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Research Article

In Silico studies of bioactive compounds from *Cleome gynandra* plant with inhibitory activity against breast cancer

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Abstract

Breast cancer (BC) is one of the commonest cancers among women globally. The methanol extract of *Cleome gynandra* (MECG) possesses very good antioxidant properties, which may be due to the presence of phenolic substances and flavonoids, and also *Cleome gynandra* leaf extracts showed free radical scavenging capacity. The primary purpose of molecular docking is to predict the affinity of a drug candidate to bind with the protein and form the most stable complex and also helps in reducing cost and time in drug design. Mainly 5 proteins i.e. ERα, PR, Ki-67, Nf-kB p65, and Caspase 3 were selected based on their involvement in the cancer development and their progression. The five-lead compound was subjected to drug-likeness, ADME profile, and toxicity analysis by using the bioinformatics online tool pre-ADMET. Glucocapparin compound showed more docking score when interacting with estrogen receptors, whereas progesterone receptors and phytosterols had the highest docking score. The interaction between Ki-67 and all bioactive compounds showed that 2-oxazolidinethione, 5-ethyl-5-methyl-, (S) have the highest docking score. The interaction between L-ascorbic acid with Caspase 3 revealed the highest interaction with docking score, and Nf-kb p65 protein showed the highest docking score with glucocapparin.

Keywords: Anticancerous, Breast cancer, *Cleome gynandra*, H-bond, *In-silico*

Highlights

- The interaction between the progesterone receptor and phytosterols showed more docking score.
- All the ligands were non-mutagen, non-carcinogenic, and non-toxic.
- Interaction of L-ascorbic acid with progesterone and Caspase 3 protein showed more H-bonding.
- The methanolic extract of the *Cleome gynandra* plant showed an anticancerous effect.

INTRODUCTION

The term "*In-silico*" defines the experimentation performed by a computer, which is related to more commonly known biological terms like *in vivo* and *in vitro*. It provides a concise and cogent depiction of the potential use of computational tools in biology, chemistry, and pharmacology (Ekins *et al.*, 2007). *In-silico* methods are a new development in chemical testing that relies on computer simulation or modelling (Beutel, 1997). Identifying drug targets via bioinformatics tool, and analyzing target structure for possible binding to active sites are done by *in-silico* methods. It also helps generate candidate molecules, check those molecules for drug-likeness, dock with the target, and rank them according to their binding affinities. The *in-silico* process technique increases the chance of success in many stages of the discovery process and development of lead compounds with desired properties (Pugazhendhi and Umamaheswari, 2013).

Cancer is one of the serious health problems which affects both developing and developed countries despite considerable efforts to improve therapy (Le *et al.*, 2018; Siegel *et al.*, 2018). Breast cancer (BC) is

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one of the commonest cancers among women globally (ISLDBIC, 2017; Bray *et al.*, 2018). It has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases (Sung *et al.*, 2021).

The methanol extract of *Cleome gynandra* (MECG) possesses very good antioxidant properties, which may be due to the presence of phenolic substances and flavonoids (Muchuweti *et al.*, 2007). Paul *et al.* (2012) studied that the *Cleome gynandra* leaf extracts showed free radical scavenging capacity which was confirmed by histological examination. Bala *et al.* (2010) reported the anticancer effect of *Cleome gynandra* against Ehrlich's Ascites Carcinoma (EAC) in Swiss albino mice. MECG showed a significant decrease in ($p<0.01$) tumor volume, viable cell count, and tumor weight and elevated the life span of EAC tumor-bearing mice. Mzondo *et al.* (2021) reported that the leaves of *Cleome gynandra* contain three dammarane-type triterpenoids including two new ones i.e. cleogynones A and B. All three compounds showed cytotoxicity against colorectal cancer (HCT-116 and HCT-15). Cleogynone B was also moderately active against lung cancer (A549).

Therefore, this study is designed to identify the molecular interaction between bioactive compounds of *Cleome gynandra* (Stinkweed) plant extract with some receptors that are linked to the development of breast cancer.

MATERIALS AND METHODS

Protein selection and preparation: Firstly, proteins were selected based on their role in different pathways associated with the cause of cancer. The 3D structure of the estrogen receptor, progesterone receptor, Ki-67, NF-kB p65 subunit, and Caspase 3 were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (http:// ww.rcsb.org). The protein name and their PDB ID along with their role in breast cancer were shown below in Table 1.

Ligand preparation: *Cleome gynandra* comes under the Plantae kingdom and Brassicales order. *Cleome*, the largest genus in the Cleomaceae family, encompasses around 601 species, holding ecological, ethnobotanical, and notably medicinal significance. The plants were mainly collected in the winter season from hilly areas. The 3D structure of bioactive compounds of *Cleome gynandra* plant extract was downloaded from PubChem digital database. According to Lipinski's rule of five, the compound was filtered as follows (Table 2). These bioactive compounds were mainly found in the whole plant except roots.

ADMET analysis: The identified lead compound was subjected to drug-likeness, ADME profile, and toxicity analysis by using the bioinformatics online tool pre-ADMET.

Table 1. Protein name, their PDB ID and role in cancer

Proteins	PDB ID	Role in cancer
ERα	3ERT	Estrogen receptors involved in breast cancer
PR	4OAR	Progesterone receptor involved in breast cancer
Ki-67	1R21	Nuclear protein associated with cellular proliferation
Nf-kB p65	6QHL	Transcription factors, regulate various other proteins involved in apoptosis, invasion, and metastasis
Caspase 3	4QTX	Pro-apoptotic protein

Table 2. Identity of bioactive compound *Cleome gynandra* plant extract

Sl. No.	Compound name	Compound ID	Molecular formula	Molecular weight (g/mol)	H-acceptors and donors	Log P-value
1	2-oxazolidinethione, 5-ethyl-5-methyl-, (S)	CID_5315964	$C_6H_{11}NOS$	145.23	2, 1	1.5
2	Cleoginol	CID_10552492	$C_{30}H_{50}O_4$	474.7	4, 2	6.3
3	Glucocapparin	CID_21600407	$C_8H_{14}NO_9S_2$	332.3	11, 4	-1.9
4	L-ascorbic Acid	CID_54670067	$C_6H_8O_6$	176.12	6, 4	-1.6
5	Phytosterols	CID_12303662	$C_{29}H_{50}O$	414.7	1, 1	9.3

Table 3. Toxicity prediction of phytocompounds

		Cleome gynandra plant extract (Methanolic)								
Sl. No.	**Compound**	**Rat_female_ NTP_ prediction**	**Rat_Female FDA**	**WOE prediction**	**DTP prediction**	**Ames prediction**	**Skin irritancy**	**Skin sensitization**	**Ocular irritancy**	**Biodegradability prediction**
1	2-oxazolidinethione, 5-ethyl-5-methyl-, (S)	Non-carcinogen	Single-carcinogen	Non-carcinogen	Non-toxic	Non-mutagen	None	None	Severe	Degradable
2	Cleoginol	Non-carcinogen	Single-carcinogen	Non-carcinogen	Non-toxic	Non-mutagen	Moderate	None	Sever	Degradable
3	Glucocapparin	Non-carcinogen	Non-carcinogen	Non-carcinogen	Non-toxic	Non-mutagen	None	None	Moderate	Non-degradable
4	L-Ascorbic Acid	Non-carcinogen	Single-carcinogen	Non-carcinogen	Non-toxic	Non-mutagen	None	None	Moderate	Degradable
5	Phytosterols	Non-carcinogen	Single-carcinogen	Non-carcinogen	Non-toxic	Non-mutagen	Moderate	Weak	None	Degradable

Table 4. ADMET analysis of phytocompounds

Sl. No.	**Phyto compound**	**Solubility**	**Solubility level**	**BBB**	**BBB level**	**EXT CYP2D6 # prediction**	**EXT Hepatotoxicity**	**EXT Hepatotoxicity # prediction**	**Absorption level**	**EXT PPB # prediction**
1	2-oxazolidinethione, 5-ethyl-5-methyl-, (S)	-1.65	4	-0.052	2	False	-2.18972	True	0	False
2	Cleoginol	-6.249	1	0.352	1	False	-4.55474	False	0	True
3	Glucocapparin	0.335	5	-0.948	4	False	-5.57571	False	3	False
4	L-Ascorbic Acid	1.402	5	-1.308	4	False	-14.7684	False	1	False
5	Phytosterols	-8.256	0	-0.18	4	False	-8.25473	False	3	True

Molecular docking: The molecular docking between the downloaded ligand and proteins was done using the commercial software Biovia Discovery Studio version 4.0 in Bioinformatics Centre, Madras Veterinary College, TANUVAS, and Chennai using the CHARM force field. The protocol for receptor-ligand interaction namely Libdock was used for molecular docking. The docking score, site of interaction, H-bond length, and amino acid residue values were observed for analysis. The protein and ligand interaction were visualized using the Discovery Studio visualizer.

RESULTS

Selection of proteins: Mainly 5 proteins i.e. ER α ,PR, Ki-67, Nf-kB p65, and Caspase 3 were selected based on their involvement in the cancer development and their progression. The 3D structures of all five proteins are given in Fig. 1.

Ligand preparation: According to Lipinski's rule of five (Lipinski *et al.*, 1997) the compounds were filtered. Toxicity prediction of all five compounds was performed and given in Table 3. All the compounds are non-mutagen predicted by the

Ames test, nontoxic, and non-carcinogen. Also, all compounds are biodegradable, have no ocular toxicity, and are weak or have no skin sensitization. Similarly, ADMET analysis of all five compounds was also performed, and the results were presented in Table 4. The 3D structures of all five compounds are given in Fig. 2.

Molecular docking: Molecular docking was performed between the receptor proteins and bioactive compounds of *Cleome gynandra* plant extract. The best docking conformation was selected based on docking score, interaction energy, and presence of H-bonding and their length. The results of molecular docking are presented in Table 5. The 3D structure of all the molecular interactions between protein and ligands along with H-Bonding (2D view) are presented in Fig. 3. Glucocapparin compound showed more docking score when interacting with estrogen receptor i.e. 100.895 and interaction energy of 41.645 as compared to other compounds. Among all five compounds interacting with progesterone receptors, phytosterols have the highest docking score of 120.73 and interaction energy of 53.3439. The interaction between Ki-67 and all bioactive compounds showed that 2-oxazolidine thione,5-ethyl-5-methyl-, (S) have

Table 5. Molecular interaction of phytocompounds with proteins

Sl. No.	Protein name	Ligand name	Site of interaction	Lib Dock score	Interaction energy	Hydrogen bond length	Amino acid residues
		2-oxazolidinethione, 5-ethyl-5-methyl-, (S)	1	61.7436	20.3583	2.57	PRO A: 325
		Cleoginol	-	-	-	-	-
1	3ERT	Glucocapparin	1	100.895	41.645	1.74	LEU A: 327
						1.76	GLU A: 353
						2.60	LEU A: 387
						2.84	GLU A: 353
						2.91	HLY A: 390
		L-ascorbic acid	3	80.1669	22.7104	2.24	MET A: 421
		Phytosterols	1	98.9979	-69.8824	-	-
		2-oxazolidinethione, 5-ethyl-5-methyl-, (S)	2	65.6794	22.5049	2.13	MET A: 756
						2.43	SER A: 757
		Cleoginol	2	111.542	30.877		
		Glucocapparin	2	111.427	43.1545	2.50	ILE A: 699
2	4OAR	L-ascorbic acid	3	87.7245	32.7424	1.63	SER A: 757
						2.35	TYR A: 753
						2.39	MET A: 756
						2.44	MET A: 756
						2.58	TYR A: 753
						2.81	SER A: 757
						2.95	TYR A: 753
		Phytosterols	1	120.73	53.3439	1.94	GLN A: 725
						2.00	ARG A: 766
		2-oxazolidinethione, 5-ethyl-5-methyl-, (S)	2	69.6794	-146.776	1.88	ILE A: 51
		Cleoginol	-	-	-	-	-
		Glucocapparin	1	56.4074	56.4074	-	-
3	1R21 (Ki-67)	L-ascorbic acid	1	57.261	24.9789	1.96	GLU A: 100
						2.04	GLU A: 98
						2.24	ARG A: 6
						2.69	ARG A: 6
						2.75	ARG A: 6
		Phytosterols	-	-	-	-	-

Cont. Table 5.

In-silico study of *Cleome gynandra* plant extract against breast cancer

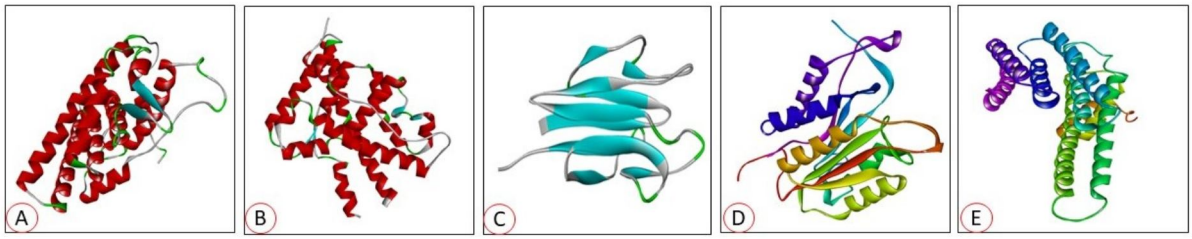

Fig. 1. A. 3D structure of ER; B. 3D structure of PR; C. 3D structure of Ki-67; D. 3D structure of Caspase 3; E. 3D structure of Nf-Kb

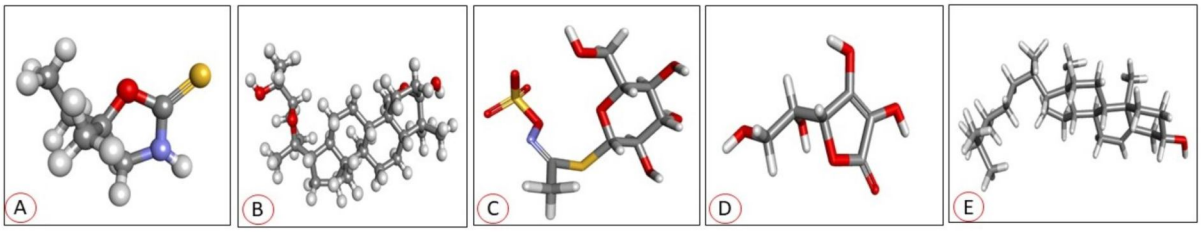

Fig. 2. A. 3D structure of 2-oxazolidinethione, 5-ethyl-5-methyl-,(S); B. 3D structure of Cleoginol; C. 3D structure of Glucocapparin); D. 3D structure of L-Ascorbic acid; E. 3D structure of Phytosterols

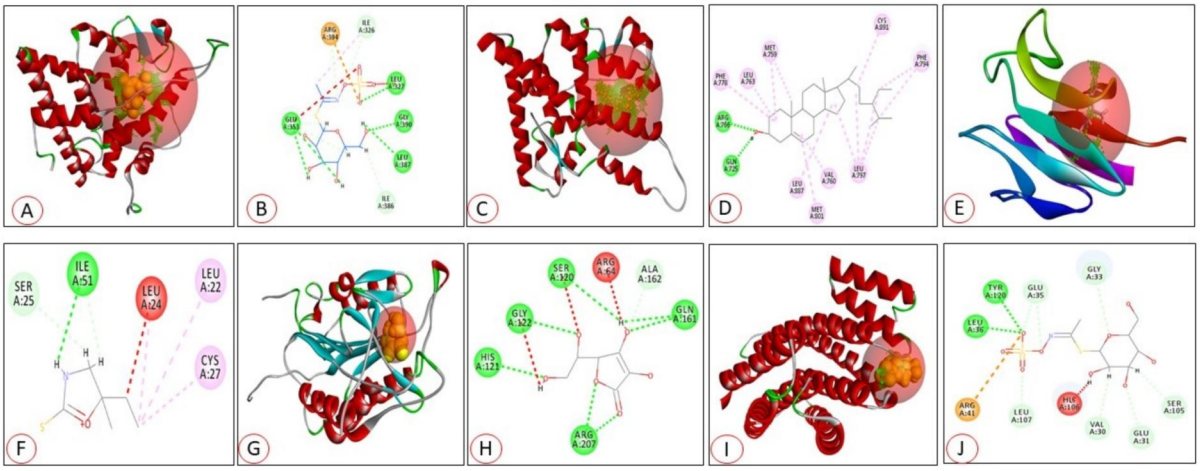

Fig. 3. A-B. Molecular interaction with H-Bond: A-B. Glucocapparin and Estrogen receptor; C-D. Phytosterols and Progesterone receptor; E-F. Oxazolidinethione, 5-ethyl-5-methyl-,(S) and Ki-67; G-H. L-Ascorbic acid and Caspase-3; I-J. Glucocapparin and Nf-Kb p65

Table 5., Cont. ...

Sl. No.	Protein name	Ligand name	Site of interaction	Lib Dock score	Interaction energy	Hydrogen bond length	Amino acid residues
		2-oxazolidinethione, 5-ethyl-5-methyl-, (S)	5	54.7602	17.8473	2.34	GLY A 122
		Cleoginol	-	-	-	-	-
4	4QTX (Caspase 3)	Glucocapparin	5	69.5034	40.6064	2.25 2.53 2.75 2.92 4.91	ARG A: 207 ARG A: 64 CYS A: 163 ARG A: 207 ARG A: 64
		L-ascorbic acid	5	84.3322	34.5058	1.63 2.11 2.39 2.42 2.84 2.93 2.94	ARG A: 207 GLN A: 161 HIS A: 121 SER A: 120 GLY A: 122 GLN A: 161 ARG A: 207
		Phytosterols	-	-	-	-	-
5	6QHL (Nf-kb p65)	2-oxazolidinethione, 5-ethyl-5-methyl-, (S)	5	60.1893	18.4079	2.26 2.83 2.88	GLY A: 78 LYS A: 77 ASN A: 70
		Cleoginol	1	55.6668	35.877	1.38 2.55	LYS A: 122 LYS A: 49
		Glucocapparin	2	96.6728	24.6912	1.71 1.98	LEU A: 36 TYR A: 120
		L-ascorbic acid	5	83.7386	30.7446	2.46 2.73 2.98	VAL A: 81 ASN A: 70 GLY A: 78
		Phytosterols	1	68.7182	30.7446	1.99 2.34 2.48 2.55	GLY A: 78 SER A: 69 LYS A: 77 ASN A: 70

the highest docking score of 69.6794 and interaction energy of -146.776. Cleoginol compound only interacts with progesterone receptors and Nf-kb p65 shows no interaction with the other three compounds. Phytosterols compound also did not show any interaction with Ki-67 and Caspase 3. The interaction between L-ascorbic acid with Caspase 3 revealed the highest interaction with a docking score of 84.3322 and interaction energy i.e. 34.5058. Nf-kb p65 protein showed interaction with all five bioactive compounds with the highest docking score of 96.6728 with glucocapparin. Glucocapparin interacted with estrogen receptors and showed five H-bondings, whereas seven H-bondings were present in L-ascorbic and progesterone receptor interaction. Five H-bondings were present in L-ascorbic acid and Ki-67 interaction. Seven and four H-bondings are present in Caspase 3 with L-ascorbic acid interaction and Nf-kb p65 with phytosterols interaction, respectively. Mostly, L-ascorbic acid interaction with different proteins showed more H-bonding.

DISCUSSION

Cancer is one of the serious health problems which affects both developing and developed countries despite considerable efforts to improve therapy (Le *et al.*, 2018; Siegel *et al.*, 2018). Breast cancer (BC) is one of the commonest cancers among women globally (Bray *et al.*, 2018). The methanol extract of *Cleome gynandra* (MECG) possesses a very good antioxidant property, which may be due to the presence of phenolic substances and flavonoids (Muchuweti *et al.*, 2007). Paul *et al.* (2012) studied that the *Cleome gynandra* leaf extracts showed free radical scavenging capacity

which was confirmed by histological examination. ER, mainly of the alpha subtype, plays an important role in the division of cancer cells and the progression of breast cancer (Platet *et al.*, 2004; Gul *et al.*, 2021). Therefore, ER is becoming a major target for breast cancer treatment (Platet *et al.*, 2004). PR helps in proliferative signals in normal as well as neoplastic mammary glands that have been observed in animal and human studies. Progesterone upregulates the target genes of signal transduction pathways via sensitizing mammary cancer cells to actions of growth (Lange and Yee, 2008). Some clinical trials showed that certain levels of Ki-67 in breast cancer support better outcomes for the patient. The FDA approved the use of CDK inhibitors for individuals whose tumors have Ki-67 levels of 20% or more. Nf-kB p65 is a transcriptional factor, i.e. belongs to the reI family, which exists in cytoplasm. In the case of tumor cells, Nf-kB p65 becomes active and then undergoes nuclear translocation where it will activate the target (Besli *et al.*, 2020). Caspase-3 is a member of the cysteine protease family, which plays a crucial role in apoptotic pathways by cleaving a variety of key cellular proteins. Loss of Caspases-3 expression may represent an important cell survival mechanism in breast cancer patients (Devarajan *et al.*, 2002). Bala *et al.* (2010) reported the anticancer effect of *Cleome gynandra* against Ehrlich's Ascites Carcinoma (EAC) in Swiss albino mice. Mzondo *et al.* (2021) reported that the leaves of *Cleome gynandra* contain three dammarane-type triterpenoids including two new ones i.e. cleogynones A and B. All three compounds showed moderate cytotoxicity against breast cancer (MDA-MB-468). After ligand binding, these receptors undergo specific ligand-based conformational changes and regulate various signalling pathways and protein expressions affecting cell proliferation and differentiation (Kucinska *et al.*, 2016). Many studies, including different chemical compounds having an affinity towards these receptors, helped in exploring different treatment strategies and the development of different selective ER (like tamoxifen) and PR modulators for breast cancer prevention (Mirkin and Pickar, 2015). The present results suggested that these bioactive compounds can act as potential molecules for the designing of anticancer drugs by interacting with multiple signalling pathways and apoptosis.

Cancer is one of the most important causes of death worldwide, and still, a lot of research is going on to find the appropriate drugs which will help to cure the disease. This research revealed that all the bioactive compounds present in the *Cleome gynandra* plant extract have the potential to alleviate the development and progression of tumors and also help in causing apoptosis.

Conflict of interest: All the authors have no conflict of interest in this study.

Author's contribution: BB, SS: Involved in conceptualization and collection of data; NP, SV: Analysis of data and preparation of original data; TSK, PJ: Engaged in supervision and final editing; GVSR: Involved in data curation, supervision and editing.

Data availability statement: All the data supporting the research findings have been presented in this paper. The corresponding author is willing to provide the raw data upon reasonable request.

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