilized to predict the strength of association or binding affinity between two molecules, employing scoring functions [9]. The computational chemistry has facilitated the identification of novel effective medications with reduced adverse effects through in silico analysis [10]. The objective of this computational study was to investigate the potential of *D. metel*in breast cancer by *in silico* molecular studies.

2 Material and Methods

2.1 Structure of Chemical Constituents of *Datura metel*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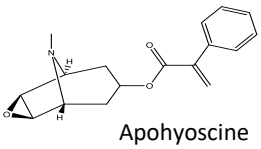
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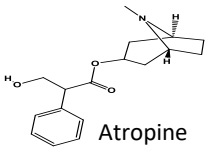
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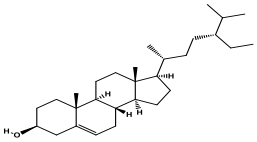
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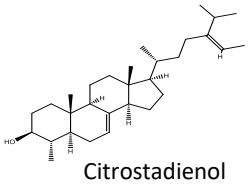
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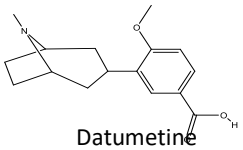
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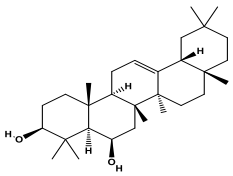
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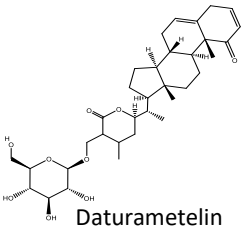
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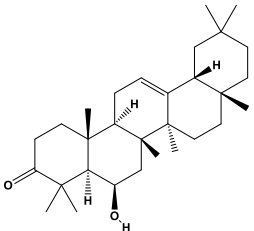
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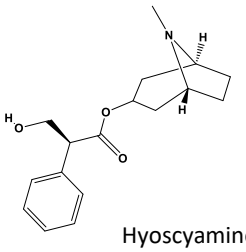
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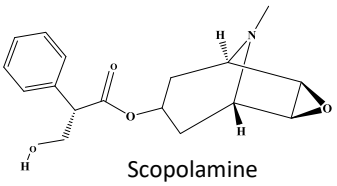
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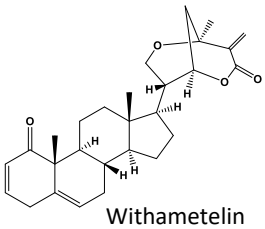
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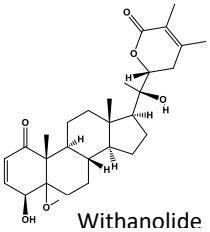

Withanolide

2.2 Analysis of *in silico* Molecular Docking

The molecular docking studies were conducted on different phytoconstituents of *D. metel*to investigate the intermolecular interactions. Tomoxifen citrate was used as a standard drug for comparing molecular interactions. Through the help of Auto Dock Tools 1.5.6 the molecular docking was carried out. The phytoconstituents of the plant were interacted with the target protein with PDB id: 7ldg. By using command prompt, the docking score was calculated. To get the docking results, receptor and ligand were both interacted by using a tool named as Discovery Studio 2021.

The molecular structures of the chemical constituents of *D. metel*such as 6- Hydroxyhyoscyamine, Apohyoscine, Atropine, Beta sitasterol, Citrostadienol, Datumetine, Daturadiol, Daturametelin, Daturaolone, Hyoscyamine, Scopolamine, Withametelin, Withanolide were obtained from https://www.pubchem.org and 2D structures were drawn by using software ChemDraw Professional 15.0. The structures were saved by using extension(.cdx) and saved as file type (ChemDraw.cdx). The energy of these molecular structures was minimized by using Chem3D 15.0 and were saved by using extension (.pdb) and saved as file type {Protein Data Bank (.pdb)}. Then, with the use of AutoDock Tools 1.5.6, the PDB file of these chemical constituents were saved as PDBQT file format [11].

2.3 Preparation of Target Protein

7ldg was selected as target protein and was downloaded from RCSB Protein Databank [12]. The water moleculeswere removed and for the preparation of protein, Kollman charges wasadded and polar hydrogens were also added to stabilize. From the target proteins, the undesired bonding, ligands were eliminated from the structure [13]. The crystal structure has a resolution of 2.56 Å and had 253 amino acids. At last, using AutoDock Tools 1.5.6 the selected PDB was then converted into PDBQT file format. Its image was prepared using Biovia Discovery Studio 2021 as shown in **Fig 1.**

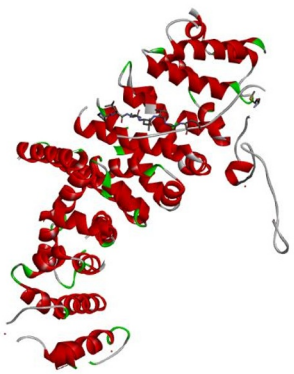


Fig1 MEILB2-BRCA2 Receptor binding protein of Breast cancer

2.4 Virtual Screening and Molecular Docking

The grid box was created for MEILB2-BRCA2 by using AutoDock Tools 1.5.6 (X= 67.587, Y= 142.726, Z= 108.729) and the dimensions in which the grid box was created are 40.00 x 40.00 x 40.00 Å. In Command prompt,the log file, out_ligand_.pdbqtwith binding affinity values in kcal/mol and output.pdbqt was generated. The same was done for all the chemical constituents. Here, the conformation of protein-ligand interactions determined that the configurations with the lowest binding energies, characterized by the most negative values, indicated the strongest binding affinities. The different binding modes of ligands were acquired from the results of docking investigations, and these files underwent analysis using Discovery Studio 2021 to identify the binding mode within the binding site cavity. The protein- ligand interactions, encompassing hydrogen bonding, carbon- hydrogen bonding, van der waals interactions, alkyl interactions, pi- alkyl interactions, and pi- pi alkyl

interactions were observed. The different atomic distances were measured associated with these interactions [14].

3 Results

In a computational molecular study, interactions with the designated target macromolecule were explored to assess the binding interactions of ligands. With the help of AutoDock vina 1.5.6 the structure of MEILB2-BRCA2 was docked with the standard drug Tomoxifen citrate with the binding energy of -4.5 kcal/mol given in **Table 1. [15,16]**

The docking score between MEILB2-BRCA2receptor and ligands of chemical constituents such as 6-Hydroxyhyoscyamine, Apohyoscine, Atropine, Beta sitasterol, Citrostadienol, Datumetine, Daturadiol, Daturametelin, Daturaolone, Hyoscyamine, Scopolamine, Withametelin, Withanolide was integrated by using AutoDock Vina with the binding energy of -6.9 kcal/mol, -7.3 kcal/mol, -6.9 kcal/mol, -7.6 kcal/mol, -7.7 kcal/mol, -7.0 kcal/mol, -7.9 kcal/mol, -7.5 kcal/mol, -8.4 kcal/mol, -6.5 kcal/mol, -6.7 kcal/mol, -9.0 kcal/mol, -8.1 kcal/mol respectively as given in **Table 1. [17,18,19]**

Table 1 Docking score of phytoconstituentswith**MEILB2-BRCA2** target protein

S. no.	Ligand	Docking score by AutoDock Vina (kcal/mol)
1.	Withametelin	-9.0 kcal/mol
2.	Daturaolone	-8.4 kcal/mol
3.	Withanolide	-8.1 kcal/mol
4.	Daturadiol	-7.9 kcal/mol
5.	Citrostadienol	-7.7 kcal/mol
6.	Beta sitasterol	-7.6 kcal/mol
7.	Daturametelin	-7.5 kcal/mol
8.	Apohyoscine	-7.3 kcal/mol
9.	Datumetine	-7.0 kcal/mol
10.	6- Hydroxyhyoscyamine	-6.9 kcal/mol
11.	Atropine	-6.9 kcal/mol
12.	Scopolamine	-6.7 kcal/mol
13.	Hyoscyamine	-6.5 kcal/mol
14	Tomoxifen citrate	-4.5 kcal/mol

4 Discussion

The molecular interaction between standard drug Tomoxifen citrate with MEILB2-BRCA2 consists of three conventional H- bonds that is PRO C:254 and its bonding distance is 1.94 Å, SER C:253 with bonding distance 2.76 Å and ASP C: 212 with bonding distance of 2.17 Å. Along with Conventional H- bonds, it contains Van der Waals forces of attraction that is GLN C:216, PHE C: 256, LEU C: 215 as shown in *Fig. 2.*

The interaction between Withametelin and MEILB2-BRCA2 consists of one Conventional H-bond SER C:253 with the distance of 3.26 Å. Carbon H-bond was only one PRO C:254 with the distance 3.21 Å. Van der Waals forces was GLY C:255. Alkyl and Pi-Alkyl were LEU C:259 and TRP C:262 respectively as shown in *Fig. 3A.*.

Daturaolone showed molecular interaction with MEILB2-BRCA2 which consists of one Pi-donor H- bond TRP C: 262 having a distance of 3.20 Å. And two Van der Waals forces were present PRO C: 258, LEU C:259 as shown in *Fig. 3B.*

Withanolide showed molecular interaction with MEILB2-BRCA2 having one Conventional H-bond ASP C:212 and have distance 2.82. LER C:215 and GLN C:216 are the two Van der Waals forces of attraction as shown in *Fig. 3C.*

Daturadiol interacted with MEILB2-BRCA2 consists of one Conventional H-bond that is GLY C: 255 with the distance of 2.95 Å. Only two Van der Waals forces of attractions were found LEU C:259, TRP C: 262 as shown in *Fig. 3D.*

The molecular interaction between Citrostadienol with MEILB2-BRCA2 consists of two Conventional H-bond that is GLY A: 146 with distance of 3.22 Å and ILE A: 144 having distance of 2.93 Å. Van der Waals forces of attractions are three in number that is LEU C: 130, THR C: 129, PHE C: 184. Two Alkyl interactions are LYS A: 149, LIE A: 144. One Pi-Alkyl interaction TRP C: 132. And one Unfavourable Acceptor-Acceptor ALA A: 143 is also present as shown in *Fig. 3E.*

Beta sitasterol interacted with MEILB2-BRCA2 consists of one Conventional H-bond that is GLU C: 270 with the distance of 2.24 Å. One Van der Waals forces of attraction were shown as THR C: 129. One Pi-Sigma

interaction TRP C: 129, three Alkyl interactions such as LEU C: 232, VAL C: 231, LYS C: 228 were present. At last, two Pi-Alkyl interactions were present that is PHE C: 184 and TRP C: 132 as shown in *Fig. 3F.*
The interaction between Daturametelin with MEILB2-BRCA2 consists of two Conventional H-bond that is ALA A: 143 with the distance of 3.29 Å, GLY C: 133 with the distance of 3.60 Å. Six Van der Waals forces of attraction VAL C: 134, SER C: 136, GLU A: 139, LEU C: 130, GLY A: 146, THR C:129. Only one Pi- Sigma bond found TRP C:129 and one Alkyl interaction ALA A: 143 as shown in *Fig. 3G.*.
The molecular interaction between Apohyoscine with MEILB2-BRCA2 consists of one Carbon H- bond that is GLU C: 287 with bonding distance of 3.53 Å. It also contains five Van der Waals forces of attraction that is VAL C: 282, LEU C:260, VAL C: 283, LEU C: 300, SER C: 299. Along with that it contains two Pi-Alkyl bond interactions that are ILE C: 257, VAL C: 279.At last it contains Pi-Pi T- shaped interaction TRP C: 261 as shown in *Fig. 3H.*
The molecular interaction of Datumetine with MEILB2-BRCA2 consists of one Conventional H-bond that is THR C: 329 with the distance of 2.57 Å. It having three Carbon H – bonds GLU C: 285 having distance of 3.43 Å, VAL C: 282 having distance of 3.47 Å, SER C: 298 having distance of 3.59 Å. The Van der Waals forces of attraction are four in number which are ASP C: 326, LEU C: 327, SER C: 299, VAL C: 279 as shown in *Fig. 3I.*
Molecular interaction between ligand, 6- Hydroxyhyoscyamine with MEILB2-BRCA2 consists of one Carbon H-bond that is VAL C: 283 having bonding distance of 3.30 Å. Other than this it contains two Van der Waals forces of attraction that is VAL C: 282, LEU C: 257. It contains four Alkyl interactions that is VAL C: 283, VAL C: 279, LEU C: 300, ILE C: 257. Also, it has two Pi- Alkyl interactions that is VAL C: 283, TRP C: 261 as shown in *Fig. 3J.*
Atropine molecularly interacted with MEILB2-BRCA2 consists of one Conventional H-bond that is GLU C: 285 with the distance of 2.48 Å. One Carbon H- bond was present that is VAL C: 283 with the distance of 3.55 Å. Three Van der Waals forces of attraction were present LEU C: 300, VAL C: 282, LEU C: 327. Other than that, two alkyl interaction was present ILE C:257, VAL C: 279. At last, two Pi- Alkyl interactions were present VAL C: 283, TRP C: 261 as shown in *Fig. 3K.*
Scopolamine showed molecular interaction with MEILB2-BRCA2 which consists of only Conventional H-bond GLU C:285 having distance of 3.04 Å. Carbon H- bond was one SER C:298 with the distance of 3.72 Å. The Van der Waals forces of attraction were two VAL C:282, LEU C:327. And only one Pi-Alkyl VAL C:283 was present as shown in *Fig. 3L.*
Hyoscyamine when interacted with MEILB2-BRCA2, then it consists of one Conventional H-bond that is GLU C: 285 having a distance of 2.63 Å. Only one Carbon H- bond VAL C:283 with the distance of 3.23 Å was seen. Two Van der Waals forces of attractions VAL C:282, LEU C:327 were present. Two Pi-Alkyl bonds were present TRP C: 261, VAL C:283. Alkyl interactions were four in number ILE C:257, LEU C:300, VAL C:279, VAL C:283 as shown in *Fig. 3M.*

The diverse interactions observed suggest that Citrostadienol, Datumetin, and Hyoscyamine bind closely to the active site, indicating their potency and efficiency in inhibiting the enzyme. The 2D interaction diagrams illustrate the docking orientation and depict ligand interactions. Across the thirteen bioactive phytoconstituents, a total of 86 types of interactions, encompassing Conventional H-Bond, C-H bond, alkyl, pi-alkyl, pi-sigma, pi-pi T-shaped, as well as various Van der Waals interactions, were identified. These findings, when compared to standard medications, highlight the robust potential of *Datura metel* L as a promising treatment for breast cancer.

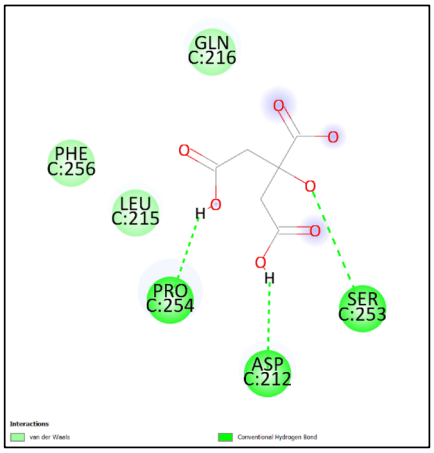
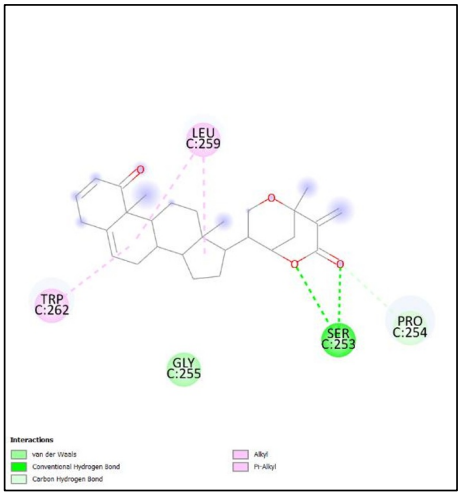


Fig 2



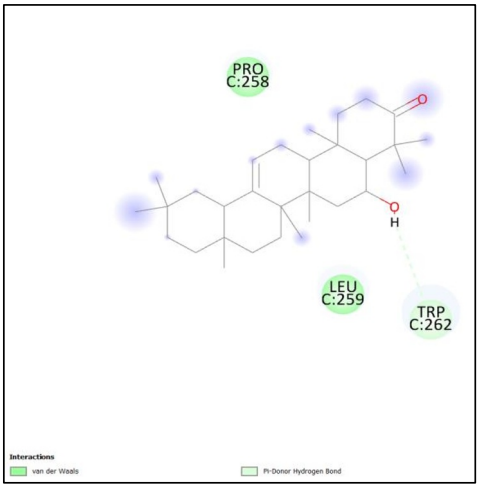
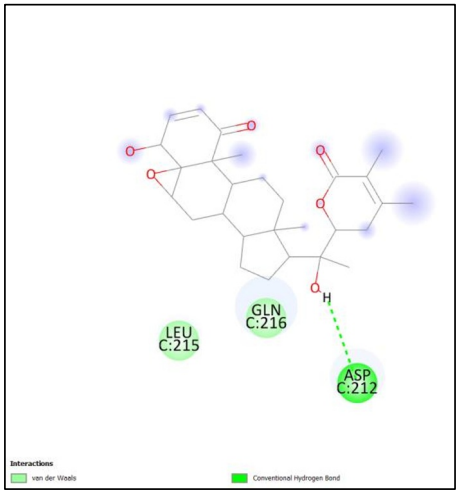
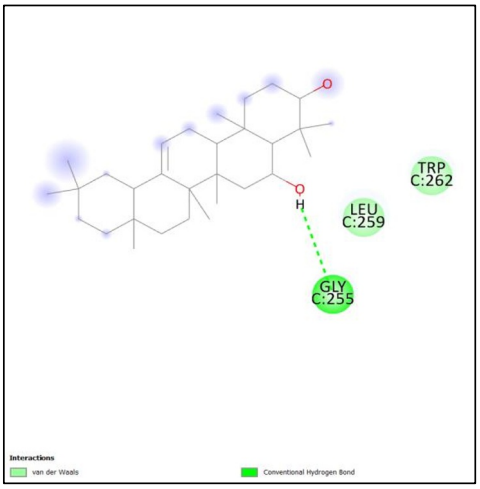


Fig. 3(A)Fig. 3(B)





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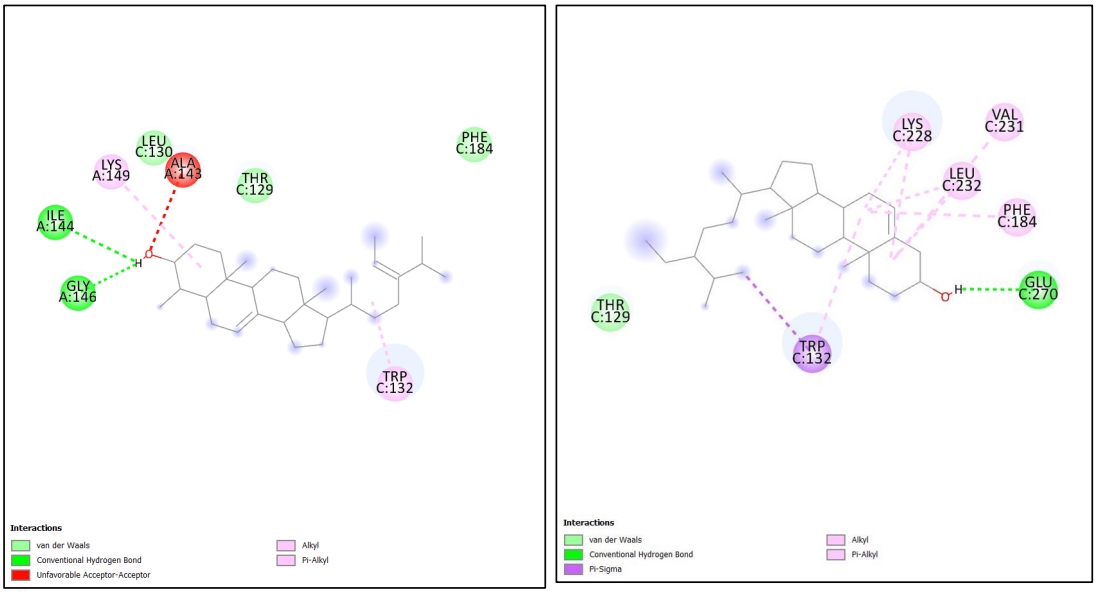


Fig. 3(E)Fig. 3(F)

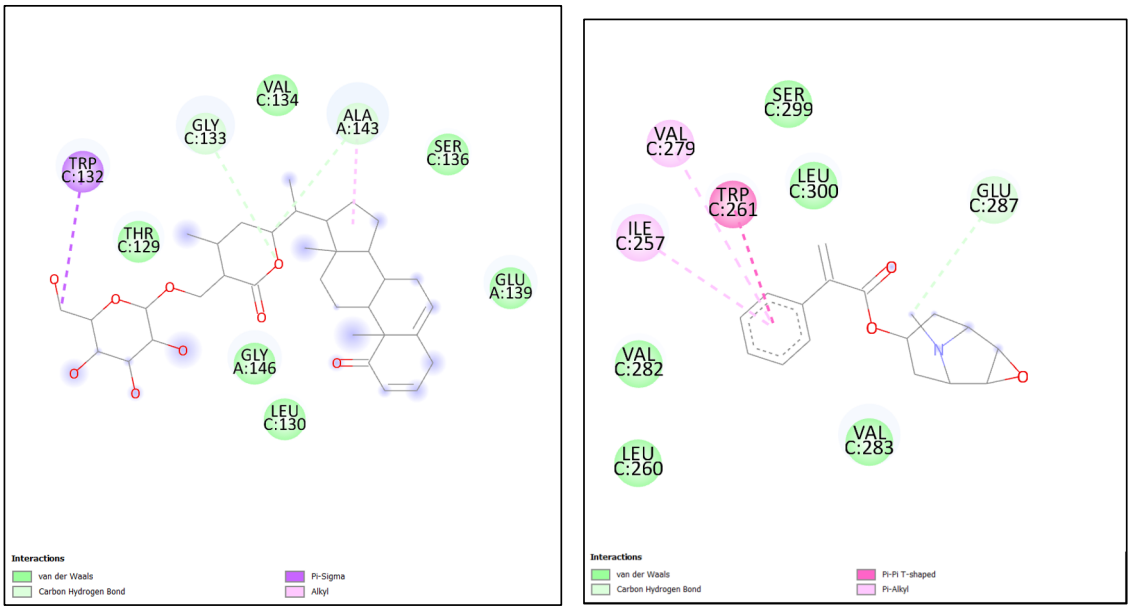
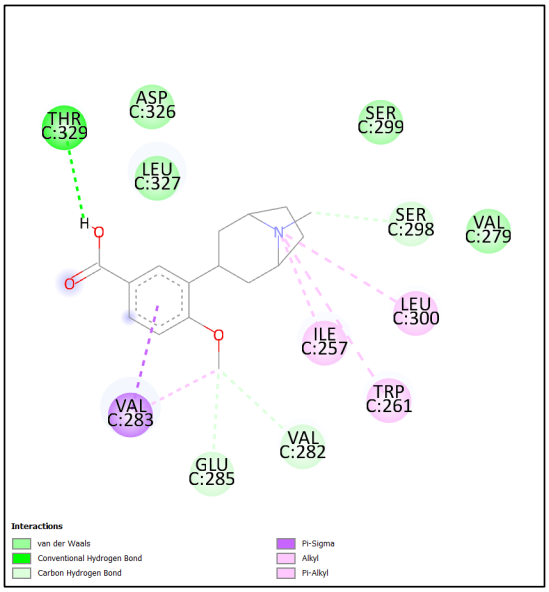


Fig. 3(G)Fig. 3(H)



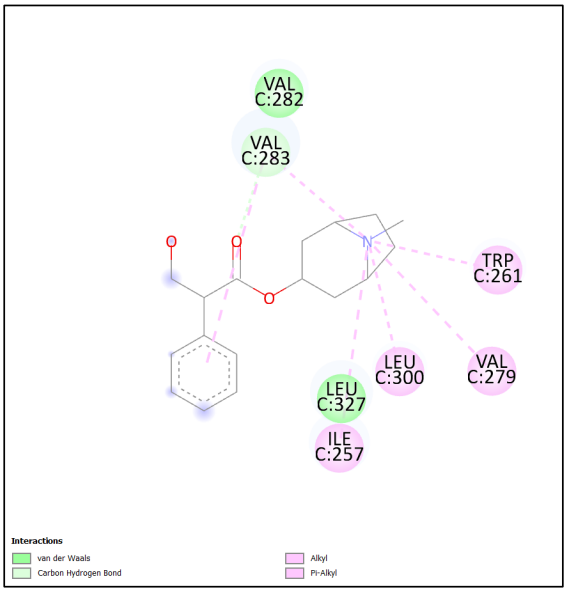
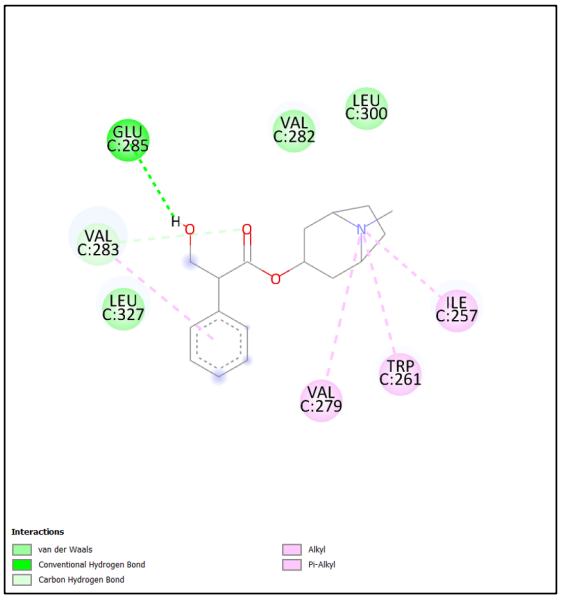


Fig. 3(I)Fig. 3(J)



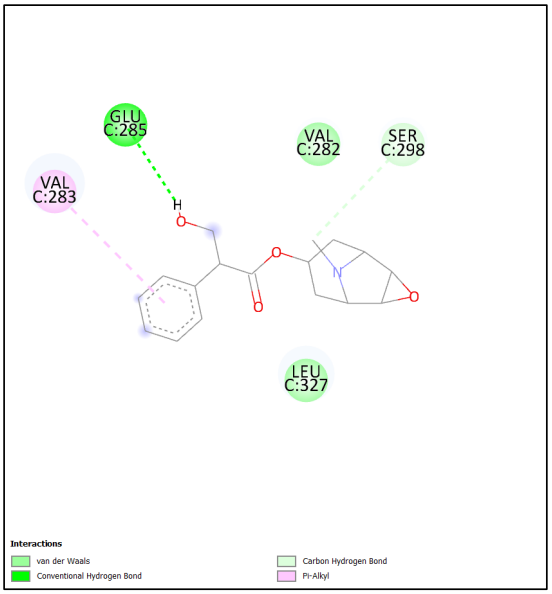


Fig. 3(K)Fig. 3(L)

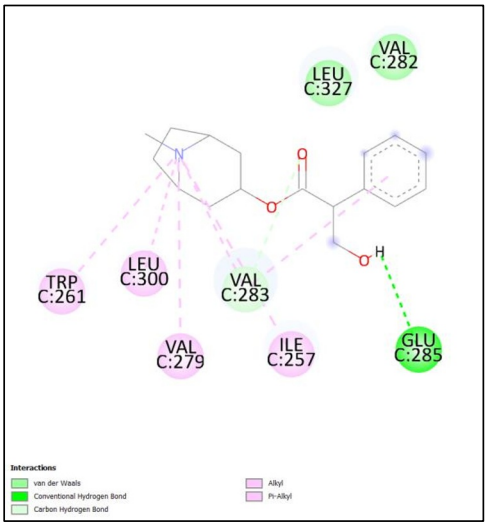


Fig. 3(M)

5 Conclusion

From the above discussion, thecomparative analysis conclude that the ligands of chemical constituents have higher affinity than the standard drug Tomixifen citrate by interacting them with the receptor protein 7ldg (MEILB2-BRCA2). The binding affinity of the ligand of standard drug is -4.5kcal when interacted with the receptor protein. Whereas, the binding affinity of the ligands 6- Hydroxyhyoscyamine, Apohyoscine, Atropine, Beta sitasterol, Citrostadienol, Datumetine, Daturadiol, Daturametelin, Daturaolone, Hyoscyamine, Scopolamine, Withametelin, Withanolide is -6.9 kcal/mol, -7.3 kcal/mol, -6.9 kcal/mol, -7.6 kcal/mol, -7.7 kcal/mol, -7.0 kcal/mol, -7.9 kcal/mol, -7.5 kcal/mol, -8.4 kcal/mol, -6.5 kcal/mol, -6.7 kcal/mol, -9.0 kcal/mol, -8.1 kcal/mol respectively. Thus, the choosen bioactive phytoconstituents demonstrated superior binding affinities in molecular docking when compared to the drug which is prescribed for the medications. But out of these Withametelin shows affinity of -9.0 kcal/mol and Daturaoloneshowed affinity of -8.4 kcal/mol when interacted with the receptor 7ldg. These results conclude that the drug *Datura metel*L. is potent enough to show its action against breast cancer.

6 References

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