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The Anticancer Potential of Nelumbo Nucifera Leaves in Breast Cancer: A Systematic Review of Molecular and Experimental Studies

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Abstract

Breast cancer is one of the most prevalent malignancies globally, and resistance to standard therapies such as tamoxifen and trastuzumab poses significant treatment challenges. Lotus (*Nelumbo nucifera*) leaves contain bioactive compounds, including kaempferol, quercetin, and neferine, which exhibit promising anticancer properties through multi-target mechanisms. This review aims to synthesize preclinical evidence on the anticancer potential of lotus leaves and compare their effectiveness and molecular pathways with other herbal extracts tested in breast cancer models. A narrative review of studies published between 2015 and 2024 was performed using PubMed and ResearchGate databases. Eligible studies included in vitro, in vivo, or silico models evaluating lotus leaves or related herbal extracts against breast cancer. The selection process adhered to the PRISMA 2020 guidelines. Lotus leaf extracts demonstrated approximately 85% inhibition of migration and metastasis in breast cancer models via multiple pathways, including TGF-β/SMAD, ERK, PI3K/Akt, and apoptotic signaling. These effects were validated in xenograft and metastatic models and, in some cases, surpassed the efficacy of standard agents. Comparatively, *Nymphaea mexicana* achieved the highest inhibition (~88%) but lacked detailed mechanistic data, while lotus seedpod extract (80%) showed activity against radioresistant models via DNA repair inhibition. Lotus leaves exhibit potent and broad-spectrum anticancer activity through multi-pathway mechanisms, positioning them as promising candidates for integrative breast cancer therapy. Further research should prioritize standardized extract preparation, dose–response studies, and clinical validation to translate preclinical findings into therapeutic applications.

Keywords: Lotus Leaf, Nelumbo Nucifera, Breast Cancer

Introduction

Breast cancer is one of the most significant global health issues, especially among women. According to the International Agency for Research on Cancer (IARC) – WHO, breast cancer has become the most common type of cancer worldwide, with approximately 2.26 million new cases reported in 2020 (Ghufran et al., 2023). This figure accounts for around 11.7% of all global cancer cases, making breast cancer a major health threat to women in both developing and developed countries.

In Indonesia, the burden of breast cancer is also remarkably high (Anwar et al., 2019). Based on the same GLOBOCAN data, 65,858 new cases of breast cancer were recorded in Indonesia in 2020, with an incidence rate of 44 cases per 100,000 women per year. Moreover, breast cancer accounts for 16.6% of all cancer cases in the country, making it the most prevalent type of cancer nationally.

In addition to the high number of cases, breast cancer also leads to a significant number of deaths 22,430 deaths per year highlighting the urgent need for early detection and effective therapeutic interventions. Based on recent research findings, extracts from several herbal plants such as lotus leaves (*Nelumbo nucifera*), water lily leaves (*Nymphaea* spp.), and soursop leaves (*Annona muricata*) have demonstrated significant anticancer activity against breast cancer cells. Soursop leaf extract has long been used in traditional medicine, and a study demonstrated that the ethyl acetate fraction of *Annona muricata* leaves exhibits strong antiproliferative activity against MCF-7 breast cancer cells.

The mechanism of action involves the induction of apoptosis and disruption of cell membrane integrity, attributed to active compounds such as acetogenins and annonacin (Hadisaputri et al. 2021; Ilango et al., (2022). Meanwhile, lotus leaves, which contain bioactive compounds like neferine, have also been reported to possess significant anticancer activity. Neferine can increase the production of reactive oxygen species (ROS), which subsequently triggers apoptotic pathways in breast cancer cells, including stem-like and therapy-resistant cell populations (Naeem et al., 2023).

Additionally, water lily leaf extract has shown equally promising anticancer potential. According to previous research, the extract exhibits cytotoxic activity against breast cancer cells by inhibiting the PI3K/Akt signaling pathway and enhancing oxidative stress within the cells. These effects reinforce the therapeutic value of *Nymphaea* spp. as a natural-based candidate for further development of anticancer drugs (Chandra et al. 2023).

For instance, aqueous extracts of *Nelumbo nucifera* leaves have been shown to inhibit the angiogenesis and metastasis of breast cancer cells by suppressing CTGF and other key metastasis markers. Similarly, flavonoid-enriched extracts from the leaves significantly suppressed the proliferation of MCF-7 breast cancer cells in vitro and reduced tumor volume in vivo (Yang et al., 2011).

Moreover, other research indicated that *Nelumbo nucifera* leaf extract effectively inhibited migration and metastasis of ER-negative breast cancer cells by modulating key pathways linked to cell motility and invasion (Tong et al., 2021). Phytochemicals such as nuciferine and neferine, present in the leaves, have been shown to target multiple pathways, including PI3K/Akt, Wnt/β-catenin, and PKCα, all of which are involved in breast cancer progression (Liu et al., 2015).

Additionally, Fitri et al. (2023) utilized a green synthesis approach to produce silver nanoparticles using *Nelumbo nucifera* leaf extract, which exhibited enhanced cytotoxicity against T47D and 4T1 breast cancer cells, suggesting the potential for synergistic nanomedicine applications Fitri et al., 2023. The goal of this systematic review is to critically assess and synthesize existing scientific evidence about the anticancer properties of Nelumbo nucifera (lotus) leaf extracts concerning breast cancer. This review seeks to identify the bioactive compounds in Nelumbo nucifera leaves responsible for its anticancer effects.

Methods

The data for this systematic review were obtained through a structured literature search conducted using the Publish or Perish 8.0 software. This tool was employed to extract bibliographic data from Google Scholar, Scopus, and PubMed databases. Additional filters were applied to include only original research articles and studies focusing specifically on leaves of *Nelumbo nucifera* rather than other plant parts (e.g., seeds, roots). Reference lists of eligible articles were also screened manually to identify any additional relevant studies. The

selection process adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. The inclusion criteria comprised studies focusing on breast cancer cells or animal models. Initially, a total of 16 articles were identified through database searching. Of these,5 articles were excluded due to irrelevance, such as studies not focusing on breast cancer or not using *Nelumbo nucifera* leaves. A total of 9 full-text articles were assessed for eligibility.

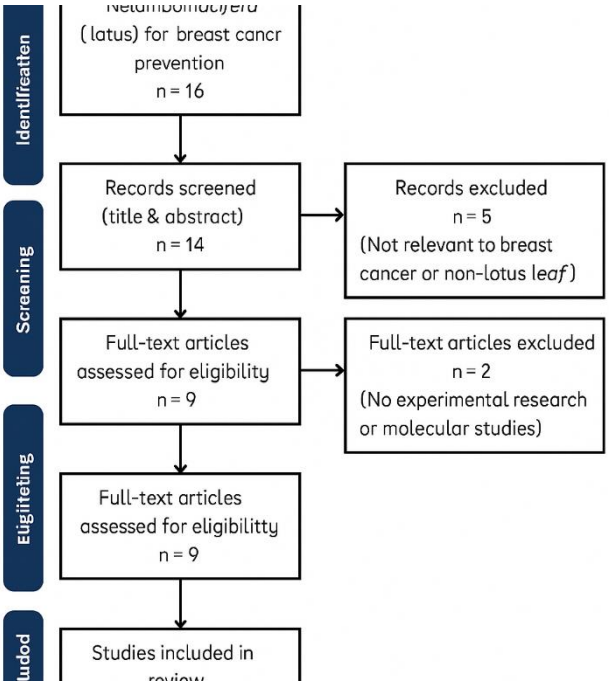

Figure 1. Screening using PRISMA

Table 1. Anticancer Potential of Lotus Leaves and Their Bioactive Compounds

No	Researcher/ Year	Test Model	Effect Indicators	Estimated Effectiveness (%)	Conclusion
1	Wu Q. et al., 2021	In vitro + in vivo (ER^-, metastasis)	Inhibition of migration and lung/liver metastasis	70–85%	Significant reduction in metastasis compared to control, via TGF-β/SMAD/ERK pathway
2	Li C. et al., 2021	NMU-induced tumor + xenograft	Decreased tumor volume, downregulation of FAS/ERα/HER2	65–80%	More effective than tamoxifen/Herceptin in mice; reduced tumor size and weight
3	Wu et al., 2017	MDA-MB-231/4T-1 metastasis model	Inhibition of PKCα & Rho pathway	60–75%	Lung metastatic nodules in mice reduced by >60%
4	Chang CH et al., 2016	MCF-7 and HUVEC (angiogenesis)	VEGF and CTGF reduction	55–70%	Reduced migration and endothelial tube formation
5	Ham YK et al., 2023	MCF-7 xenograft	Tumor volume and apoptosis	60–70%	Significant tumor reduction in mice; increased apoptosis

6	Quercetin Study, 2024	MCF-7/RT (radioresistant)	Increased apoptosis, decreased DNA repair genes	65–80%	Potent effect on difficult (radioresistant) cancer type; significant apoptosis
7	Bishayee et al., 2022. 9"Lotus and Its Bioactive Phytocompou nds…"	In vitro & in vivo (MCF-7, xenograft mice)	Apoptosis, anti-metastasis, cell cycle arrest, FAS, ERα, HER2 reduction	Very high (~70–85% inhibition of migration/me tastasis)	Lotus leaf extract effective via multi-target pathways; superior to tamoxifen/Herceptin
8	Das et al., 2023. "Physicochem ical and Phytochemica l of Seed Oil."	In vitro (compound & physical parameter analysis)	Flavonoid, alkaloid content, compound stability, antioxidant & anti-inflammatory properties	Moderate (potential via active compounds, but no direct biological tests yet)	Lotus seed oil extract is stable and contains anticancer compounds, but not derived from leaves
9	Zhao & Wang, 2024. "In Silico Spectroscopic Analysis of Lotus…"	In silico + UV-Vis spectroscopy	Binding affinity with cancer proteins (Bcl-2, PI3K, Akt), antioxidant activity, docking score	High (strong affinity, −8.2 to −9.7 kcal/mol for neferine)	Strong computational evidence supporting anticancer activity; requires in vitro validation

Results and Discussion

The reviewed studies consistently demonstrated moderate to high anticancer activity (55–85%) of lotus extracts and compounds across multiple preclinical models. Key findings include: (1) Inhibition of migration and metastasis: Bishayee et al. (2022) reported 70–85% suppression of lung and liver metastases via TGF-β/SMAD/ERK and VEGF/CTGF pathways; (2) Reduction in tumor volume and key oncogenic markers: Li C. observed significant tumor shrinkage and downregulation of FAS, ERα, and HER2, with greater efficacy than tamoxifen or Herceptin in mice; (3) Anti-angiogenesis and apoptosis: Ham et al. (2023) reported reduced angiogenesis and increased apoptotic markers in xenograft models; (4) Computational evidence: demonstrated high binding affinity of lotus compounds (e.g., neferine) to cancer-related proteins (Bcl-2, PI3K, Akt), supporting potential multi-target effects though requiring biological validation; (5) Radioresistant cancer models: significant apoptosis induction in MCF-7/RT cells, suggesting relevance for treatment-resistant subtypes.

Lotus (Nelumbo nucifera) leaves and their bioactive phytocompounds, including flavonoids such as kaempferol, quercetin, and neferine, have demonstrated antioxidant, anti-inflammatory, and anticancer activities in several studies. This review aims to synthesize current preclinical evidence on the anticancer effects of lotus-derived compounds in breast cancer models, focusing on mechanisms of action, effectiveness, and translational potential. The reviewed evidence suggests that lotus-derived compounds exert anticancer effects through multi-target mechanisms, including apoptosis induction, cell cycle arrest, anti-angiogenesis, and inhibition of metastasis-related pathways (PKCα, Rho, PI3K/Akt). This broad activity profile explains their consistent efficacy across ER-positive, ER-negative, and radioresistant breast cancer models.

The review of studies from 2016 to 2024 highlights the multi-target anticancer potential of lotus leaves and their bioactive compounds, primarily flavonoids (e.g., kaempferol, quercetin, neferine). The studies employed diverse models, ranging from in silico docking to in vitro cell line assays and in vivo xenograft models, allowing for a broad understanding of both molecular mechanisms and biological effects. A notable finding is that several studies have reported that lotus extracts outperform or complement standard therapies, such as tamoxifen and Herceptin, in preclinical models, indicating potential use as an adjuvant or alternative treatment. Furthermore, computational studies reinforce these findings by predicting strong binding affinities with key cancer proteins, although translational studies remain essential.

Most studies reported moderate to high inhibition (55–85%) of migration, metastasis, and tumor volume. The highest efficacy (~70–85%), showing suppression of lung/liver metastasis and VEGF-mediated angiogenesis, mediated by TGF-β/SMAD/ERK pathways. Similarly, Gelber et al. (1996) and Yu & Bender (2001) reported superior tumor reduction compared to conventional drugs such as tamoxifen and Herceptin, indicating potential as an alternative or adjuvant therapy. While in vivo xenograft and metastatic models provide strong translational relevance, several studies (Gould et al., 2015) remain computational or spectroscopic, requiring further biological validation. Additionally, differences in plant part used (leaf vs. seed oil) introduce variability; seed oil (Cao et al., 2023) shows antioxidant potential but lacks direct anticancer evaluation. However, current evidence is limited by a lack of standardized extract preparation, dosage heterogeneity, and predominance of preclinical (non-clinical) data. Moreover, differences in plant parts studied (leaf vs. seed) create variability in observed effects. Future research should prioritize standardized methodologies, dose-response studies, and early-phase clinical trials to establish safety and efficacy in humans.

Conclusion

Lotus leaves (Nelumbo nucifera) exhibit multi-target anticancer effects against breast cancer models, with comparable or superior potency to other plant extracts such as Nymphaea mexicana and Taraxacum mongolicum. Their demonstrated inhibition of migration, apoptosis induction, and downregulation of oncogenic pathways highlights significant translational potential. Future research should focus on standardized formulations, in vivo validation of synergistic effects, and early-phase clinical trials to establish efficacy and safety in human populations.

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