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Original Research Article

Potential of Persimmon (*Diospyros kaki* L.) Compounds for the Treatment of Breast Cancer: A Network Pharmacology Study

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ABSTRACT

The persimmon (*Diospyros kaki* L.) fruit is known for its wide range of health benefits, but its potential in breast cancer treatment has not been extensively studied. This study aimed to explore the bioactive compounds of persimmon using a network pharmacology approach to determine their therapeutic potential against breast cancer. The bioactive compounds of persimmon were collected from literature studies, while breast cancer target proteins were identified using the GeneCards and DisGeNET databases. Protein-protein interaction visualization was conducted using STRING, and molecular signaling pathway analysis was performed through KEGG. The results identified 350 target proteins of persimmon compounds, 23 of which interacted with breast cancer. Analysis revealed that among these 23 target genes, 10 key genes (ESR1, BRCA1, BRCA2, PIK3CA, TP53, PTEN, AKT1, KRAS, MYC, ESR2) were associated with the active compounds gallic acid, ferulic acid, ellagic acid, P-coumaric acid, chlorogenic acid, and protocatechuic acid, demonstrating significant potential as therapeutic agents in breast cancer treatment. These substances work by preventing cell division, triggering programmed cell death, and controlling pertinent molecular signalling pathways. Therefore, the active compounds in persimmon fruit hold great potential as natural therapeutic agents for breast cancer, providing a foundation for further research into the development of plant-based therapies.

Keywords: Bioactive Compounds, Breast Cancer. Network Pharmacology, Persimmon Fruit, Target Proteins.

Introduction

Persimmon (*Diospyros kaki* L.) is a fruit from the *Diospyros* genus within the *Ebenaceae* family. The most extensively grown and frequently consumed species is *Diospyros kaki*. The term “Diospyros” is a Greek word that translates to "Food of the Gods", suggesting that this fruit is both favoured and beneficial.[1] The shape of the persimmon fruit is round, resembling a tomato. When unripe, its skin is green and gradually changes to orange or red as it matures.[2] Persimmons can grow in various locations with low temperatures, high humidity, and partial sunlight (shade or cloudy conditions). In Indonesia, the largest producers of persimmons are East Java and West Java, where the fruit is typically cultivated in highland mountainous areas.[3] Persimmons are popular in many countries due to their sensory characteristics, excellent nutritional quality, including their rich fiber, vitamins, and phenolic compounds contents, and their potential applications in various industrial sectors.[1] Persimmon fruit contains health-promoting phytochemicals such as organic acids, flavonoids, carotenoids, phenolic acid derivatives, vitamins, and protein derivatives. Persimmon fruit contains various essential nutrients per 100 grams. It has approximately 0.6 grams of protein and 0.4 grams of fat, along with 78 kilocalories of energy. The fruit also contains 0.44 grams of ash and has a pH of 5.40. In terms of minerals, persimmon provides 0.27 mg of iron, 15 mg of calcium, 11 mg of magnesium, 10 mg of sodium, 203 mg of potassium, and 27 mg of phosphorus. Additionally, it is a source of vitamins, including 12 mg of vitamin C, 2710 IU of vitamin A, and 0.05 mg of vitamin B1 per 100 grams. These nutritional components contribute to the health benefits of persimmon fruit.[4] Traditional Chinese medicine frequently uses persimmon fruit because of its beneficial impacts on human health, especially in the treatment of hypertension, hemorrhage, and fever.[5] Traditional Chinese medicine has utilized persimmon to treat a number of illnesses, including angina, ischemic stroke, atherosclerosis, hypertension, internal bleeding, and various infectious diseases.[6] Different parts of the persimmon fruit contain bioactive compounds, including tannins, flavonoids, steroids, carotenoids, naphthoquinones, sugars, lipids, and amino acids. Furthermore, previous studies suggest that persimmon possesses antioxidant properties and may help combat free radicals, diabetes, cancer, and dermatological conditions.[7,8] Persimmon also exhibits cytotoxic effects, anti-HIV properties, and promising activity against multidrug resistance bacteria.[6] Persimmon's bioactive qualities make it a promising treatment option for a number of illnesses, including breast cancer. Cancer is characterized by malignant growth, abnormal cell division, tissue invasion, and metastasis. Breast cancer specifically refers to malignancies occurring in the mammary glands.[9] In Indonesia, breast cancer is among the most common cancers. According to the 2018 Basic Health Research study, Indonesia has a 1.79% cancer prevalence, with females having a higher prevalence (2.85%) than males (0.74%). By 2020, the number of new cancer cases in Indonesia had approached 400,000, with a mortality rate of approximately 200,000 deaths. As to the Cancer Today 2020 study by the Global Cancer Observatory, breast cancer ranked first in terms of new cancer

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cases, with 2.2 million cases reported worldwide. According to Hero (2021)[10], breast cancer remained the most common type of cancer in Indonesia in 2020, with approximately 65,000 reported cases.[10] Additionally, Subekti (2020)[11] reported that 0.5% of Indonesians were estimated to have breast cancer, equating to approximately 61,628 cases.[11] Different subtypes of breast cancer are clinically identified based on their histopathological appearance and the expression of hormone receptors and growth factors, including the estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2].[12] With rising incidence rates, ER-positive breast tumors make up the majority of cases. Other uncommon histological subtypes include mixed ductal or lobular carcinoma, invasive lobular carcinoma, accounting for 5 to 15% of cases.[13] Rarely diagnosed before age 40 (probability <1%), breast cancer risk increases with age, reaching a peak at age 70 (median age at diagnosis is 62 years), then decline.[14] Breast lumps, nipple discharge or alterations, nodules, and skin abnormalities surrounding the breast are typical indicators of breast cancer.[15] Given the severity and high prevalence of breast cancer worldwide, particularly in Indonesia, preventive and promotive efforts for breast cancer therapy are essential. In this study, network pharmacology was employed to assess the correlation between target genes and the bioactive compounds of persimmon fruit from a pharmacological network perspective. The relevance and novelty of this research method lies in the results of exploring the interaction of target genes with breast cancer through biological processes and signaling pathways. The therapeutic potential of persimmon bioactive compounds in breast cancer treatment remains largely unexplored. This research is expected to have dual impacts: advancing persimmon cultivation and development while contributing to breast cancer treatment innovations.

Materials and Methods

Tools

The Kyoto Encyclopedia of Genes and Genomes (KEGG) PATHWAY (https://www.genome.jp/kegg/), DisGeNET (https://disgenet.com/), STRING version 12.0 (https://www.string-db.org/), GeneCards version 5.24 (https://www.genecards.org) to obtain target gens, and Cytoscape v3.10.1 software (https://cytoscape.org) were the software used in this network pharmacology study.

Network pharmacology

Network pharmacology explains the complex biological system from a network perspective. Through network pharmacology, health conditions and diseases in the human body can be understood by constructing and analyzing biological networks, which can then be used as targets for designing effective drug intervention methods. Additionally, the methodical, relevant, and predictable aspect of network pharmacology allows it to quantify the regulatory effects of medications on biomolecular networks from a comprehensive and systematic standpoint.[16]

According to Noor *et al*.[17], In order to identify the fundamental processes behind the synergistic therapeutic activities of conventional medications, network pharmacology employs an integrative *in silico* method to build protein-compound or disease-gene networks.[17] The "one target, one drug" paradigm has given way to a "network-target, multi-component therapy" model as a result of this development.

The compounds of persimmon (*Diospyros kaki*), which are essential for the prevention of breast cancer were examined using network pharmacology. The following is the workflow of the network pharmacology approach (Figure 1).

Collection of bioactive compounds of Diospyros kaki

Using the search keywords "Diospyros Kaki Compounds" in Google Scholar, the bioactive compounds of persimmon fruit were derived from reviews of other scientific publications. Based on worldwide papers indexed by Scopus and comparative literature search, a total of ten (10) high quality articles that met the search criteria were selected and reviewed for adequacy of research and methodological relevance.[18] The same search query was also used to incorporate peer-reviewed publications from other significant databases, like Web of Science and Science Direct.

Collection and screening of target proteins related to Diospyros kaki

The target genes and proteins related to breast cancer were retrieved from GeneCards.[19] GeneCards is the biggest global database on human genes, it provides integrated genetic, genomic, and biological information to help researchers understand human health and illness. Integrative GeneCards database is a comprehensive and searchable database that contains easily accessible details on every human gene, both known and predicted.[20] GeneCards can only produce results for Targets having a relevance value of ≥10.00 since this value is thought to meet database requirements.[21]

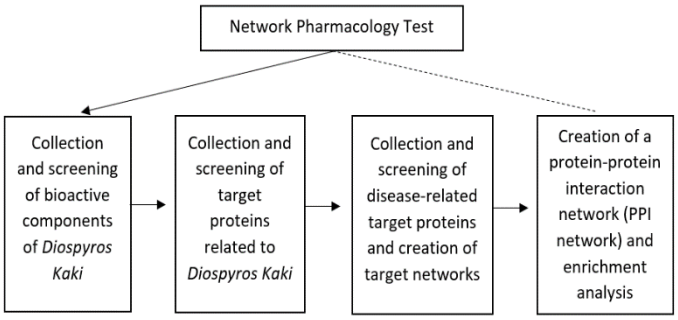

Figure 1: Workflow of the Network Pharmacology Test

Collection and screening of disease-related target proteins and creation of target networks

DisGeNET was used to investigate target genes linked to breast cancer. DisGeNET is a method for gathering data on disease targets by looking through a database that gathers details about the relationships between proteins and disease targets.[22] Thereafter, using Cytoscape v3.10.3, a target network pertaining to persimmon was created. This network combined into a similarity network and a target-component network was used to visualize the targets. "Nodes" stand for the bioactive and target proteins ingredients of persimmon, while "edges" indicate the proteins interactions. The purpose of the DisGeNET Cytoscape software was to compare user-provided data with DisGeNET information and to view, search, and examine gene-disease and variant-disease network representations connections found in DisGeNET. The DisGeNET Cytoscape application offers a collection of tools for network biology-based querying, analysis, and visualization of DisGeNET data.[23]

Visualization of protein-protein interaction (PPI) network and Pathway Enrichment Analysis

The STRING platform was used to select gene targets at the intersection of the active ingredient and the disease for further analysis. Protein-protein interactions (PPIs) are highly significant due to their great specificity, adaptability, and flexibility. Functional interactions between important targets were provided by the database, which yielded the PPI network of key targets (common genes). Subsequently, network analysis was done using important network data to determine which genes will have the highest degree of linkage.[17] To construct PPI networks, A minimum interaction score of 0.400 was used for common target proteins.[21] Gene functions and interactions were described by concepts or classes found in the GO biological process (BP) category. A database called KEGG was used to comprehend the high-level capabilities and operations of biological systems. Using GO analysis, common genes were categorized and visualized.[20]

Results and Discussion

Bioactive compounds of Diospyros kaki

Based on literature search on Google Scholar with the term "Diospyros kaki Compounds", 25 compounds from 6 groups of bioactive molecules

were identified. The collected data on the bioactive molecules found in persimmon (*Diospyros kaki*) are presented in Table 1.

Target proteins related to Diospyros kaki

Based on the target proteins associated with persimmon (*Diospyros kaki*) with a relevance score of ≥10.00, a total of 623 target proteins were identified, accumulated from 10 bioactive compound components. Among these 623 compounds, several overlapping molecular compounds were found. After further screening, 350 heterogeneous molecular compounds were obtained. The result of the persimmon target protein screening is presented in Table 2).

Table 1: Bioactive compounds of *Diospyros kaki* L.

Compound Name	Molecular Type	Pubchem CID	References
Gallic acid		370	37, 1, 5, 7, 38, 6
Ellagic acid	Hydrobenzoic acids	5281855	37
Caffeoylquinic acid		1794427	38, 5
Caffeic acid		689043	37, 5, 7, 38
P-coumaric Acid	Hydroxycinnamic acids	637542	37, 1, 5, 7, 38
Ferulic acid		445858	37, 1, 7
Chlorogenic acid		1794427	37, 5
Protocatechuic acid		72	37, 5, 7
Quercetin		5280343	37, 8, 1, 7, 6, 39
Proanthocyanins		32387820	37, 1, 6, 39, 7
(Epi)catechin		72276	37, 8, 1, 40, 38, 6
Kaempferol-3-*O*-*β*-D-200-coumaroylgalactoside	Flavonoids	44258862	37, 8, 41, 7
Quercetin 3–200-galloylglucoside		13889202	37, 8, 41, 5, 7, 40, 38
quercetin 3-*O*-glucoside		5280804	37, 8, 7, 38
Kaempferol		5280863	1, 5, 7, 40, 6, 39
Kaempferol-3-*O*-glucoside		5282102	37, 8, 5, 7, 40, 38,
kaempferol 3-(200-galloylglucoside)		44258858	37, 8, 7, 40, 38
Myricetin		5281672	8, 7
(epi)gallocatechin	Tannin	72277	37, 8
β-carotene		5280489	1, 7, 38
β-cryptoxanthin		21421799	1, 7, 38
α-carotene	Carotenoids	6419725	1, 7,
zeaxanthin		5280899	1, 7, 38
Lutein		5281243	1, 7, 38
2-Methoxy-1, 4-benzoquinone	Quinone	129850988	37, 5

Table 2: Target Protein Screening Results

Compound Type	Number of Gene Targets	Gifts Range	Relevance Range
Gallic acid	247	55-33	47.9-10.01
Ellagic acid	110	61-54	41.9-10.35
P-Coumaric acid	32	61-50	42.06-10.41
Ferulic acid	88	61-56	41.97-10.05
Chlorogenic acid	63	66-19	41.4-10.02
Protocatechuic acid	41	66-19	42.43-10.01
Quercetin	8	66-50	13.63
(Epi)catechin	1	19	11.07
quercetin 3-O-glucoside	7	66-16	13.67-10.42
Lutein	26	59.39-10.33	68-38

Disease-related target proteins and target networks

Based on the screening results of 350 persimmon target proteins, further screening was conducted to identify target proteins associated with breast cancer using DisGeNET. Figure 2 presents the results of the association between persimmon target proteins and breast cancer.

Based on the Venn diagram (Figure 2), the yellow colour represents persimmon target proteins, while the blue colour represents breast cancer target proteins. The results show that 23 target proteins interact with breast cancer, including ESR1, BRCA1, BRCA2, PIK3CA, TP53, CDH1, PTEN, ATM, CHEK2, FGFR2, AKT1, KRAS, CAV1, CYP19A1, MYC, ESR2, STAT3, TNF, IL6, IGFBP3, VDR, CDKN2A, and ADIPOQ.

Based on the target network visualization (Figure 3), 23 target proteins were identified originating from 8 types of compounds (Table 4). According to Komari *et al*. (2022)[24], the HER-2 protein is a key target for the treatment of breast cancer and is necessary for the growth of breast epithelial cells, interacts with gallic acid through 12 amino acid residues.[24] Additionally, by modifying the cancer cell cycle, triggering apoptosis, and controlling surrounding proteins, ferulic acid can prevent the growth of cancer by encouraging the death of breast cancer cells.[25]

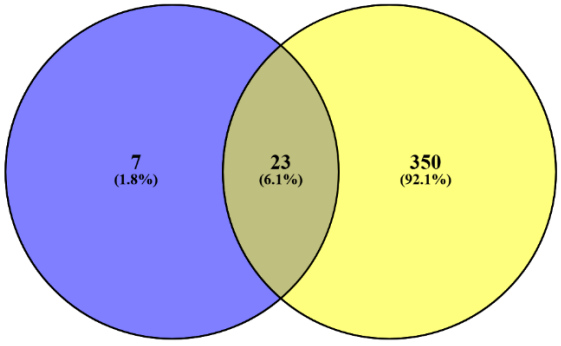

Figure 2: Venn diagram of 350 target proteins of Persimmon fruit against breast cancer

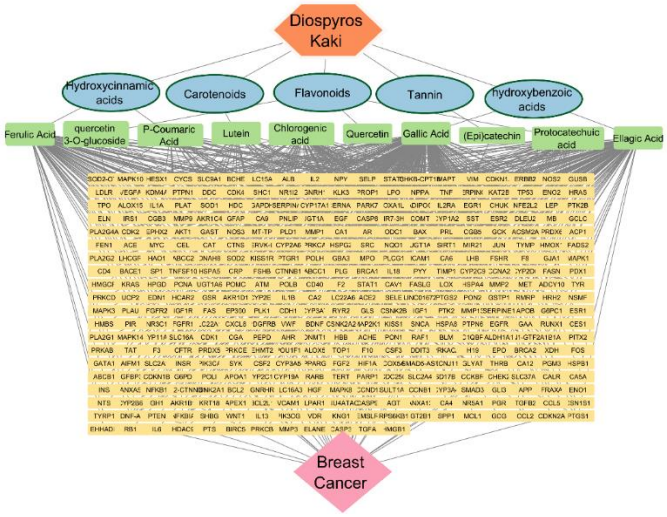

Figure 3: Visual network of Persimmon fruit (Orange: plant name, blue: compound class, Green: bioactive components, pink: disease, yellow: target proteins)

In addition, hydroxybenzoic acids derivatives such as gallic acid, ferulic acid, and ellagic acid and flavonoids such as protocatechuic acid have been shown to exhibit anticancer properties.[26,27] These substances act as antioxidants, promote apoptosis, restrict proliferation, cause cell cycle arrest, and stop breast cancer from spreading. These effects are linked to the compounds' molecular geometry, electronic charge distribution, lipophilicity, and acidity. Furthermore, it has been demonstrated that hydroxycinnamic acids, including p-coumaric acid, ferulic acid, and chlorogenic acid, increase cytotoxicity, prevent cell migration, and reverse resistance in a variety of breast cancer types.[28]

Outcome of protein-protein interaction (PPI) network visualization and pathway enrichment analysis

Protein-protein interactions (PPI) are the physical or functional bonds that exist between two or more proteins and are essential to many biological functions. Proteins joined together by PPI form multimolecular machines called protein complexes.[29] The results of this study focused on the interactions between persimmon-derived target proteins and breast cancer biological processes through network pharmacology. By analyzing network pharmacology, the molecular mechanisms of persimmon's effects on breast cancer can be comprehensively explained at the signaling pathway level.

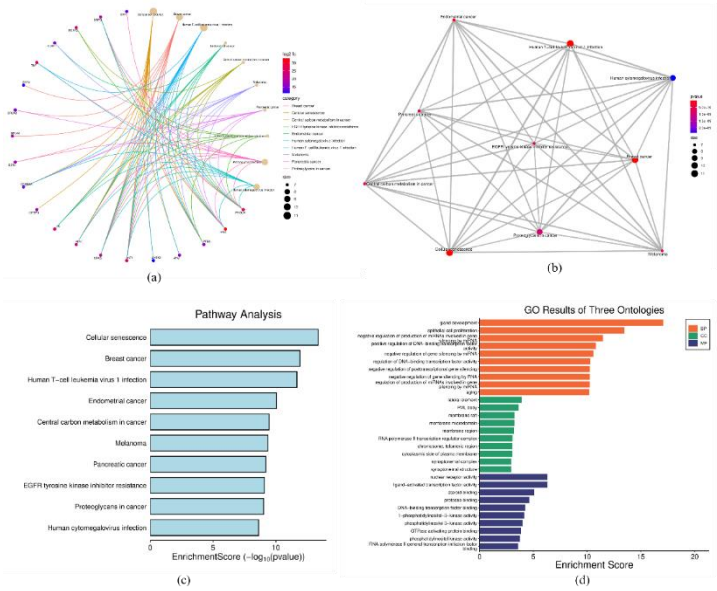

Figure 4: KEGG Gene Ontology and Pathway Enrichment Analysis; **(a)** Pathway analysis of target proteins with potential disease; **(b)** Pathway analysis of potential disease; **(c)** GO bar diagram enrichment for pathway analysis; **(d)** GO bar diagram enrichment for biological processes, molecular function, and cellular components.

Based on the result presented in Figure 4, it can be observed that persimmon target proteins have a high potential against various diseases, particularly cancer, with a strong emphasis on breast cancer (Figures 4a, 4b, and 4c) with an enrichment score >10 and a p-value of 0.00005. As shown in Figure 4d, this potential incorporates a variety of biological processes, molecular activities, and cellular components. Figure 5 presents a more specific network analysis of potential target proteins related to breast cancer.

Based on the analysis using the STRING database (Figure 5), 17 out of the 23 target genes were identified as specific to breast cancer, including ESR1, BRCA1, BRCA2, PIK3CA, TP53, CDH1, PTEN, ATM, CHEK2, FGFR2, AKT1, KRAS, CYP19A1, MYC, ESR2, VDR, and CDKN2A. These target genes are associated with six compound groups: Protocatechuic acid, p-coumaric acid, gallic acid, ferulic acid, ellagic acid, and chlorogenic acid. These six compound groups belong to the hydroxybenzoic acids, hydroxycinnamic acids, and flavonoid molecular types. Further analysis was carried out on the signaling pathways and biological processes related to breast cancer for these potential target genes.Based on the results from the signaling pathway analysis (Figure 6) and KEGG gene interaction analysis (Table 5),

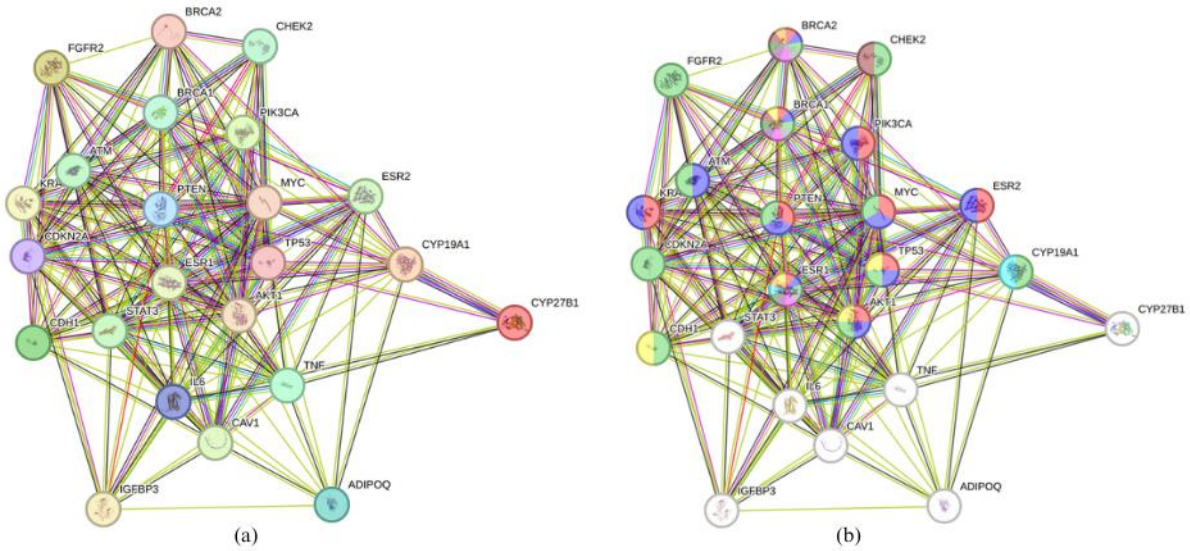

Figure 5: Twenty-Three (23) core protein interaction network from the STRING database (pPI enrichment p-value: 8.1e-15, 23 nodes, 189 edges); **(a)** 23 target genes interact with breast cancer; **(b)** 17 target genes involved in breast cancer biological processes

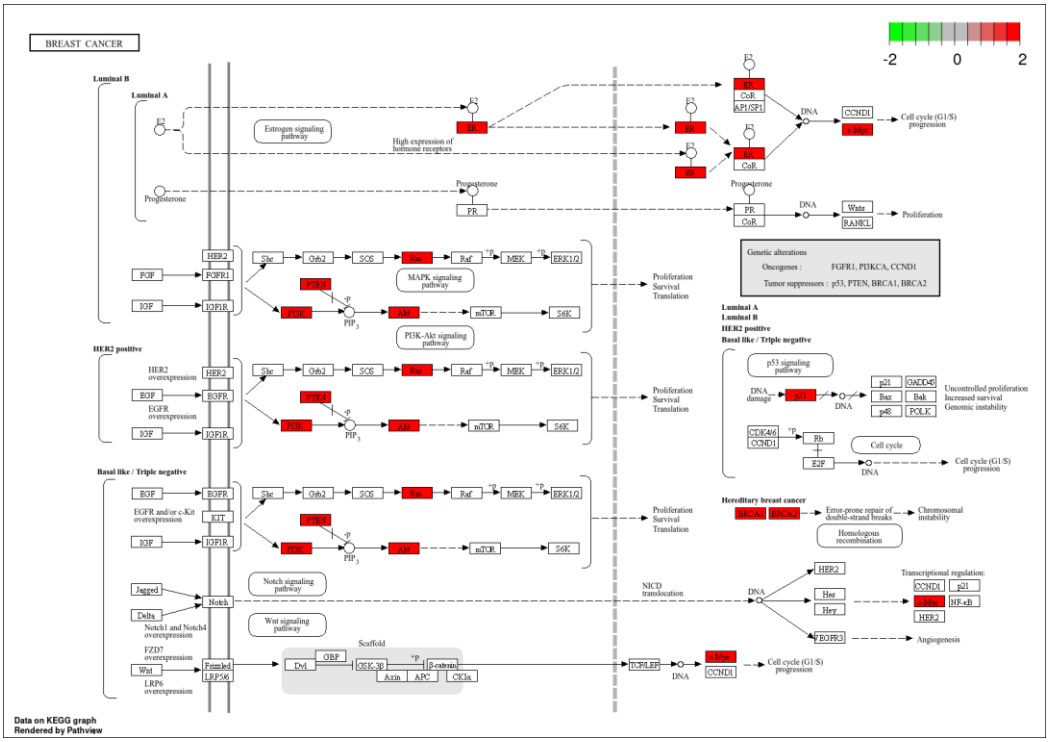

Figure 6: Signaling Pathway involving 10 potential target gens (red marks) in breast cancer activity

Diospyros kaki (persimmon) interacts with the biological processes and breast cancer signaling pathways through 10 target genes: ESR1, BRCA1, BRCA2, PIK3CA, TP53, PTEN, AKT1, KRAS, MYC, and ESR2.

Estrogen Receptor 1, also known as ESR1, is a nuclear hormone receptor that is involved in controlling gene expression in eukaryotes, which in turn affects target tissue cell proliferation and differentiation. ESR1 mutations typically lead to resistance to primary therapy, namely estrogen inhibition via Aromatase Inhibitor (AI), which includes agents targeting estrogen receptors such as degraders, covalent antagonists, and specific modulators of the estrogen receptor. This occurs in metastatic breast cancer that is hormone receptor-positive.[30] ESR1 mutations are seen in 20 - 40% of patients treated with aromatase inhibitor for metastatic breast cancer (MBC). The location of metastasis affects the frequency of these mutations. ESR1 mutations are a major contributor to endocrine therapy resistance mechanisms in breast cancer patients, rendering the disease insensitive to estrogen-lowering therapies like aromatase inhibitor.[31]

The production of polyubiquitin chains connected to "Lys-6" is specifically mediated by BRCA1, or breast cancer type 1, which supports cellular responses to DNA damage, cell cycle regulation, genomic stability maintenance, and other essential physiological processes, all of which are essential for DNA repair. The chance of getting breast, ovarian, prostate, and other cancers is greatly increased by mutations or abnormalities in the BRCA1 gene. People who have BRCA1 mutations are more likely to get cancer; depending on the kind and location of the mutation, their lifetime chance of getting breast

cancer is estimated to be around 80%, and their chance of developing ovarian cancer ranges from 40% to 65%.[32] Likewise, homologous recombination and/or double-strand break repair are involved in BRCA2, or breast cancer type 2. Proteins essential for homologous recombination DNA repair are encoded by BRCA1 and BRCA2. A breakdown in the homologous recombination repair system is suggested in biallelic inactivation and pathogenic triple-negative breast cancer. Pathogenic triple-negative breast cancer is more likely to develop in people with BRCA1 mutations, which is characterized by negative results for the HER-2, estrogen, and progesterone receptors. Meanwhile, estrogen receptor-positive tumors are more frequently found in patients with pathogenic BRCA2 variants.[33]

Table 4: Results of the KEGG gene interaction analysis

Pathways	Description	Gene Ratio	Gene ID
hsa04218	Cellular senescence	11/23	PIK3CA/TP53/PTEN/ATM/CHEK2/AKT1/KRAS/MYC/IL6/IGFBP3/CDKN2A
hsa05224	Breast cancer	10/23	ESR1/BRCA1/BRCA2/PIK3CA/TP53/PTEN/AKT1/KRAS/MYC/ESR2
hsa05230	Central carbon metabolism in cancer	7/23	PIK3CA/TP53/PTEN/FGFR2/AKT1/KRAS/MYC
hsa01521	EGFR tyrosine kinase inhibitor resistance	7/23	PIK3CA/PTEN/FGFR2/AKT1/KRAS/STAT3/IL6
hsa05205	Proteoglycans in cancer	9/23	ESR1/PIK3CA/TP53/AKT1/KRAS/CAV1/MYC/STAT3/TNF
hsa04917	Prolactin signaling pathway	6/23	ESR1/PIK3CA/AKT1/KRAS/ESR2/STAT3
hsa04115	p53 signaling pathway	6/23	TP53/PTEN/ATM/CHEK2/IGFBP3/CDKN2A
hsa05207	Chemical carcinogenesis -receptor activation	8/23	ESR1/PIK3CA/AKT1/KRAS/MYC/ESR2/STAT3/VDR
hsa05206	MicroRNAs in cancer	9/23	BRCA1/PIK3CA/TP53/PTEN/ATM/KRAS/MYC/STAT3/CDKN2A
hsa04151	PI3K-Akt signaling pathway	9/23	BRCA1/PIK3CA/TP53/PTEN/FGFR2/AKT1/KRAS/MYC/IL6
hsa05225	Hepatocellular carcinoma	7/23	PIK3CA/TP53/PTEN/AKT1/KRAS/MYC/CDKN2A
hsa04210	Apoptosis	6/23	PIK3CA/TP53/ATM/AKT1/KRAS/TNF
hsa04211	Longevity regulating pathway	5/23	PIK3CA/TP53/AKT1/KRAS/ADIPOQ
hsa05222	Small cell lung cancer	5/23	PIK3CA/TP53/PTEN/AKT1/MYC

PIK3CA or Phosphoinositide-3-kinase (PI3K) catalytic subunit alpha isoform encodes the alpha catalytic subunit (p110α) of the PI3K protein, which is frequently mutated in breast cancer, particularly in Human epidermal growth factor receptor 2-negative/hormone receptor-positive (HR+/HER2−) breast cancer, also known as the luminal subtype. In breast cancer, the PI3K signaling pathway is activated by two main pathways. First, the PI3K pathway genes may be activated through alterations, such as gene amplification or activating mutations. Second, the PI3K pathway may be activated by receptor tyrosine kinase activation, which is upstream of the PI3K pathway, thereby activating this pathway and contributing to tumor formation.[34]

Cellular tumor antigen p53, also known as TP53, acts in a number of tumor types as a tumor suppressor, causing either apoptosis or growth arrest based on the kind of cell and physiological circumstances. By modulating a group of genes required for cell division, it acts as a trans-activator to negatively influence the cell cycle. Cyclin-dependent kinase inhibitors are among the genes that are activated. Either the expression of the BAX and FAS antigens is stimulated, or the expression of Bcl-2 is suppressed, to induce apoptosis. The "Guardian of the Genome" is the p53 tumor suppressor, which controls cell division, senescence, and apoptosis. Furthermore, p53 is a transcription factor that, depending on the kind of cellular stress signals it receives, influences a number of biological processes. p53 regulates senescence, cell cycle arrest, apoptosis, and DNA repair in response to hypoxia, oncogene activation, DNA damage, and malnutrition. The growth and progression of cancer is accelerated when the TP53 gene is dysregulated because it promotes cell invasion, survival, and proliferation.[35]

Phosphatase and tensin homolog (PTEN) are tumor suppressors that dephosphorylate proteins phosphorylated on tyrosine, serine, and threonine by acting as a dual-specificity protein phosphatase. It also exhibits lipid phosphatase activity and serves as an inhibitor of the carcinogenic PI3K/AKT pathway. PTEN activation occurs through various mechanisms, such as mutations, deletions, epigenetic silencing, transcriptional repression, microRNA dysregulation, post-translational modifications, and abnormal localization. In order to block the PI3K/AKT/mTOR pathway, which regulates cell growth and survival, PTEN is essential. Unchecked cell proliferation results from this pathway becoming overly active when PTEN is deleted or inactivated. In several cancer types, including breast cancer, where PTEN dysregulation is commonly seen is associated with more aggressive tumors, treatment resistance, and a poorer prognosis. Hormone receptor-positive and HER2-positive breast tumors frequently have mutations or changes in the PI3K/AKT/mTOR pathway.[36]

Overall, imbalances in these ten target genes can cause genetic mutations that trigger breast cancer growth and proliferation. Persimmon fruit compounds can upregulate gene expression to prevent mutations, making them a promising target in breast cancer treatment.

Conclusion

Findings from this research indicate that persimmon (*Diospyros kaki* L.) fruit contains various bioactive compounds such as gallic acid, ferulic acid, ellagic acid, P-coumaric acid, chlorogenic acid, and protocatechuic acid, which have therapeutic potential for breast cancer treatment. Pharmacological network analysis identified ten key target genes (ESR1, BRCA1, BRCA2, PIK3CA, TP53, PTEN, AKT1, KRAS, MYC, ESR2) related to breast cancer, which are influenced by the active compounds in persimmon fruit. These substances work through intricate biological processes, such as apoptosis induction, cell growth inhibition, and molecular signaling pathway modulation. Therefore, this study reinforces persimmon fruit's potential as a natural source for developing effective, plant-based breast cancer therapy.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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