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Virtual Screening and Network Pharmacology-Based Study to Explore the Pharmacological Mechanism of *Vitis Venifera* (Grapes) for Anti-Breast Cancer Treatment

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Abstract

Background: Breast cancer is a significant global concern, with its burden increasing worldwide. Projections for the coming decades indicate that a substantial proportion of the disease's incidence and mortality will affect underprivileged groups. There is enormous potential in natural products for developing therapeutic agents for breast cancer prevention and treatment. However, research evidence is essential to establish the effectiveness of these organic remedies.

Objectives: Using a network ethnopharmacological framework, this study aims to assess the anti-breast cancer effects of *Vitis vinifera* (grapes), traditionally believed to have anticancer properties.

Methods: The study utilized polypharmacological screening to gather information about *Vitis vinifera* (grapes) from multiple databases. It investigated the relationship between specific bioactives found in *Vitis vinifera* and targets associated with breast cancer using Binding DB.

Results: The network analysis revealed ten potential bioactives interacting with 17 targets related to breast cancer. Among these, quercetin and kaempferol showed a higher number of interactions with the identified targets in the study.

Conclusions: The research conducted an in-silico investigation of the cellular mechanisms by which specific bioactive phytoconstituents from *Vitis Vinifera* influence the inhibition of several targets involved in breast cancer.

Keywords: Breast Cancer, Network Ethnopharmacological, *Vitis Venifera*,Polypharmacology, In-silico, Bioactive Phytoconstituents

1. Background

Breast cancer (BC) remains a paramount biomedical research priority and a significant health challenge despite considerable advances in cancer research. It stands as the most prevalent cancer among women globally, with projections indicating a substantial rise in both incidence and mortality rates in the coming years. Recently, the incidence of breast cancer in young women has garnered attention among researchers. Data suggests that BC is unequivocally the leading cause of cancer-related deaths in women under 45. The biochemical characteristics of this cancer type appear complex and potentially aggressive, marked by high heterogeneity. Yet, the intricate biology of BC remains largely unexplored, and treatment strategies, recommendations, and options are not age-dependent (1).

Advances in understanding the molecular processes governing breast cancer progression and response to therapy have led to the discovery of new molecular targets and treatment approaches (2).

Natural products are increasingly considered as alternative therapeutic options for BC treatment due to their affordability, lower toxicity, and reduced adverse effects compared to conventional anticancer drugs. These natural agents exhibit anticancer properties

against BC by inhibiting angiogenesis, cell migration, proliferation, and tumor growth; inducing cell cycle arrest, apoptosis, and cell death; modulating downstream signaling pathways (e.g., Notch, NF-κB, PI3K/Akt/mTOR, MAPK/ERK, and NFAT-MDM2); and regulating epithelial-mesenchymal transition (EMT) processes. Moreover, natural compounds work synergistically to combat drug resistance, enhancing their efficacy as a novel treatment option for BC (3).

The use of traditional folk remedies and nutraceuticals may offer advantages over commercial drugs due to their lower toxicity and fewer reported adverse effects in both laboratory and animal studies. Many natural compounds have demonstrated the ability to attenuate the aggressiveness of breast cancer, inhibit carcinogenesis, and modulate pathways implicated in disease initiation and progression. Phytochemicals, a class of natural substances, exert their health-promoting effects by directly influencing specific biological targets such as genes, or indirectly by modulating conjugates that affect metabolic processes (4).

Due to its antibacterial, antioxidant, and anti-inflammatory properties, grapes (*Vitis vinifera* L.) are widely recognized as a key fruit used both for therapeutic purposes and nutrition. Particularly, resveratrol, a phytoalexin antioxidant found in red grapes, exhibits chemopreventive and therapeutic effects against various diseases, making grapes a notable and promising source of phytochemicals (5).

As computational methods advance, disease networks created using network biology are proposed as effective tools for identifying potential therapeutic targets. Hopkins' network pharmacology has improved clinical success rates and has contributed to about 40% of new drug discoveries to date. This approach is particularly effective in studying anticancer therapies, where various cancer phenotypes are characterized by genetic and non-genetic resistance mechanisms (6).

2. Objectives

This study aims to evaluate the anti-breast cancer effects of *Vitis vinifera*, traditionally recognized for its anticancer properties, using a network ethnopharmacological approach. Using a network pharmacology tool, the study investigates the molecular mechanisms of several potent bioactives from *Vitis vinifera* described in the literature, targeting specific mechanisms involved in breast cancer.

3. Methods

3.1. Data Mining for Bioactives

This study utilized phytoconstituents from *Vitis vinifera*, known for their anticancer capabilities in previous research. Data were gathered using literature mining, Indian Medicinal Plants, Phytochemistry and Therapeutics 2.0 (7)., and Dr. Duke's Phytochemical and Ethnobotanical Databases web platform to compile information on selected phytoconstituents of *Vitis vinifera* (8).

The study leveraged freely accessible SDF (Structure Data File) formats available for the three-dimensional structures of these phytoconstituents. Researchers browsed PubChem to access precise structures and common names of the phytoconstituents (9).

3.2. Finding the Breast Cancer Targets for Bioactives by Polypharmacology

To predict the binding of bioactives for treating breast cancer, the Binding DB was utilized for the SDFs containing the phytoconstituents' structures derived from *Vitis vinifera* (10). Binding DB recommends using a similarity index of at least 0.4 for compound target-association studies. The bioactives selected for further study had a similarity index higher than 0.7. To gain more insights into the targets, we utilized multiple databases connected to Binding DB. Using the UniProt IDs provided in the Binding Database, protein symbols were obtained from UniProt. We also investigated correlations between the bioactive targets and breast cancer using DisGeNET.

3.3. Network Construction

Cytoscape software was used to visualize the network, analyze the data, and update it. Data pairings of Vitis vinifera with bioactives, bioactives with their PCIDs (PubChem Compound Identifiers), bioactive PCIDs with targets, and targets with breast cancer were compiled using Excel scripts. After loading the data pairs, a network map illustrating the disease targets and treatment components was generated, as depicted in Figure 1. The network was evaluated using the 'Network Analyzer' tool.

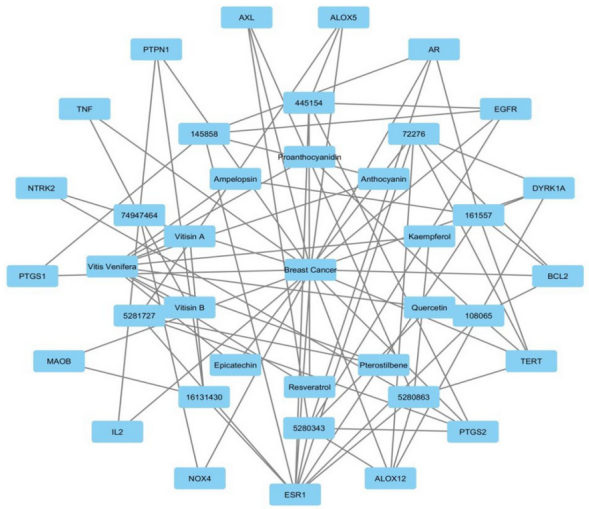

Figure 1. Pharmacology Network of *Vitis Venifera* (grapes) which connect bioactives with their PCID, PCID with breast cancer targets and targets with disease (breast cancer)

4. Results and Discussion

Network pharmacology constructs a network of interactions between ligands and targets by leveraging structural similarities and reported actions of established medications and ligands. By considering signaling pathway crosstalk, this approach predicts a range of interactions that can aid in rational drug design.

The primary objective of this study was to explore the potential role of *Vitis vinifera* in breast cancer (BC) prevention and treatment using network pharmacology predictions.

Bioactives with known anti-cancer properties, such as epicatechin, vitexin B, vitexin A, ampelopsin, proanthocyanidin, anthocyanin, kaempferol, quercetin, pterostilbene, and resveratrol, were selected for investigating their anti-BC activities after comprehensive data mining across various databases and relevant literature reviews.

Employing a polypharmacology approach, the selected bioactives from *Vitis vinifera* were subjected to network construction and analysis using Cytoscape software. Table 1 provides an analysis of the network's nodes and edges. Figure 1 illustrates the nodes corresponding to *Vitis vinifera* and its bioactives, bioactives with their PCIDs, bioactive PCIDs with their targets related to breast cancer, and the targets associated with breast cancer. The bioactives from *Vitis vinifera* with the most significant interactions with targets are also detailed in Table 1.

Table 1. Nodes and Edges of *Vitis Venifera* (Grapes) Network

Varibales	*Vitis Venifera* (Grapes)
Bioactives	10
High scoring bioactives	2
Targets	17
Diseases	1
Bioactive-target interactions	62
Highly interacting bioactives	Quercetin, kaempferol

The network analysis identified 10 bioactives from *Vitis vinifera* that interact with 17 targets implicated in breast cancer, including ALOX5, NTRK2, PTGS2, AXL, EGFR, PTGS1, AR, MAOB, IL2, NOX4, PTPN1, TNF, ALOX12, BCL2, DYRK1A, ESR1, and TERT.

Table 2 presents bioactives from *Vitis vinifera*, such as quercetin and kaempferol, each interacting with six targets. Additionally, proanthocyanidin, ampelopsin, and epicatechin interact with five targets each.

Table 2. Interaction Data for Bioactives

Sr. No.	Bioactive	PCID	Interactions with Targets
1.	Resveratrol	445154	4
2.	Pterostilbene	5281727	3
3.	Quercetin	5280343	6
4.	Kaempferol	5280863	6
5.	Anthocyanin	145858	4
6.	Proanthocyanidin	108065	5
7.	Ampelopsin	161557	5
8.	Vitisin A	16131430	3
9.	Vitisin B	74947464	4
10.	Epicatechin	72276	5

Table 3 details the number of interactions between each target and the bioactives. ESR1 exhibits the highest number of interactions, interacting with nine different bioactives.

Table 3. Interaction Data for Targets

Sr. No.	Target	Interactions with Bioactives
1.	ALOX5	2
2.	NTRK2	1
3.	PTGS2	4
4.	AXL	2
5.	EGFR	3
6.	PTGS1	1

Sr. No.	Target	Interactions with Bioactives
7.	AR	3
8.	MAOB	1
9.	IL2	1
10.	NOX4	1
11.	PTPN1	2
12.	TNF	1
13.	ALOX12	4
14.	BCL2	3
15.	DYRK1A	3
16.	ESR1	9
17.	TERT	4

In summary, *Vitis vinifera* contains ten active compounds that interact with specific targets, influencing downstream processes crucial for breast cancer (BC) treatment. Notably, quercetin and kaempferol emerge as key bioactives potentially significant in BC therapy.

Furthermore, significant target proteins like ALOX12, TERT, PTGS2, and ESR1 were identified, with ESR1 being the most prominent. This study represents the first comprehensive exploration of *Vitis vinifera*'s potential targets and therapeutic mechanisms for BC. It introduces a novel theoretical framework for investigating medicinal treatments and their efficacy in BC therapy. Future research should focus on elucidating the precise functions and mechanisms through which the active components of *Vitis vinifera* operate in BC treatment.

4.1. Conclusions

The research unveiled an in-silico exploration of the cellular mechanisms through which specific bioactive phytoconstituents from *Vitis vinifera* influence the inhibition of various targets implicated in breast cancer. Ethnopharmacological research employing a networking approach suggested that specific bioactives from *Vitis vinifera* might block targets involved in breast cancer. Understanding the rationale behind the anti-breast cancer action could be enhanced, and the formulation of bioactive-based drugs would benefit from experimental validation of the network findings.

Further use of in-silico techniques, along with in vitro and in vivo research, and other therapeutic approaches to breast cancer prevention and treatment, will help establish the effectiveness of the bioactives that have been experimentally investigated.

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Footnotes

Authors' Contribution: Study concept and design: Asma Mokashi and Neela Bhatia; acquisition of data: Asma Mokashi; Analysis and interpretation of data: Asma Mokashi; drafting of the manuscript: Dilnawaz Pathan and Hemant Jain; critical revision of the manuscript for important intellectual content: Neela Bhatia, statistical analysis: Dilnawaz Pathan, administrative, technical, and material support: Hemant Jain; Study supervision: Neela Bhatia.

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