# SYSTEMATIC LITERATURE REVIEW OF BIOACTIVE COMPOUNDS IN PERSIMMON VINEGAR AGAINST BREAST CANCER

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## Abstract

Breast cancer is a malignant tumor or abnormal lump that develops in breast tissue, either from the ductal epithelium or lobules. In 2022, a number of new cases of breast cancer worldwide reached 2.3 million. Breast cancer therapy includes various treatment methods such as radiation and chemotherapy. However, these therapies are not selective and damage normal cells, causing adverse side effects for patients. Persimmon vinegar has various health benefits, but its potential in breast cancer treatment is still limited. This study aims to identify potential compounds in persimmon vinegar and their mechanisms against breast cancer. This study was conducted using the Systematic Literature Review (SLR) method using the Google Scholar, Pubmed, and ScienceDirect databases. The results showed that there were 13 articles that met the inclusion criteria. Based on the analysis, there were 24 compounds that had breast anticancer activity, namely β-cryptoxanthin, zeaxanthin, β-carotene, lycopene, gallic acid, catechin, epigallocatechin, p-coumaric acid, vanillic acid, caffeic acid, epicatechin, ferulic acid, gallocatechin, chlorogenic acid, epicatechin gallate, procyanidin A2, rutin, catechin hydrate, phloridzin, tartaric acid, succinic acid, citric acid, betaine and 2,3-butanediol. These results indicate that persimmon vinegar has potential as a chemopreventive treatment for breast cancer, providing a basis for further research on its development.

***Keywords:*** *Bioactive Compounds, Breast Cancer, Persimmon Vinegar*

## Introduction

Cancer is characterized by the abnormal growth of cells that have the potential to invade or spread to other parts of the body. To this day, cancer remains one of the major diseases affecting human health and is the leading cause of death worldwide (Suwarman et al., 2024). According to data from the Global Burden of Cancer (GLOBOCAN) published by the World Health Organization (WHO) in 2022, there were 19,976,499 new cancer cases worldwide, with a total of 9,743,832 deaths. In Indonesia, the number of new cases reached 408,661, with 242,988 recorded deaths. The most common type of cancer occurring in Indonesia is breast cancer (WHO, 2022)

Breast cancer is one of the most significant public health challenges worldwide with an increasing prevalence (Burguin et al., 2021). In 2022, it is estimated that there will be around 2.3 million new cases of breast cancer worldwide, accounting for nearly 23.8% of all cancer cases in women (Zhang et al, 2025). Based on data from the WHO Global Cancer Observatory in 2022, breast cancer ranks first in Indonesia with 66,271 new cases, accounting for 16.2% of all cancer cases in Indonesia (WHO, 2022).

Breast cancer is a malignant tumor or abnormal lump that develops in breast tissue, originating from either the ductal epithelium or the lobules (Rizka et al., 2022). Breast cancer may be invasive, meaning it spreads to surrounding tissues, or non-invasive, where it remains confined to its original site of growth. The development of breast cancer can be influenced by genetic factors, such as mutations in the Breast Cancer 1 (BRCA1) and Breast Cancer 2 (BRCA2) genes, as well as environmental factors, including exposure to carcinogenic substances that are activated by cytochrome P-450 enzymes into reactive compounds capable of inducing genetic mutations. These mutations typically involve key regulatory genes responsible for controlling cell proliferation, differentiation, and apoptosis (Liambo et al., 2022). One of the most crucial genes involved is p53. When this gene becomes damaged or mutated, it produces an abnormal p53 protein, which disrupts DNA repair mechanisms and interferes with proper regulation of the cell cycle (Cristiandari, 2018).

The main treatments for cancer generally include surgery, chemotherapy, radiotherapy, and targeted therapy. However, these treatments are not yet optimal due to side effects that are harmful to patients (Mutiah et al., 2017). Surgery and therapy in cancer patients often cause painful side effects associated with systemic complications such as inflammation, tissue damage, or nerve damage (Gan, 2017). This pain is not just physical discomfort, but one of the most common, severe, and feared symptoms of cancer patients. Chronic or severe pain can significantly affect quality of life, decrease appetite, disrupt sleep, worsen emotional conditions, and even hinder the healing process (Aniarti, 2024). As the main therapeutic strategy, chemotherapy utilizes various single or combination drugs to reduce cancer cell division (Banerjee et al., 2017). Conventional chemotherapy drugs such as cisplatin and paclitaxel remain the primary treatments for various types of cancer due to their ability to effectively inhibit tumor cell proliferation. However, the use of these two agents is often accompanied by significant cytotoxic side effects because of their low selectivity for cancer cells, which also damages normal cells. Cisplatin is known to cause nephrotoxicity, neurotoxicity, ototoxicity, and gastrointestinal disturbances, while paclitaxel is associated with peripheral neuropathy, neutropenia, and hypersensitivity reactions that can limit the success of therapy. Therefore, the development of anticancer therapies with higher selectivity is crucial to enhance therapeutic efficacy while minimizing damage to normal cells, one of which involves utilizing natural substances (Cecati et al., 2026; Mutiah et al., 2017)

The use of natural resources as a new therapeutic agent is a solution offered to reduce cytotoxic side effects and resistance, and increase selectivity against cancer cells. Persimmon (*Diospyros kaki*) is a type of subtropical fruit plant that is rare in Indonesia and has potential as an anticancer agent. In particular, the flavonoids found in persimmons can kill cancer cells without damaging normal cells, thereby contributing to the programmed destruction of cancer cells. Persimmon fruit is enriched with many bioactive compounds, including polyphenols and flavonoid (Khazbak et al., 2023). Persimmons are reported to contain B-cryptoxanthin, a natural carotenoid pigment with significant potential for use as a candidate in cancer prevention (Choudhary et al., 2023).

Persimmons are highly perishable and spoil quickly, so they need to be converted into products that can be stored for long periods of time and are easy to consume. One alternative is to ferment them into vinegar, which can be used as a prebiotic. Fermentation not only extends the shelf life of a product but also increases its bioactive compound content (Sahab, 2023). Fermentation plays an essential role in shaping the metabolite profile of persimmon vinegar through the metabolic activity of specific microorganisms involved during alcoholic and acetic

acid fermentation. In persimmon vinegar production, yeasts such as Saccharomyces cerevisiae, Saccharomyces uvarum, and Torulaspora delbrueckii, together with acetic acid bacteria including Acetobacter aceti and Gluconobacter oxydans, contribute to the biotransformation of phytochemicals into more bioactive and bioavailable compounds. These microorganisms produce various hydrolytic and oxidative enzymes, including β-glucosidase, tannase, esterase, and feruloyl esterase, which catalyze the degradation of complex polyphenols and bound phenolic compounds into simpler metabolites (Direito et al., 2021). The chemical content that has several pharmacological functions in persimmon vinegar works by regulating the molecular pathways involved in carcinogenesis, including increasing carcinogen inactivation, inhibiting proliferation, inducing cell cycle arrest and apoptosis, inhibiting cancer cell metastasis, and regulating the immune system with minimal side effects on normal cells. Based on this, further research is needed to examine the bioactive compounds in persimmon vinegar that have anticancer activity against breast cancer.

## Method

This type of research uses a Systematic Literature Review (SLR), which is a research method that aims to collect and evaluate various research results related to a specific topic. The keywords used in the literature search were “Persimmon vinegar” OR “fermented persimmon” OR “*Diospyros kaki* vinegar” AND “bioactive compound”. The database sources used were Google Scholar, Pubmed, and ScienceDirect. The eligibility criteria in this study included inclusion and exclusion criteria. The inclusion criteria in this study were 1) Articles in the form of scientific journals, 2) Article sources include PubMed, Google Scholar, ScienceDirect, 3) articles that are accessible in full text, 4) articles in English or Indonesian, 5) articles published between 2016 and 2026, 6) articles discussing bioactive compounds in persimmon vinegar. Meanwhile, the exclusion criteria in this study were 1) Articles that were not in the form of scientific journals, 2) Articles not sourced from PubMed, Google Scholar, ScienceDirect, 3) Articles that are not accessible in full text, 4) Articles written in languages other than English and Indonesian, 5) Articles published before 2016, 6) Articles that do not discuss bioactive compounds in persimmon vinegar. Literature selection was performed using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method. The PRISMA flow diagram in this study is shown in Figure 1.

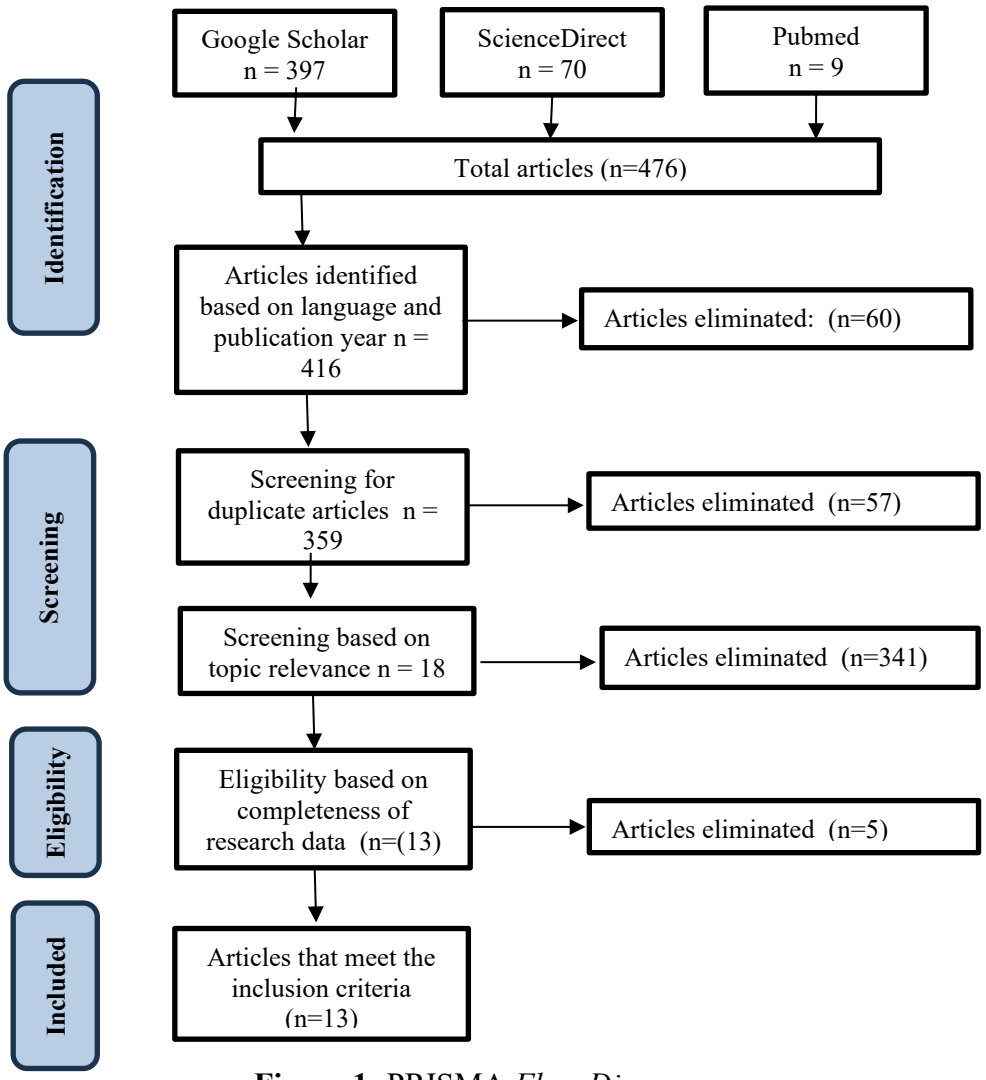


**Figure 1:** PRISMA *Flow Diagram*

## Result and Discussion

Based on the search results in Google Scholar 397 articles were found, 70 articles in ScienceDirect, and 9 articles in PubMed. The total search results from the three databases were 476 articles. From the analysis using the PRISMA method, 13 articles were found to meet the criteria for eligibility and data completeness. The details are 8 articles from the Google Scholar database, 1 article from Pubmed and 4 articles from ScienceDirect. The articles that met the criteria were then reviewed and analyzed in depth, leading to the conclusion that there are active compounds in peach vinegar that have anticancer activity against breast cancer. The following table shows the results of the analysis of the compounds found in persimmon vinegar.

**Table 1:** Bioactive compounds in persimmon vinegar that exhibit anticancer activity against breast cancer

| Compound Name | Class of Compound | PubChem CID | References |
|---|---|---|---|
| β-cryptoxanthin | | 21421799 | (Bordiga *et al.,* 2023) |
| Zeaxanthin | | 5280899 | (Bordiga *et al*., 2023) |

| | | | |
|---|---|---|---|
| β-carotene | Carotenoids | 5280489 | (Bordiga *et al*., 2023) |
| Lycopene | | 446925 | (Bordiga *et al*., 2023) |
| Gallic acid | Phenolic | 370 | (Hosseininejad *et al.,* 2022), (Hosseini *et al*., 2025), (Xia *et al*., 2020), (Chen *et al*., 2016), (Özdemir *et al*., 2022), (Zou, et al., 2017), (Yildrim, et al., 2026) |
| Ferulic acid | | 445858 | (Wu *et al*., 2023), (Hosseini *et al*., 2025), (Xia *et al*., 2020) |
| p-Coumaric acid | | 637542 | (Hosseininejad *et al*., 2022), (Wu *et al*., 2023), (Hosseini *et al*., 2025), (Xia *et al*., 2020), (Chen *et al*., 2016) |
| Caffeic acid | | 689043 | (Hosseini *et al*., 2025), (Xia *et al*., 2020), (Chen *et al*., 2016) |
| Vanillic acid | | 8468 | (Chen *et al*., 2016), (Zou, et al., 2017) |
| Chlorogenic acid | | 1794427 | (Hosseini *et al*., 2025), (Xia *et al*., 2020), (Chen *et al*., 2016), (Özdemir *et al*., 2022), (Kuang, et al., 2026) |
| Phlorizin | | 6072 | (Hosseini *et al*., 2025), (Xia *et al*., 2020), (Chen *et al*., 2016) |
| Catechin | | 9064 | (Hosseininejad *et al*., 2022), (Wu *et al*., 2023), (Xia *et al*., 2020), (Chen *et al*., 2016), (Özdemir *et al*., 2022) |
| Tartaric acid | Organic acid | 444305 | (Wan, et al., 2026), (Kuang, et al., 2026) |
| Succinic acid | | 1110 | (Wan, et al., 2026), (Kuang, et al., 2026) |
| Citric acid | | 311 | (Wan, et al., 2026), (Tak, et al., 2025), (Kuang, et al., 2026) |
| Betaine | Amino acid derivative | 247 | Ge, *et al.,* 2025 |
| 2,3-Butanediol | Glycol | 262 | Ge, *et al.,* 2025 |
| Epigallocatechin | Flavonoids | 72277 | (Hosseininejad *et al*., 2022), (Hosseini *et al*., 2025), (Xia *et al*., 2020), (Chen *et al*., 2016), (Zou, et al., 2017) |
| Epicatechin | | 72276 | (Wu *et al*., 2023), (Xia *et al*., 2020), (Chen *et al*., 2016), (Özdemir *et al*., 2022), (Zou, et al., 2017), (Yildrim, et al., 2026) |
| Epicatechin gallate | | 107905 | (Hosseini *et al*., 2025), (Xia *et al*., 2020) |
| Gallocatechin | | 65084 | (Xia *et al*., 2020), (Zou, et al., 2017) |
| Catechin hydrate | | 439533 | (Hosseini *et al*., 2025), (Xia *et al*., 2020) |
| Rutin | | 5280805 | (Hosseini *et al*., 2025), (Xia *et al*., 2020) |
| Procyanidin A2 | Proanthocyanidin | 124025 | (Hosseini *et al*., 2025) |

Based on Table 1 compounds were found to have anticancer activity. These compounds have anticancer activity against breast cancer through several mechanisms. Carotenoid

compounds, namely β-carotene and lycopene, have been tested on MCF-7, MDA-MB-231, and MDA-MB-235 breast cancer cell lines, where both carotenoids were shown to inhibit cell proliferation, arrest the cell cycle at various phases (G0/G1 and G2/M), and enhance apoptosis (Gloria et al., 2014). Additionally, other carotenoids, namely zeaxanthin, have the potential to reduce cancer risk, and β-cryptoxanthin can enhance immune function and reduce inflammation (Wei et al., 2023).

Gallic acid (GA) has been shown to possess significant anticancer activity against triple-negative breast cancer (TNBC) cells. GA is capable of reducing the viability of MDA-MB-231 and HS578T cells in a dose-dependent manner, with relatively low toxicity toward normal breast fibroblast cells (MCF-10F). Cell cycle analysis showed that GA induced an increase in the G0/G1 and sub-G1 phase ratios in MDA-MB-231 cells, indicating cell cycle arrest in the G0/G1 phase. Additionally, GA also induced apoptosis through the activation of caspase-9 and caspase-3, which are key components of the mitochondria-dependent intrinsic apoptosis pathway (Lee, et al., 2017).

Ferulic acid, and chlorogenic acid have anti-breast cancer properties through the induction of apoptosis, inhibition of cell growth, and modulation of molecular signaling pathways (Mutiah et al., 2025). In addition, ferulic acid can also reduce Reactive Oxygen Species (ROS). Excessive amounts of ROS can cause cell damage (oxidative stress) and inhibit lipid peroxidation (Fong et al., 2016).

Catechin compounds, including epigallocatechin, epicatechin, epicatechin gallate, and catechin hydrate, have been tested on MCF-7, T47D, MDA-MB-231, and HS578T breast cancer cell lines. High concentrations of these compounds can inhibit the proliferation of multiple cancer cell lines. Epigallocatechin specifically suppresses VEGF expression, thereby inhibiting endothelial cell formation and angiogenesis, while catechin hydrate inhibits breast cancer cell proliferation and induces apoptosis (Xiang et al., 2016).

p-Coumaric acid has been evaluated on MCF-7 and breast cancer stem cells (BSCS), demonstrating anticancer activity through inhibition of proliferation, G1/S phase cell cycle arrest via downregulation of Cyclin D1, and induction of apoptosis mediated by the JNK and p38 MAPK pathways, with increased caspase-3/7 activity and a decreased Bcl-2/Bax ratio (Burhanoğlu et al., 2025). Rutin has antitumor effects related to interactions with signaling processes such as Wnt. Rutin can inhibit cell proliferation, regulate apoptosis, and cell cycle in cancer cell lines (Satari et al., 2023).

Phloridzin has been studied across various tumor models including breast, glioblastoma, prostate, and colorectal cancer. As a GLUT inhibitor, phloridzin disrupts glucose metabolism, limits cancer cell proliferation and migration, and inhibits epithelial-mesenchymal transition (EMT) by downregulating N-cadherin and upregulating E-cadherin. It also targets the PI3K/AKT/mTOR pathway, suppressing tumor cell survival. In breast cancer specifically, phloridzin derivatives have been tested on MDA-MB-231 cells, demonstrating cytotoxic effects and apoptosis induction (Dhyani et al., 2025).

Citric acid has been studied for its anti-breast cancer activity in MCF-7 and MDA-MB-231 cells. Citric acid exerts its anti-breast cancer effects through multiple pathways simultaneously. This compound inhibits the enzyme phosphofructokinase (PFK), thereby cutting off the cancer cells' primary energy supply from the glycolysis pathway. Additionally, citric acid suppresses TCA cycle activity and inhibits IGF-1R phosphorylation, which leads to PTEN activation and increased p-eIF2α expression, thereby inhibiting cancer cell survival and proliferation. At the cellular level, this compound also induces permanent cancer cell senescence through excessive lipid accumulation that disrupts tumor metabolism via the ATM, MAPK, and mTOR pathways (Ren et al., 2017; Zhao et al., 2021).

Succinic acid and tartaric acid disrupt the pH homeostasis of MDA-MB-231 breast cancer cells. As dicarboxylic acids, these compounds donate more protons to the extracellular environment than monocarboxylic acids, thereby creating extracellular acidification that exceeds

the adaptive capacity of cancer cells. This condition reduces cell viability, alters morphology, and decreases cell density (Lee, 2025).

Betaine induces apoptosis in MCF-7 cells by increasing the expression of the pro-apoptotic protein Bax, which triggers the release of cytochrome c from the mitochondria and subsequently activates caspase-3 as the primary executor of programmed cell death. Concurrently, betaine inhibits the PI3K/AKT and NF-κB signaling pathways that support cancer cell survival. As an active methyl group donor, betaine also stabilizes normal DNA methylation patterns in tumor suppressor genes. In an in vivo model (DMBA-induced cancer in mice), betaine was shown to activate caspase-3 in mammary tissue, increase the activity of the antioxidant enzymes SOD and CAT, and reduce malondialdehyde levels as a marker of oxidative stress (Fahmy et al., 2023; Hasan et al., 2025).

2,3-butanediol exhibits anticancer activity by inducing an anti-Warburg-type metabolic rearrangement that reverses the dependence of 4T1 cancer cells on aerobic glycolysis, accompanied by the induction of mild oxidative stress. These two changes synergistically reduce the proportion of cancer stem cells and suppress the metastatic potential and recurrence of breast cancer cells (Uljaki et al., 2023; Schwarcz et al., 2024).

Procyanidin A2 has anticancer activity through its ability to modulate the PIK3K, AKT, and MAPK signaling pathways (Yang et al., 2025). Vanillic acid has anticancer activity in breast cancer through the inhibition of proliferation and increased apoptosis of cells (Hao et al., 2025). Caffeic acid induces apoptosis in breast cancer cells via the mitochondrial pathway by targeting apoptosis-regulating proteins and tumor suppressor transcription factors. An in vitro study using MCF-7 breast cancer cells reported that caffeic acid and gallic acid induce toxic effects and morphological changes through the induction of apoptosis. These two compounds affect the expression of the P53, Mcl-1, and P21 genes, where changes in gene expression occur concurrently with the activation of the intrinsic apoptosis signaling pathway (Rezaei-Seresht et al., 2019).

Based on the above, 24 compounds with breast anticancer activity were identified. The anticancer potential of persimmon vinegar is not attributed to a single bioactive compound, but rather to the collective contribution of carotenoids, phenolics, flavonoids, amino acid derivative, organic acid, glycol and proanthocyanidin that act synergistically through multiple molecular targets involved in cancer progression. This multi-targeted mechanism is considered more effective than single-agent therapies because cancer development is a complex and multifactorial process involving oxidative stress, chronic inflammation, uncontrolled proliferation, angiogenesis, metastasis, and resistance to apoptosis. his collective mechanism produces a broader therapeutic effect than single-agent therapies, which often target only one pathway and may lead to drug resistance. Therefore, the phytochemical complexity of persimmon vinegar provides a promising multi-targeted strategy for suppressing cancer cell development and supports its potential application as a functional anticancer agent (Catalano, 2016; Talib et al., 2024).

## Conclusion

Based on the results of systematic research, it can be concluded that there are 24 bioactive compounds in persimmon vinegar that have breast cancer-fighting properties. These compounds come from various groups of bioactive metabolites, including carotenoids, phenolics, flavonoids, amino acid derivative, organic acid, glycol and proanthocyanidin, which work through various biological mechanisms. The main mechanisms involved include inhibition of cancer cell proliferation, induction of apoptosis, inhibition of angiogenesis, regulation of the cell cycle, suppression of oxidative stress, and modulation of molecular signaling pathways. Considering that breast cancer remains one of the leading causes of cancer-related mortality worldwide and the most common cancer in Indonesia, the exploration of accessible natural products such as persimmon vinegar is becoming increasingly important. Therefore, persimmon vinegar has

promising potential to be developed as a natural chemopreventive agent or complementary supportive therapy for breast cancer management.

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**References**

Aniarti, R. 2024. Pengetahuan dan Efikasi Diri terhadap Pengendalian Nyeri pada Pasien Kanker Serviks. *Jurnal Keperawatan Muhammadiyah*, 9(1), pp. 142-148.

Banerjee, A., Pathak, S., Subramanium, V. D., Dharanivasan, G., Murugesan, R., and Verma, R. S. 2017. Strategies for targeted drug delivery in treatment of colon cancer: current trends and future perspectives. *Drug discovery today*, 22(8), pp. 1224-1232. https://doi.org/10.1016/j.drudis.2017.05.006

Bordiga, M., Guzzon, R., Manfredi, M., Barberis, E., Grasso, S., Benitez-Gonzalez, A.M., Martínez, A.J.M., Travaglia, F., Arlorio, M. and Coisson, J.D., 2023. Characterisation of Diospyros kaki (persimmon) vinegars produced with different microorganisms. *Food Bioscience*, 55, p.102987. https://doi.org/10.1016/j.fbio.2023.102987

Burguin, A.; Diorio, C. and Durocher, F., 2021, Breast cancer treatments: updates and new challenges. *Journal of personalized medicine*., 11: 808 https://doi.org/10.3390/jpm11080808

Burhanoğlu, T., Halbutoğulları, Z.S., Turhal, G. and Demiroglu-Zergeroglu, A., 2025. Evaluation of the anticancer effects of hydroxycinnamic acid isomers on breast cancer stem cells. *Medical Oncology*, 42(3), p.73. https://doi.org/10.1007/s12032-025-02618-3

Catalano, E. (2016). *Role of phytochemicals in the chemoprevention of tumors* (Versi 1). arXiv. https://doi.org/10.48550/ARXIV.1605.04519

Cecati, M., Pozzi, V., Pompei, V., Schiavoni, V., Fumarola, S., Romagnoli, A., Tossetta, G., Montana, A., Polizzi, A., Sartini, D., & Campagna, R. (2026). Cisplatin as a Xenobiotic Agent: Molecular Mechanisms of Actions and Clinical Applications in Oncology. *Journal of Xenobiotics*, *16*(1), 9. https://doi.org/10.3390/jox16010009

Chen, H., Chen, T., Giudici, P., & Chen, F. (2016). Vinegar functions on health: Constituents, sources, and formation mechanisms. *Comprehensive Reviews in Food Science and Food Safety*, 15(6), 1124-1138. doi: 10.1111/1541-4337.12228 https://doi.org/10.1111/1541-4337.12228

Choudhary, R., Singh, A., Upadhyay, A., Singh, R., Thangalakshmi, S., Dar, A. H., ... and Shukla, S. 2023. Exotic god fruit, persimmon (Diospyros kaki): Pharmacological importance and human health aspects. *eFood*, 4(1), e52. https://doi.org/10.1002/efd2.52

Cristiandari, E. M., 2018, Uji efek ekstrak dan fraksinasi daun salung (Psychotria viridiflora Reinw. Ex. Blume) pada sel kanker payudara t47d. *JPP (Jurnal Kesehatan Poltekkes Palembang).,* 13: 9-20.

Dhyani, P., Sati, P., Chand Attri, D., Sharma, E., Soni, R., Sharifi-Rad, J. and Calina, D., 2025. Phloridzin as a Nutraceutical for Cancer Prevention and Therapy: A Comprehensive Review of Its Mechanisms, Bioavailability Challenges and Future Applications. *Food science & nutrition*, 13(8), p.e70744. https://doi.org/10.1002/fsn3.70744

Direito, R., Rocha, J., Sepodes, B., and Eduardo-Figueira, M. 2021. From Diospyros kaki L.(persimmon) phytochemical profile and health impact to new product perspectives and waste valorization. *Nutrients*, 13(9), pp. 3283. https://doi.org/10.3390/nu13093283

Fahmy, S.A., Ramzy, A., El Samaloty, N.M., Sedky, N.K. and Azzazy, H.M.E.S., 2023. PEGylated chitosan nanoparticles loaded with betaine and nedaplatin hamper breast cancer: in vitro and in vivo studies. *ACS omega*, *8*(44), pp.41485-41494. doi: 10.1021/acsomega.3c05359

Fong, Y., Tang, C.C., Hu, H.T., Fang, H.Y., Chen, B.H., Wu, C.Y., Yuan, S.S., Wang, H.M.D., Chen, Y.C., Teng, Y.N. and Chiu, C.C., 2016. Inhibitory effect of trans-ferulic acid on proliferation and migration of human lung cancer cells accompanied with increased endogenous reactive oxygen species and β-catenin instability. *Chinese medicine*, 11(1), p.45. DOI 10.1186/s13020-016-0116-7

Gan, T. J. 2017. Poorly controlled postoperative pain: prevalence, consequences, and prevention. Journal of pain research, pp. 2287-2298. https://doi.org/10.2147/JPR.S144066

Ge, Y., Wu, Y., Aihaiti, A., Wang, L., Wang, Y., Xing, J., Zhu, M. and Hong, J., 2025. The metabolic pathways of yeast and acetic acid bacteria during fruit vinegar fermentation and their influence on flavor development. *Microorganisms*, *13*(3), p.477. https://doi.org/10.3390/microorganisms13030477

Gloria, N. F., Soares, N., Brand, C., Oliveira, F. L., Borojevic, R., & Teodoro, A. J. (2014). Lycopene and beta-carotene induce cell-cycle arrest and apoptosis in human breast cancer cell lines. *Anticancer research*, *34*(3), 1377-1386.

Hao, X., Gao, Z. and Hu, M., 2025. Anti-tumor role and molecular mechanism of vanillic acid. *Discover Oncology*, 16(1), p.20.

Hassan, M.S., Khalid, T., Akhlaq, M., Hameed, A., Sharif, F., Rana, S. and Uroos, M., 2025. Therapeutic potential of betaine and its derivatives in cancer treatment: a comprehensive review. *RSC advances*, *15*(26), pp.20605-20622. doi: 10.1039/D5RA00755K

Hosseini, E., Tsegay, Z.T., Smaoui, S. and Varzakas, T., 2025. Lactic Acid Bacteria in Vinegar Fermentation: Diversity, Functionality and Health Benefits. Foods, 14(4), p.698. https://doi.org/10.3390/foods14040698

Hosseininejad, S., González, C.M., Hernando, I. and Moraga, G., 2022. Valorization of persimmon fruit through the development of new food products. *Frontiers in Food Science and Technology*, 2, p.914952. doi: 10.3389/frfst.2022.914952

Khazbak, A. E. R. A., Salem, S. M., Rady, H. H., and Bashandy, M. A. (2023). Regulation of breast cancer stem cells associated-miRNAs by ginger and persimmon extracts. Egyptian Academic *Journal of Biological Sciences. C, Physiology and Molecular Biology*, 15(1), pp. 109-119. 10.21608/EAJBSC.2023.282963

Kuang, H., Ye, Q., Tong, J., Fu, H., Shi, Z., Zhu, B. and Yang, G., 2026. Lactobacillus plantarum-fermented persimmon juice alleviates alcohol-induced hepatic ferroptosis by activating the Keap1/Nrf2 antioxidant axis. *Frontiers in Microbiology*, *17*, p.1679233. doi: 10.3389/fmicb.2026.1679233

Lee, HL, Lin, CS, Kao, SH dan Chou, MC, 2017. Asam galat menginduksi penghentian fase G1 dan apoptosis sel kanker payudara triple-negatif MDA-MB-231 melalui sumbu p38 mitogen-activated protein kinase/p21/p27. *Obat antikanker* , *28* (10), hlm. 1150-1156. Doi: 10.1097/CAD.0000000000000565

Lee, S. (2025). Influence of pH on the cytotoxic activity of organic acids against breast cancer cells. *Bioorganic & Medicinal Chemistry*, 118330.

Liambo, I. S.; Frisitiohady, A.; Malaka, M. H. dan Kendari, M., 2022, Review: Patofisiologi, epidemiologi, dan lini sel kanker payudara. Pharmauho: *Jurnal Farmasi, Sains, dan Kesehatan.,* 8:17-22

Mutiah, R., Indradmojo, C., Dwi, H. H., Griana, T. P., Listyana, A., & Ramdhani, R. (2017). Induction of apoptosis and phase-cell cycle inhibition of G0-G1, S, G2-M of T47D breast cancer cells on treatment with ethyl acetate fraction of jackfruit parasite leaves (Macrosolen cochinensis). *Journal of Applied Pharmaceutical Science*, 7(10), 138-143. DOI: 10.7324/JAPS.2017.71020

Mutiah, R., Rachmawati, E., Taufik, I., Sari, R.A., Rahmadani, N. and Milliana, A., 2025. Potential of Persimmon (Diospyros kaki L.) Compounds for the Treatment of Breast Cancer: A Network Pharmacology Study. *Tropical Journal of Natural Product Research*, 9(8). DOI 10.26538/tjnpr/v9i8.30

Özdemir, N., Budak, N.H., Filiz, B.E. and Özer, E., 2022. Occurrences and changes in aroma-associated volatile compound profiles and prominent bioactive compounds at different stages of persimmon vinegar production process. *Journal of Food Processing and Preservation*, 46(11), p.e17048. https://doi.org/10.1111/jfpp.17048

Ren, J. G., Seth, P., Ye, H., Guo, K., Hanai, J. I., Husain, Z. and Sukhatme, V. P., 2017. Citrate suppresses tumor growth in multiple models through inhibition of glycolysis, the tricarboxylic acid cycle and the IGF-1R pathway. *Scientific reports*, *7*(1), 4537. doi: 10.1038/s41598-017-04626-4.

Rezaei-Seresht, H., Cheshomi, H., Falanji, F., Movahedi-Motlagh, F., Hashemian, M. dan Mireskandari, E., 2019. Aktivitas sitotoksik asam kafeik dan asam galat terhadap sel kanker payudara manusia MCF-7: Studi in silico dan in vitro. *Jurnal fitomedisin Avicenna* , *9* (6), p.574. doi: 10.22038/ajp.2019.13475

Rizka, A.; Akbar, M. K. and Putri, N. A., 2022, Carcinoma Mammae Sinistra T4bN2M1 Metastasis Pleura. *AVERROUS: Jurnal Kedokteran Dan Kesehatan Malikussaleh.*, 8:23-31.

Sahab, N. R. M. 2023. Jus Buah Terfermentasi sebagai Minuman Probiotik. *Jurnal Riset Teknologi Pangan Dan Hasil Pertanian (RETIPA)*, pp. 18-28. https://doi.org/10.54367/retipa.vi.3019

Satari, A., Ghasemi, S., Habtemariam, S., Asgharian, S. and Lorigooini, Z., 2023. Rutin: A flavonoid as an effective sensitizer for anticancer therapy; insights into multifaceted mechanisms and applicability for combination therapy. *Evidence-Based Complementary* https://doi.org/10.1155/2021/9913179

Schwarcz, S., Nyerges, P., Bíró, T. I., Janka, E., Bai, P. dan Mikó, E., 2024. Cytostatic bacterial metabolites interfere with 5-fluorouracil, doxorubicin and paclitaxel efficiency in 4T1 breast cancer cells. *Molecules*, *29*(13), 3073. https://doi.org/10.3390/molecules29133073

Suwarman, A.; Astuti, I.; Pratiwi, W. R., and Yahya, S. A. S. Cytotoxicity of hantap (Sterculia oblongata Mast) leaves extracts against breast cancer cell line (T47D): effect on apoptosis and caspase-3 mRNA expression. *Indonesian Journal of Pharmacology and Therapy.*5 https://doi.org/10.22146/ijpther.10147

Tak, H.J., Yang, S., Kim, S.Y., Lee, N.R. and Lee, C.H., 2025. Qualitative and Quantitative Metabolite Comparison of Grain, Persimmon, and Apple Vinegars with Antioxidant Activities. *Antioxidants*, *14*(8), p.1029. doi: 10.3390/antiox14081029

Talib, W. H., Abed, I., Raad, D., Alomari, R. K., Jamal, A., Jabbar, R., Alhasan, E. O. A., Alshaeri, H. K., Alasmari, M. M., & Law, D. (2024). Targeting Cancer Hallmarks Using Selected Food Bioactive Compounds: Potentials for Preventive and Therapeutic Strategies. *Foods*, *13*(17), 2687. https://doi.org/10.3390/foods13172687

Ujlaki, G., Kovács, T., Vida, A., Kókai, E., Rauch, B., Schwarcz, S., ... dan Bai, P., 2023. Identification of bacterial metabolites modulating breast cancer cell proliferation and epithelial-mesenchymal transition. *Molecules*, *28*(15), 5898. doi: 10.3390/molecules28155898

Wan, N., Wang, M., Wang,L. and Wang, D.,2026. Improvement of the quality and flavor profiles of persimmon vinegar by bioaugmented inoculation with Lactobacillus acidophilus, Lactiplantibacillus plantarum and Wickerhamomyces anomalus. *Food Chemistry,35*, 2590-1575. https://doi.org/10.1016/j.fochx.2026.103725

Wei, J., Li, Y., Ye, Z., Li, Y. and Zhou, Z., 2023. Citrus carotenoid extracts exert anticancer effects through anti proliferation, oxidative stress, and mitochondrial-dependent apoptosis in MCF-7 cells. *Foods*, 12(18), p.3469. https://doi.org/10.3390/foods12183469

Wu, Q., Kong, Y., Liang, Y., Niu, M., Feng, N., Zhang, C., Qi, Y., Guo, Z., Xiao, J., Zhou, M. and He, Y., 2023. Protective mechanism of fruit vinegar polyphenols against AGEs-induced Caco-2 cell damage. *Food Chemistry*: X, 19, p.100736. https://doi.org/10.1016/j.fochx.2023.100736

Xia Ting, X.T., Zhang Bo, Z.B., Duan WenHui, D.W., Zhang Jin, Z.J. and Wang Min, W.M., 2020. Nutrients and bioactive components from vinegar: a fermented and functional food. *Journal of Functional Foods* pp. 1756 4646 https://doi.org/10.1016/j.jff.2019.103681

Xiang, L.P., Wang, A., Ye, J.H., Zheng, X.Q., Polito, C.A., Lu, J.L., Li, Q.S. and Liang, Y.R., 2016. Suppressive effects of tea catechins on breast cancer. *Nutrients*, 8(8), p.458. https://doi.org/10.3390/nu8080458

Yang, X., Liu, S., Liu, Y., Wang, Y., Cui, D., Lan, T., Zhu, D., Su, Z., Hao, E., Qin, L. and Guo, H., 2025. Total flavonoids of litchi seed inhibit breast cancer metastasis by regulating the PI3K/AKT/mTOR and MAPKs signaling pathways. *Pharmaceutical* https://doi.org/10.1080/13880209.2025.2488135

Yıldırım, G.B., Ünsal Gürer, Ç., Kurt Celep, İ., Yener, I., Akdeniz, M., Yigitkan, S., Yilmaz, M.A., Tireki, S., Ertas, A. and Barla Demirkoz, A., 2026. Quince and persimmon vinegars as functional foods: phenolic characterization and bioactivity assessment. *European Food Research and Technology*, *252*(5), p.194. https://doi.org/10.1007/s00217-026-05101-z

Zhang, Y.; Ji, Y.; Liu, S.; Li, J.; Wu, J.; Jin, Q.; Liu, X.; Duan, H.; Feng, Z.; Liu, Y. and Zhang, Y., 2025, Global burden of female breast cancer: new estimates in 2022, temporal trend and future projections up to 2050 based on the latest release from GLOBOCAN. *Journal of the National Cancer Center:* 1-30. doi:10.1016/j.jncc.2025.02.002

Zhao, Y., Liu, X., Si, F., Huang, L., Gao, A., Lin, W. and Peng, G., 2022. Citrate promotes excessive lipid biosynthesis and senescence in tumor cells for tumor therapy. *Advanced Science*, *9*(1), 2101553. doi: 10.1002/advs.202101553

Zou, B., Wu, J., Yu, Y., Xiao, G. and Xu, Y., 2017. Evolution of the antioxidant capacity and phenolic contents of persimmon during fermentation. *Food Science and Biotechnology*, *26*(3), pp.563-571. doi: 10.1007/s10068-017-0099-x