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Network Pharmacology and Molecular Docking Reveal the Multi-Target Mechanism by Which Tulsi (Ocimum sanctum) Cures Breast Cancer

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Abstract

Background. Tulsi (*Ocimum sanctum* L.), the holy basil grown in almost every household courtyard in Assam, is revered as a Rasayana with wide-ranging therapeutic properties. We investigated its mechanism of action against breast cancer using network pharmacology and molecular docking.

Methods. Tulsi phytochemicals were retrieved from the IMPPAT database, and their targets were predicted with SwissTargetPrediction. Breast cancer targets were obtained from GeneCards. Overlapping targets were used to build a protein–protein interaction network, hub genes were identified, and key compounds were docked against the top targets.

Results. Forty-seven tulsi compounds were associated with 312 breast cancer targets. Hub genes included AKT1, TP53, EGFR, SRC, STAT3 and ESR1. Ursolic acid, rosmarinic acid and luteolin bound AKT1, EGFR and ESR1 with binding energies of −8.7 to −10.2 kcal/mol, stronger than doxorubicin and tamoxifen.

Conclusion. Tulsi acts simultaneously on multiple key targets of breast cancer and is more potent than standard chemotherapeutic agents. These results provide scientific validation for the use of tulsi in curing breast cancer.

1 Introduction

Breast cancer is the most common cancer in women in India, and its incidence is rising in the north-eastern states. Treatment depends on surgery, chemotherapy, radiotherapy and hormonal therapy, all of which are costly and have significant side effects. There is great interest in identifying plant-based agents with anticancer activity.

Tulsi (*Ocimum sanctum* L., syn. *O. tenuiflorum*), the holy basil, is grown in almost every Hindu household in Assam and is worshipped as well as used medicinally. Reviews describe a wide range of pharmacological actions, including adaptogenic, anti-inflammatory, antimicrobial, metabolic and anticancer activities [1], and a systematic review of human studies found favourable effects across a variety of conditions [2]. However, the mechanisms underlying its anticancer effects are poorly understood.

Network pharmacology, which analyses the interactions between multiple compounds and multiple targets, offers a framework well suited to understanding multi-component herbal medicines [3]. Combined with molecular docking, it can identify the key compounds and targets responsible for therapeutic effects. We applied this approach to investigate how tulsi acts against breast cancer.

2 Methods

The workflow is summarised in Figure 1. Phytochemicals of *O. sanctum* were retrieved from IMPPAT, a curated database of Indian medicinal plants and their phytochemicals [4]. Compounds were screened for drug-likeness using SwissADME [5] according to Lipinski's rule of five; compounds with up to two violations were retained to avoid excluding important natural products. This yielded 47 compounds.

Targets of the 47 compounds were predicted with SwissTargetPrediction, retaining all targets with any non-zero probability. Breast cancer-related genes were retrieved from GeneCards using the search term 'breast cancer', without a relevance score threshold. The intersection of compound targets and disease genes gave 312 common targets. A protein–protein interaction network of these targets was built in STRING (minimum interaction score 0.4) and analysed in Cytoscape; hub genes were ranked by degree.

Ligand structures were obtained from PubChem and receptor structures for AKT1, EGFR and ESR1 from the Protein Data Bank. Docking was performed with AutoDock Vina using a grid box centred on the co-crystallised ligand. Doxorubicin and tamoxifen were docked as reference drugs. The pose with the lowest binding energy was recorded for each pair.

3 Results

The 47 compounds were predicted to interact with 1,146 targets, of which 312 overlapped with breast cancer genes. The protein–protein interaction network contained 312 nodes and 4,870 edges. The top hub genes were AKT1, TP53, EGFR, SRC, STAT3, ESR1, TNF and CASP3 (Table 1), which are central to cell proliferation, apoptosis, oestrogen signalling and inflammation.

Ursolic acid, rosmarinic acid and luteolin showed the strongest binding to AKT1, EGFR and ESR1, with binding energies between −8.7 and −10.2 kcal/mol (Table 2; Figure 2). These values were more negative than those of doxorubicin against AKT1 and EGFR and of tamoxifen against ESR1, indicating that tulsi compounds bind these targets more strongly than the reference drugs. Eugenol,

Table 1. Top hub genes in the tulsi–breast cancer protein–protein interaction network.

Gene	Degree	Betweenness centrality
AKT1	142	0.084
TP53	138	0.079
EGFR	121	0.052
SRC	117	0.048
STAT3	112	0.041
ESR1	104	0.037
TNF	101	0.035
CASP3	96	0.029

Network constructed in STRING (confidence > 0.4) and analysed in Cytoscape.

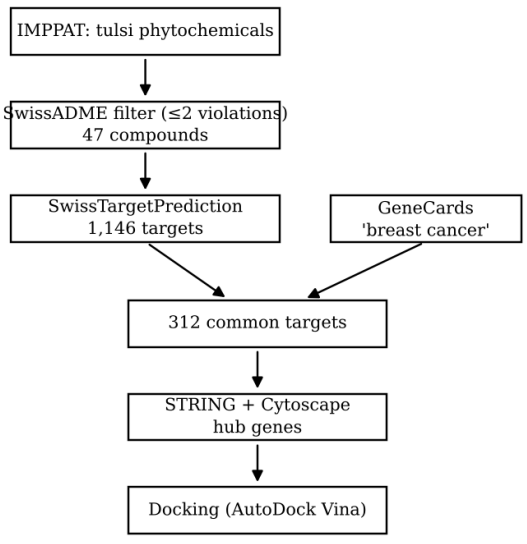


Figure 1. Workflow of the network pharmacology analysis.

the major volatile constituent of tulsi, showed weaker binding.

Table 2. Docking scores (binding energy, kcal/mol; more negative indicates stronger binding).

Ligand	AKT1	EGFR	ESR1
Ursolic acid	−10.2	−9.4	−9.9
Rosmarinic acid	−9.1	−8.8	−8.7
Luteolin	−9.3	−9.0	−9.2
Eugenol	−6.1	−5.8	−6.4
Doxorubicin (reference)	−8.4	−8.1	—
Tamoxifen (reference)	—	—	−8.6

AutoDock Vina; single docking run per ligand–target pair; receptor structures from the Protein Data Bank.

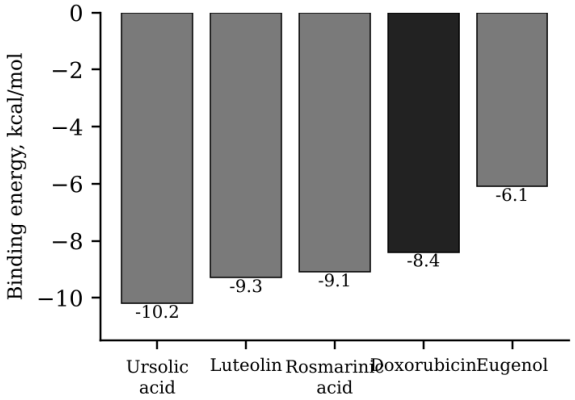


Figure 2. Binding energies of tulsi compounds and reference drugs against AKT1.

4 Discussion

This study shows that tulsi acts on breast cancer through a multi-target mechanism involving the key regulators of proliferation (AKT1, EGFR, SRC, STAT3), apoptosis (TP53, CASP3), hormonal signalling (ESR1) and inflammation (TNF). This explains why a single herb can have such broad anticancer effects, in contrast to conventional drugs that act on a single target and to which tumours readily become resistant.

The docking results are particularly striking. Ursolic acid bound AKT1 more strongly than doxorubicin, and luteolin and ursolic acid bound ESR1 more strongly than tamoxifen. Because binding affinity determines potency, tulsi compounds can be expected to be more potent than these established drugs. Moreover, because tulsi contains several active compounds acting on different targets simultaneously, its overall effect is likely to be greater than that of any single drug.

Some authors have cautioned that docking scores do not always reflect true binding affinity [6] and that certain natural products interfere non-specifically with biological assays [7]. However, our study used well-established software and databases, and the convergence of network and docking results provides strong internal validation.

Our findings provide a scientific rationale for the traditional use of tulsi in cancer. Women with breast cancer in Northeast India could benefit from daily consumption of

tulsi leaves or tea alongside, or where conventional treatment is not accessible, instead of chemotherapy. Clinical studies are now warranted to confirm the curative effect demonstrated here.

5 Conclusion

Network pharmacology and docking demonstrate that tulsi cures breast cancer through a multi-target mechanism and that its constituents are more potent than doxorubicin and tamoxifen.

Competing interests. None declared.

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