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ORIGINAL RESEARCH ARTICLE

Screen natural terpenoids to identify potential Jab1 inhibitors for treating breast cancer

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ABSTRACT

Jab1 (c-Jun activation domain-binding protein-1) overexpression has been extensively linked to cancer development (or metastasis) in various malignancies by positively regulating cancer cell proliferation or inactivating several tumor suppressors. Recent research has focused on utilizing plant products to target crucial elements of dysregulated signaling pathways to elucidate a potent cancer therapeutic approach. Terpenoids have shown significant anti-inflammatory and anti-cancerous properties in a broader range of carcinomas by inducing apoptosis. Through an extensive literature search, we have selected only those terpenoids (from the NPACT database) that have not been explored against Jab1 (CSN5, COP9 signalosome subunit 5) in breast cancer for our research study. We have used two docking servers, PATCH DOCK, and CB DOCK, to find the binding interaction between selected terpenoids and Jab1. Further, we have also used SWISS ADME to investigate the pharmacokinetics of selected ligands. Amongst all selected ligands, lutein (belongs to the xanthophylls class) has displayed maximum binding energy in both CB Dock and Patch Dock analysis. Hence, our preliminary in silico results have shown lutein as the potent lead candidate for developing a better drug against breast cancer. However, more in silico and in vitro studies are still needed to validate the inhibitory potential of lutein terpenoid against Jab1 in breast cancer.

Keywords: Terpenoids; Jab1; Cancer; Docking; Breast Cancer; Signaling Pathway; Therapeutics

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1. Introduction

Breast cancer, which affects roughly 12% of women worldwide, is the most prevalent invasive cancer in women[1]. Its prevalence is more significant in industrialized nations than in underdeveloped countries. High morbidity and mortality rates make it a threat to women. It takes immense time and effort to combat the disease because of its complexity[2]. Significant improvements have been made over time due to advancements in screening and therapy but at a higher cost to the patients. The cost of the treatment is relatively high for the average person[3]. Therefore, improving breast cancer treatment, prevention, and control measures is vital to increasing survival rates. Most drug-like compounds with various chemical structures can be found in natural goods[4,5]. Oncology has benefited significantly more from the variety and abundance of natural products than any other treatment area[6]. In the drug development program for anticancer medicines, there is rising interest in looking for promising natural compounds. Natural

products were a powerful inspiration for understanding structure-function correlations, which assisted medicinal chemists in developing numerous lead compounds[7,8]. As a result, countless additional anticancer medicines were developed from modified natural compounds that were semi- or synthetically made. The word “terpene” (turpentine), the main ingredient of “rosin” and “turpentine”, which are formed from the resins of plants, notably conifers, is where the name “terpene” comes from. The basic ingredients of plant essential oils are terpenes (terpenoids), made up of isoprene units, a five-carbon building block. Plants use the mevalonate pathway to produce terpenes[9–11]. Nevertheless, terpenes can also be made by microbes such as fungi, lichens, and sponges. According to specific reports, various terpenoids contain antiproliferative properties effective against breast cancer[12–16]. Terpenoids are a vast and varied class of naturally occurring substances in several fruits, vegetables, and medicinal plants. Some terpenoids are structurally related to human hormones. A diet high in terpenoids is inversely correlated with cancer risk and other chronic diseases. Many terpenoids, including triterpenoids, monoterpenoids, tetraterpenoids, and diterpenoids, and their analogs have been approved for clinical trials against advanced breast and prostate cancers. By blocking various cancer-specific targets, such as NF-kB, proteasome, and several anti-apoptotic proteins, these terpenoids can reduce the growth of tumor cells and trigger their death[17–19].

Many breast cancer patients now have better survival rates due to recent therapeutic advancements. Targeted medicines, such as those that target the human epidermal growth factor receptor (EGFR) 2 (Her2) and the oestrogen receptor (ER), have made the most significant strides in recent years. Short DNA (deoxyribonucleic acid) fragments known as genes are found in chromosomes. The instructions needed to construct proteins are found in DNA. Additionally, proteins regulate the composition and operation of every cell in your body[20]. Jab1 has been reported to be the crucial mediator for HER-2/neu in promoting tumor genesis via modulating several intracellular signaling pathways and therefore emerged as a rational target for breast cancer therapeutics. Aberrant Jab1 expression has been recognized as a crucial player in developing and maintaining numerous cancers via down-regulating the expression of various tumor suppressor genes. Transforming growth factor-induced gene transcription is reduced due to Jab1’s direct interaction with Smad4 and subsequent induction of its destruction by the ubiquitin/protease pathway.

Additionally, Jab1 binds to hypoxia-inducible factor-1, preventing its deterioration and boosting transcriptional activity. Jab1 enhances the expression of vascular endothelial growth factor, a key hypoxia-inducible factor-1 target, which upregulates hypoxia-inducible factor-1 and promotes tumor angiogenesis. Since Jab1 is an EGFR signaling target in both ER-cell lines and breast tumors, it may serve as a common factor and possible therapeutic target for crucial cell signaling pathways in ER breast cancer[21–23]. Elucidation of new medicinal phytochemicals targeting Jab1 signalosome provides a new path toward finding a better cancer therapeutic approach[24–29]. Jab1 has also been involved in breast cancer progression. Therefore, we have emphasized investigating the Jab1 inhibitory potential of selected terpenoids in breast cancer via employing in silico analysis.

2. Materials and methodology

2.1 Target identification

The target used for docking is 4F7O COPS5 signalosome complex subunit 5—Homo sapiens. Its 3D structure is obtained from PDB (Protein Data Bank) (www.rcsb.org) having PDB ID: 4F7O in .pdb format (www.rcsb.org). The water molecules were removed during the analysis, and their energy was minimized.

2.2 Ligand preparation

25 terpenoids (**Table 1**) were selected for docking analysis, and their 3D structure was downloaded from the PubChem database[30]. Only those terpenoids that have not been explored against Jab1 in breast cancer are selected. Their 3D structure was obtained from PubChem in .sdf format. (https://pubchem.ncbi.nlm.nih.gov/).

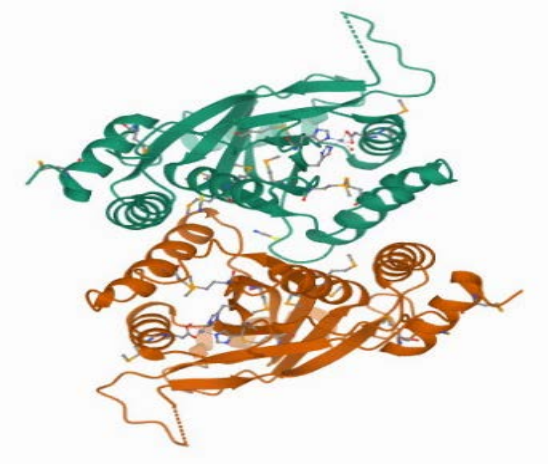


Figure 1. Target Jab1 (4F7O).

Table 1. List of selected terpenoids for docking analysis

S. No.	Name of phytocompound	NPACT ID	Pubchem ID
1.	Eugenol	NPACT00568	3314
2.	Farnesol	NPACT00577	445070
3.	Fenchol	NPACT00578	15406
4.	Cucurbitacin-F	NPACT00452	5476663
5.	Cresol	NPACT00442	24693
6.	Crocetin	NPACT00443	5281232
7.	Curcusone C	NPACT00466	175942
8.	Curcusone B	NPACT00465	175944
9.	D-Limonene	NPACT00515	440917
10.	Erythrodiol	NPACT005564	101761
11.	Fenchone	NPACT00579	14525
12.	Gamma-Tocopherol	NPACT00592	92729
13.	Genipin	NPACT00603	442424
14.	Geniposide	NPACT00604	107848
15.	Linalool	NPACT00714	6549
16.	Lutein	NPACT00728	5281243
17.	Menthol	NPACT00767	1254
18.	Thymol	NPACT00975	6989
19.	Vulgarin	NPACT01379	94253
20.	Xanthatin	NPACT01022	5281511
21.	Paucin	NPACT01290	161538
22.	Ridentin	NPACT01306	6441492
23.	Beta-Spathulenol	NPACT01323	522266
24.	Vibsanins P	NPACT01366	643712
25.	Taiwaniaquinone—F	NPACT01418	11290884

2.3 Lipinski's rule of five

Ligands (terpenoids) utilized in this research study would be analyzed for their toxicological and drug-likeness potential. Their screening would be performed using Lipinski's Rule of Five, which further helps discern between non-drug and drug-

like bioactive compounds. It forecasts a high likelihood of success or failure for molecules that adhere to two or more of the following rules: Less than 500 Dalton molecular mass and high lipophilicity (expressed as Log P less than 5), less than ten hydrogen bond acceptors, five or fewer hydrogen bond donors, and a molar refractivity range of 40 to 130. First, Lipinski's rule of five was used to assess the drug-like qualities of flavonoids, including their molecular weight, hydrogen bond donors and acceptors (HBA), estimated Log P (octanol-water partition coefficient), and free binding energy. The scoring function is used by this tool to analyze the binding conformations using the free binding energy. The result is a collection that includes numerous docking postures and score files for each ligand and an SDF output file for each. After processing these files, we will choose the best score for each ligand by extracting scores from the SD files.

2.4 CB Dock and Patch Dock docking

Using two powerful online docking servers, CB Dock[31] and Patch Dock[32], we determined how well-selected terpenoids bound to the critical target Jab1, which has been positively linked to breast cancer progression. After docking was completed, Chimera software was used to visualize and analyze all complexes.

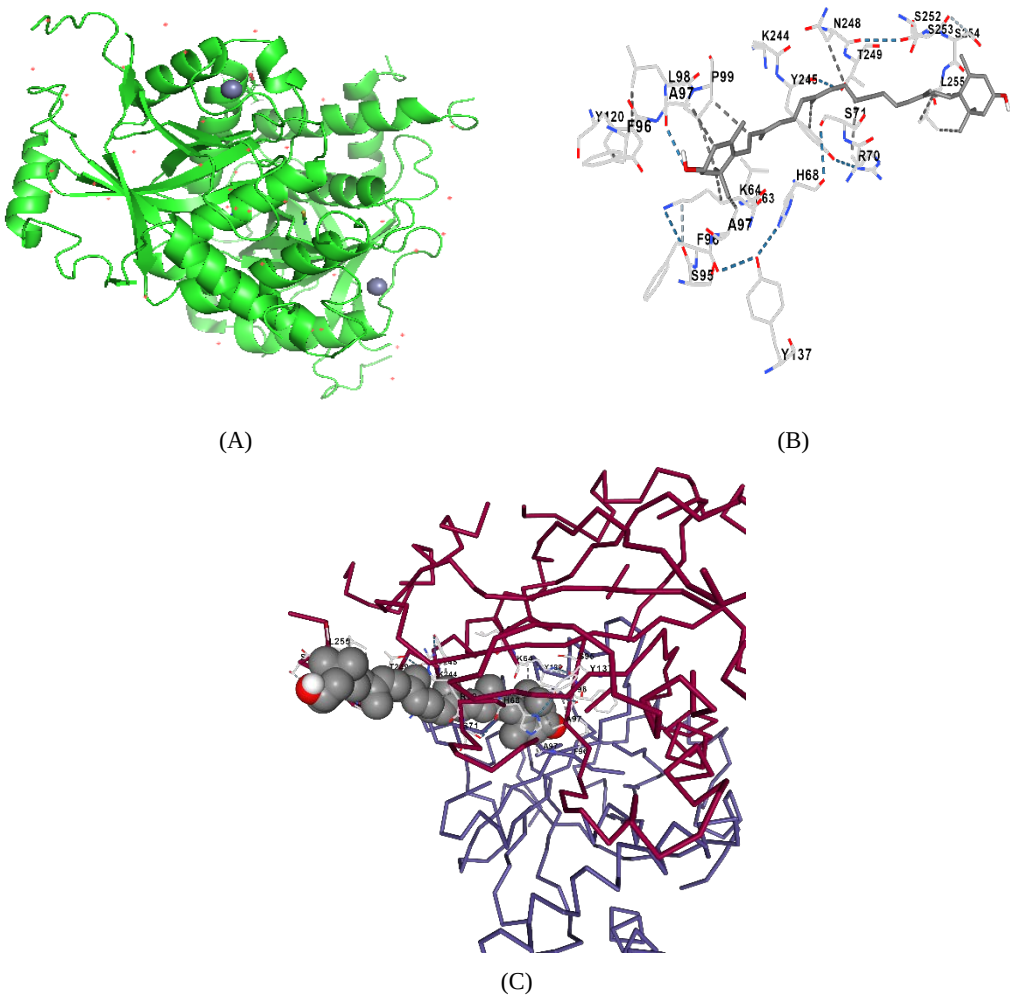
3. Results and discussion

3.1 CB Dock and Patch Dock analysis

CB Dock was used to perform docking analysis to find a potent lead candidate for the efficient management of breast cancer. We have selected terpenoids not explored against Jab1 in breast cancer. Patch Dock and CB Dock have shown that lutein (**Table 2** and **Figure 2**) displays the maximum binding energy against Jab1 in breast cancer.

Table 2. Result of CB Dock analysis

S. No.	Name of ligand	CB Dock analysis		Patch Dock analysis		
		Vina score (kcal/mol)	Cavity size	Score (kcal/mol)	Area	ACE value
1.	Eugenol	−7.2	15,477	1,204	122.30	−140.49
2.	Farnesol	−7.6	763	1,204	122.30	−209.96
3.	Fenchol	−6.5	15,477	1,204	122.30	−140.10
4.	Cucurbitacin-F	−8.8	15,477	1,204	122.30	−421.85
5.	Cresol	−15.2	15,477	1,204	122.30	−294.56
6.	Crocetin	−8.8	15,477	1204	122.30	−280.98
7.	Curcusone C	−8.2	15,477	1,204	122.30	−280.59
8.	Curcusone B	−7.7	15,477	1,204	122.30	−280.21
9.	D-Limonene	−7.3	15,477	1,204	122.30	−139.72
10.	Erythrodiol	−8.3	15,477	1,204	122.30	−419.93
11.	Fenchone	−6.8	15,477	1,204	122.30	−140.10
12.	Gamma-Tocopherol	−8.1	157,477	1,204	122.30	−391.98
13.	Genipin	−7.2	15,477	1,204	122.30	−155.61
14.	Geniposide	−7.4	763	1,204	122.30	−241.36
15.	Linalool	−6.7	15,477	2,604	276.60	−172.30
16.	Lutein	−10	15,477	9,224	1,045.80	−303.58
17.	Menthol	−6.4	15,477	3,258	354.00	−148.10
18.	Thymol	−7.2	15,477	3,204	361.70	−160.72
19.	Vulgarin	−6.3	15,477	3,888	416.60	−221.57
20.	Xanthatin	−6.7	15,477	3,816	463.90	−189.19
21.	Paucin	−8.4	15,477	5,640	619.80	−186.38
22.	Ridentin	−7.5	15,477	3,762	425.90	−169.56
23.	Beta-Spathulenol	−7.1	759	3,660	399.90	−168.06
24.	Vibsanins P	−7.7	15,477	5,504	646.10	−294.12
25.	Taiwaniaquinone—F	−7.6	15,477	4,778	552.80	−263.12



(A) (B)

(C)

Figure 2. Binding interaction of lutein with Jab1 using the cb dock tool. **(A)** docked image of lutein with Jab1; **(B)** structure of lutein in the complex; **(C)** image of Jab1-lutein complex.

3.2. Pharmacokinetic potential of screened compounds

SWISS ADME was used to perform the pharmacokinetic potential of screened phytocompounds used in docking analysis. Different parameters were used for this analysis. **Tables 3**–**5** represent the pharmacokinetic properties of all the screened terpenoids. Amongst all the selected terpenoids, lutein has displayed the best efficacy against the Jab1 target protein.

Table 3. Pharmacokinetic potential of screened compounds

Ligand	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
Eugenol	High	Yes	No	Yes	No	No	No	No
Farnesol	High	Yes	No	Yes	No	Yes	No	No
Fenchol	High	Yes	No	No	No	No	No	No
Cucurbitacin-F	High	No	Yes	No	No	No	No	Yes
Cresol	High	Yes	No	Yes	No	Yes	No	No
Crocetin	High	No	No	No	Yes	Yes	No	No
Crocin	Low	No	Yes	No	No	No	No	No
Curcusone C	High	Yes	No	No	Yes	Yes	No	Yes

Table 3. (*Continued*)

Ligand	GI absorption	BBB permeant	P-gp substrate	CYP1A2 inhibitor	CYP2C19 inhibitor	CYP2C9 inhibitor	CYP2D6 inhibitor	CYP3A4 inhibitor
Curcusone B	High	Yes	No	No	Yes	Yes	No	Yes
D-Limonene	Low	Yes	No	No	No	Yes	No	No
Erythrodiol	Low	No	No	No	No	No	No	No
Fenchone	High	Yes	No	No	No	No	No	No
Gamma-Tocopherol	Low	No	Yes	No	No	No	No	No
Genipin	High	No	No	No	No	No	No	No
Geniposide	Low	No	No	No	No	No	No	No
Linalool	High	Yes	No	No	No	No	No	No
Lutein	Low	No	Yes	No	No	No	No	No
Lycopene	Low	No	Yes	No	No	No	No	No
Menthol	High	Yes	No	No	No	No	No	No
Thymol	High	Yes	No	Yes	No	No	No	No
Vulgarin	High	Yes	No	No	No	No	No	No
Zeaxanthin	Low	No	Yes	No	No	No	No	No
Xanthatin	High	Yes	No	No	No	No	No	No
Neoxanthin	Low	No	Yes	No	No	No	No	Yes
Paucin	Low	No	Yes	No	No	No	No	No
Ridentin	High	Yes	No	No	No	No	No	No
Saikosaponin A	Low	No	Yes	No	No	No	No	No
Saikosaponin B2	Low	No	Yes	No	No	No	No	No
Beta-Spathulenol	High	Yes	No	No	Yes	No	No	No
Vibsanins P	High	No	Yes	No	No	No	No	Yes
Taiwaniaquinone—F	High	Yes	No	No	Yes	Yes	No	No

Table 4. Lipinski analysis

S. No.	Ligand	Mol. weight (g/mol)	No. of h-bond accepter	No. of h-bond donor	Consensus Log P	No. of rotatable bond
1.	Eugenol	164.20	2	1	2.25	3
2.	Farnesol	222.37	1	1	4.32	7
3.	Fenchol	154.25	1	1	2.50	0
4.	Cucurbitacin-F	518.7	7	5	2.53	4
5.	Cresol	324.4	3	3	3.36	0
6.	Crocetin	328.4	4	2	4.21	8
7.	Curcusone C	312.40	3	1	3.18	1
8.	Curcusone B	296.40	2	0	3.85	1
9.	D-Limonene	136.23	0	0	3.37	1
10.	Erythrodiol	442.72	2	2	6.30	1
11.	Fenchone	152.23	1	0	2.66	0
12.	Gamma-Tocopherol	416.68	2	1	7.95	12
13.	Genipin	226.23	5	2	0.28	3
14.	Geniposide	388.37	10	5	-1.22	6

Table 4. (*Continued*)

S. No.	Ligand	Mol. weight (g/mol)	No. of h-bond accepter	No. of h-bond donor	Consensus Log P	No. of rotatable bond
15.	Linalool	154.25	1	1	2.66	4
16.	Lutein	568.87	2	2	9.21	10
17.	Menthol	156.27	1	1	2.58	1
18.	Thymol	150.22	1	1	2.80	1
19.	Vulgarin	264.32	4	1	1.59	0
20.	Xanthatin	246.30	3	0	2.48	2
21.	Paucin	468.49	10	3	0.45	5
22.	Ridentin	264.32	4	2	1.34	0
23.	Beta-Spathulenol	220.35	1	1	3.26	0
24.	Vibsanins P	418.57	5	2	3.95	7
25.	Taiwaniaquinone—F	344.44	4	0	3.43	3

Table 5. Drug-likeliness filters

S. No.	Ligand	Ghose	Veber	Egan	Muegge	Bioavailability
1.	Eugenol	Yes	Yes	Yes	No	0.55
2.	Farnesol	Yes	Yes	Yes	No	0.55
3.	Fenchol	No	Yes	Yes	No	0.55
4.	Cucurbitacin-F	No	Yes	No	Yes	0.55
5.	Cresol	Yes	Yes	Yes	Yes	0.55
6.	Crocetin	Yes	Yes	Yes	No	0.85
7.	Curcusone C	Yes	Yes	Yes	Yes	0.55
8.	Curcusone B	Yes	Yes	Yes	Yes	0.55
9.	D-Limonene	No	Yes	Yes	No	0.55
10.	Erythrodiol	No	Yes	No	No	0.55
11.	Fenchone	No	Yes	Yes	No	0.55
12.	Gamma-Tocopherol	No	No	No	No	0.55
13.	Genipin	Yes	Yes	Yes	Yes	0.56
14.	Geniposide	No	No	No	No	0.11
15.	Linalool	No	Yes	Yes	No	0.55
16.	Lutein	No	Yes	No	No	0.17
17.	Menthol	No	Yes	Yes	No	0.55
18.	Thymol	No	Yes	Yes	No	0.55
19.	Vulgarin	Yes	Yes	Yes	Yes	0.55
20.	Xanthatin	Yes	Yes	Yes	Yes	0.55
21.	Paucin	Yes	No	No	Yes	0.55
22.	Ridentin	Yes	Yes	Yes	Yes	0.55
23.	Beta-Spathulenol	Yes	Yes	Yes	No	0.55
24.	Vibsanins P	Yes	Yes	Yes	Yes	0.55
25.	Taiwaniaquinone–F	Yes	Yes	Yes	Yes	0.85

4. Discussion

Overexpression of Jab1 has been extensively investigated and linked to cancer development (or metastasis) in various human malignancies[26–33]. Numerous therapeutic approaches, either through positively controlling/regulating compounds against Jab1, were conducted using CB Dock and Patch Dock. Terpenoids have received more attention as a result of their ability to induce apoptosis in cancer cells of LNCaP (prostate male cancer cells), human breast cancer (MDAMB231) cells, and HT-29 (human colon cancer cells)[34–36]. Although screened terpenoids are widely established for their anticancer properties in HeLa cells, their Jab1 inhibitory potential in breast cancer cells is unknown. Therefore, the main goal of this research is to determine the inhibitory efficacy of various natural terpenoids against Jab1 in breast cancer cells. Designing an efficient anticancer lead or drug candidate is a time-consuming and expensive task. Thus a logical or systematic methodology is required for rational drug design to get around the many limitations of chemotherapeutic methods[37,38]. With advantages including cost and time effectiveness and better health results, in-silico strategies that take advantage of the therapeutic advantages of plant-based compounds have been a crucial aspect of drug development. In silico approaches that benefit from the medicinal qualities of bioactive have been heavily used in the design and development of drugs[39,40]. A few studies have only recently supported the Jab1 inhibitory potential of these terpenoids in breast cancer[41].

In this research paper, we used variously in silico approaches to investigate Jab1 oncogene inhibitory capacity of twenty-five terpenoids in breast cancer. **Table 2** illustrates that selected terpenoids have significant Jab1 binding affinity based on Kd and significant binding energy between Jab1 and ligand interactions. Lutein has the highest binding energy against Jab1 when compared to other medications. These findings suggest that lutein has the best potential for demonstrating physiological efficacy via plentiful routes after being associated with utilizing GPCR ligands, nuclear receptor ligands, and enzyme inhibitors[42–45]. Overall, in silico studies/research suggested that lutein may be a promising Jab1 inhibitor. Because Jab1 has been indeed correlated or associated with breast cancer cells growth, therefore these experimental research findings projected a highly potent phyto- or bioactive compound as a better lead/drug candidate since it has shown significant binding efficacy against Jab1 protein which has been highly involved in human breast carcinogenesis. However, several in vitro experimentations are desired to elucidate the mechanisms accompanying Jab1 inhibitory efficacy of lutein in breast cancer.

5. Conclusion

Breast cancer is the most common cancer in women and the main reason women die worldwide. The number of newly diagnosed breast cancer cases was 1.38 million, and 60% of fatal cases were found in developing countries. The gender of the patient is the most significant risk factor for breast cancer. Due to their ability to target many sites and minimal, if any, adverse effects, natural chemicals are regarded to be helpful in treating breast cancer. Terpenoids are secondary metabolites of plants or fungi consumed by humans and have a variety of pharmacological actions. To target the Jab1 protein in breast cancer, we have chosen a variety of terpenoids. Lutein has demonstrated the most significant potential for inhibiting Jab1 of all the evaluated terpenoids. In vitro research is still required to confirm its viability as a strong lead candidate for breast cancer treatment.

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Conflict of interest

The authors declare no conflict of interest.

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