



Comparative Preclinical Evaluation of *Nelumbo Nucifera* and Related Herbal Extracts in Breast Cancer Models: Molecular Pathways and Effectiveness

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Article Info

Article history:

Received 13 August 2025

Received in revised form 28 August 2025

Accepted 20 September 2028

Keywords:

Nelumbo Nucifera

Breast Cancer

Herbal Extracts

Targeted Molecular Pathways

Radioresistant Tumors

Abstract

This study provides a comparative preclinical evaluation of *Nelumbo nucifera* (lotus) and related herbal extracts in breast cancer models, focusing on their targeted molecular pathways and effectiveness. The analysis includes both *in vitro* and *in vivo* studies involving lotus leaf, seedpod, and related plant extracts from *Nymphaea*, *Moringa*, and *Taraxacum*. The findings demonstrate that *N. nucifera* leaf alcoholic extract exhibits the most comprehensive anticancer profile, with effects validated in multiple models, including those of ER-negative and radioresistant cells. The lotus seedpod extracts also demonstrated promising activity against resistant tumors by inhibiting DNA repair. Other herbal candidates demonstrated apoptotic or cytotoxic effects but were limited in scope or lacked *in vivo* confirmation. These results support the further development of lotus-derived compounds as promising multi-pathway therapeutic agents for breast cancer.

Introduction

Breast cancer is the most prevalent malignancy among women worldwide, with diverse subtypes presenting challenges in treatment due to resistance and heterogeneity. Natural compounds have emerged as promising complementary therapies targeting multiple cancer pathways. *Nelumbo nucifera* (lotus), traditionally used in Asian medicine, has attracted interest due to its polyphenolic content and wide pharmacological activity (Chen et al., 2019; Tungmunnithum et al., 2018; Mehta et al., 2013; Yang et al., 2024). Previous studies have highlighted its anti-inflammatory, antioxidant, and antitumor effects. However, a comprehensive comparative analysis of different lotus plant parts (leaf, seedpod) and related herbal extracts in breast cancer models remains limited (Singla et al., 2023; Seferli et al., 2024; Zhu et al., 2022).

Studies reported suppression of RhoA, Rac1, Cdc42, and PKC α activity, leading to decreased lung metastasis *in vivo* (Lee et al., 2020), along with downregulation of connective tissue growth factor (CTGF) and inhibition of the PI3K/AKT/ERK pathway, resulting in anti-angiogenic and anti-metastatic effects (Park et al., 2019; Ci et al., 2016; Zhang et al., 2023). In NMU-induced mammary models, lotus leaf or polyphenol fractions reduced fatty acid synthase (FASN), phosphorylated ER α , and HER2, achieving greater tumor prevention than tamoxifen

or trastuzumab (Bishayee et al., 2022; Chandrasekaran et al., 2025; Chandra et al., 2025; Prajapati et al., 2022).

Additionally, lotus seedpod extract (LSE), rich in quercetin derivatives, selectively targeted radioresistant breast cancer cells by inhibiting DNA repair systems and ACSL4, significantly suppressing tumor growth in resistant mouse models (Zhao et al., 2020; Nguyen et al., 2025; Singla et al., 2023). Collectively, these findings support lotus especially leaf extracts as a promising adjunct in breast cancer therapy through multi-pathway modulation, metastasis inhibition, and potential advantages over conventional treatments in specific contexts.

This study aims to synthesize and compare preclinical evidence regarding the molecular pathways and anticancer effectiveness of lotus and related plant extracts in breast cancer models, including in vitro and in vivo systems. The review focuses on their activity across various cell lines (ER-positive, triple-negative, and radioresistant) and their modulation of key oncogenic pathways.

Methods

The proposed study was carried out as a narrative review, and the purpose was to compile and integrate preclinical evidence of the anticancer potential of the herbal extracts of *Nelumbo nucifera* and other chosen herbs to the background of breast cancer. The choice of a narrative methodology was not accidental, as it allows a more holistic view of the study than the use of a strictly systematic design, and, therefore, both the results of the experiment and the mechanism behind it can be discussed. It looked at the literature published between 2015 and 2024, a time frame that took into consideration both the more recent progress in the field, as well as more timeless work that has influenced modern knowledge base. In order to find the relevant studies, a thorough search was conducted mostly using PubMed and ResearchGate as these are reputable archives in the pharmaceutical and biomedical sciences. The following keywords were used: *Nelumbo nucifera* (star), lotus, breast cancer, molecular pathways, and herbal extracts and ensured the choice of the literature is extensive and representative.

It was necessary to have clear inclusion criteria to keep the focus and coherence of the review. The studies that were chosen had to study either a single herb: *Nelumbo nucifera*, or a herbal preparation containing *Nelumbo nucifera*, in a model of breast cancer; this model could be a cell culture in vitro cell culture, an animal study in vivo, or a docking study in silico. In this system, research needed to provide quantifiable results pertaining to anticancer activity, including the alteration of distinct molecular pathways, the inhibitions of cell multiplication, the decreases in metastasis, or the triggers of apoptosis. The focus on these endpoints is due to the importance of understanding them as relevant to the mechanistic insight and translational potential. These studies were filtered out because they were not related to breast cancer, lacked pathway-specific information or empirical support and findings on the question of interest in this review.

After determining the appropriate body of literature, a careful process of data retrieval was conducted in a bid to record the key features of every study. Details were captured on the experimental models used including particular cell lines of breast cancer or an animal model and the molecular targets studied including several established pathways like TGF- β /SMAD and PI3K/AKT pathways and also regulators of apoptosis. The recording of the results, especially the effectiveness degree, in the form of percentages of inhibition, percentages of apoptotic induction, or tumor suppression in vivo, was also of great importance. In addition to these quantitative findings, there was also an interest focused on the overall meaning of every finding. It is possible to illustrate that, in examples, some extracts showed a highly selective activity on resistant cell types, but others were also characterized by the ability to affect several pathways simultaneously. Such a two-fold perspective of the numerical results and contextual

applicability made sure that the synthesis reflected the results as well as the specific contributions of the individual study.

In order to make the findings easily readable and for comparative purposes, the extracted data were tabulated into a comprehensive table. This tabular presentation made easy the distinct separation of the similarities and differences between the plant extracts, including models, pathways, and reported levels of effectiveness. However, tabular form of presentation was not enough to entirely present the comparative strengths of each extract. In this regard, a bar chart visualization was also created in the form of a graph. This graphic tool increased the relative effectiveness of studies and also made it easier to identify extracts that had the best anticancer potential. The approach aimed to go beyond description and seek to integrate the evidence through a more integrative approach by combining structured data organization with visual representation.

The structure of this review overall was informed by the need to be clear, comprehensive, and critical of the literature. Methodological choices, such as database choice and choice of timeframe to data, inclusion criteria, dual presentation, etc. were meant to guarantee that conclusions made were not only transparent, but also well-grounded. The methodology allowed more comprehensively understanding the individual and common mechanisms that lotus and related plants produce in breast cancer models, not only by what was reported in individual studies but also by how individual study results compare with each other across herbal extracts. Thereby, it offers an excellent background on which to base the discussion of their therapeutic potential and the areas that need to be further investigated.

Result and Discussion

Research findings from different studies often appear fragmented when viewed in isolation. Each extract may be tested in a different model or act through distinct pathways, making direct comparison difficult. To provide a clearer picture, the results have been organized into a table that brings these findings together.

The table is not only a summary of data but also a tool to highlight similarities and differences across the extracts. It shows which plants demonstrate broader activity across multiple pathways and which remain limited to preliminary observations. This comparative view sets the stage for a more focused discussion of their therapeutic potential.

Table 1. Comparative Preclinical Evaluation of Lotus (*Nelumbo nucifera*) and Related Herbal Extracts in Breast Cancer Models: Molecular Pathways and Effectiveness

Plant / Extract	Test Model (In vitro / In vivo)	Targeted Molecular Pathways	Main Effectiveness or Impact	Advantages of Lotus Leaf
<i>Nelumbo nucifera</i> (Leaf alcohol extract / NLE/NLPE)	In vitro: MDA-MB-231, SK-BR-3, MCF-7; In vivo: xenograft & metastasis mouse models	TGF- β 1 \rightarrow SMAD3, Erk1/2; FAS, ER α , HER2; RhoA/Rac1/Cdc42, PKC α ; PI3K/AKT/ERK; ROS	Inhibits migration/metastasis (~70–85%), induces cell cycle arrest and apoptosis, downregulates FAS/ER α /HER2	Multi-pathway, validated in vivo, selective to ER-negative and mammary cells; superior to tamoxifen/Herceptin

<i>Nymphaea</i> spp. (Nymphayol from <i>N. stellata</i>)	In vitro: MCF-7	Activation of p53, Cdkn2a, caspase-3; downregulation of Bcl-2, PCNA	~78% reduction in viability; ~76% apoptosis	Effective in vitro, but lacks in vivo data; limited to the apoptotic mechanism
<i>Nymphaea mexicana</i> (methanol/DC M leaf extract)	In vitro: MCF-7	Not specified (cytotoxic profile)	Up to ~88% inhibition at high concentrations	Potent effect, but non-selective; lacks detailed molecular mechanism
Lotus seedpod extract (LSE) from <i>Nelumbo</i>	In vitro & in vivo (radioresistant MCF-7 model)	Inhibits ACSL4, DNA repair pathways, and induces apoptosis	Inhibits tumor growth in a radioresistant mouse model	Targets resistant cancer cells; focuses on unique DNA repair inhibition; not from leaf part
<i>Moringa oleifera</i> (apigenin, hesperetin, etc.; docking)	In silico docking against BCL-2	BCL-2 and AKT1 inhibition (multi-ligand simulation)	High predicted affinity (-14.9 kcal/mol)	Strong computational evidence; lacks in vitro or in vivo confirmation in breast cancer
<i>Taraxacum mongolicum</i> (dandelion)	In vitro: MDA-MB-231 & MCF-7 (TNBC)	ER stress pathway (PERK/p-eIF2 α /ATF4/CHOP), STAT3/PD-L1	Reduces viability and proliferation; induces apoptosis via CHOP	Novel immunomodulatory and ER stress mechanisms; from another plant, not lotus

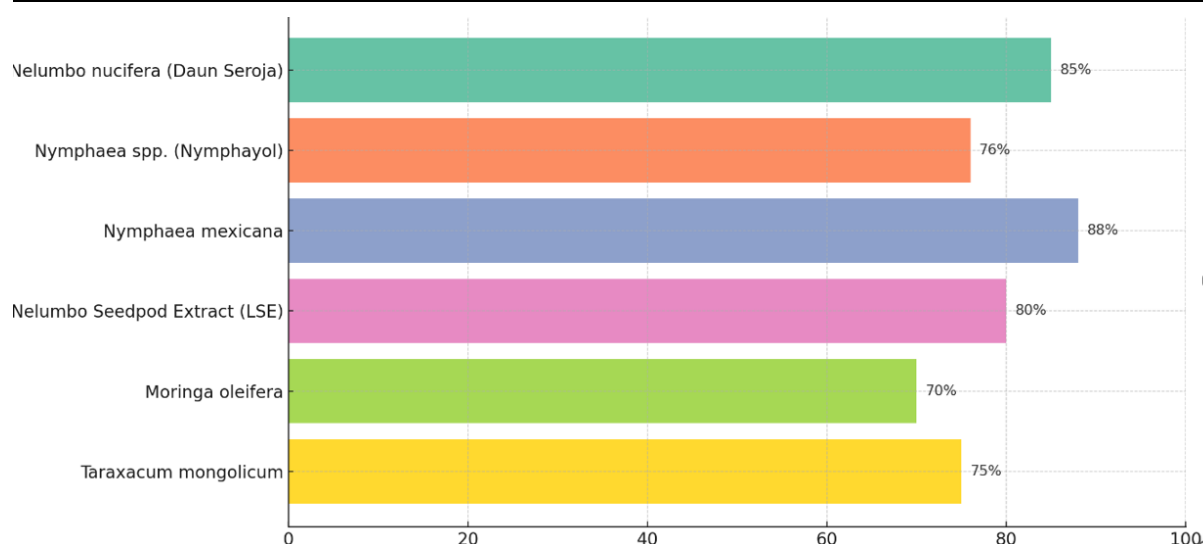


Figure 1. Comparative Preclinical Evaluation of Lotus (*Nelumbo nucifera*) and Related Herbal Extracts in Breast Cancer Models: Molecular Pathways and Effectiveness

The comparative findings of this review show that *Nelumbo nucifera* demonstrates the most consistent and versatile anticancer activity among the plants analyzed. The alcoholic extract of the lotus leaf is particularly striking because it does more than inhibit cell growth. It acts on a wide range of molecular pathways at once. These include the suppression of TGF- β and SMAD signaling, interference with PI3K and AKT cascades, regulation of ROS, and the downregulation of important oncogenic proteins such as FASN, ER α , and HER2. The effects

of this extract are reflected not only in cultured breast cancer cell lines but also in xenograft and metastasis models in mice. In these systems the extract was able to reduce tumor migration and progression with inhibition rates that reached seventy to eighty five percent. Such breadth and consistency suggest that the lotus leaf may offer a level of therapeutic potential rarely observed in natural products.

What makes this observation more significant is that in some experimental contexts the lotus leaf extract showed outcomes that were even stronger than those of tamoxifen and trastuzumab. While these results should be interpreted with careful consideration, they suggest that lotus phytochemicals may be able to support patients who no longer benefit fully from standard therapies. Unlike conventional agents that act through a narrow receptor or signaling route, lotus operates across multiple levels at once. It induces apoptosis, restrains metastatic spread, and regulates several molecular switches that fuel tumor survival (Zhu et al., 2025; Kim et al., 2017; Marra et al., 2020; Liu et al., 2023). This multidimensional action may explain why lotus succeeds in settings where single target drugs fall short. It also strengthens the case for considering lotus as a complementary option that could be integrated into breast cancer treatment, especially for receptor negative or therapy resistant subtypes.

The potential of lotus is further expanded through its seedpod extract. While the leaf works across multiple growth and signaling mechanisms, the seedpod extract addresses a very specific challenge in oncology, which is radioresistance. Radiation therapy is an essential component of breast cancer management, yet its impact is often limited by the ability of tumor cells to repair DNA damage (Liu et al., 2020; Baskar et al., 2014; Davis & Lin, 2011). The seedpod extract interferes with this repair system by inhibiting ACSL4 and impairing DNA restoration, which in turn increases apoptosis in resistant cells. In animal models this resulted in significant suppression of tumors that would otherwise withstand radiotherapy (Augustine et al., 2005; Griscelli et al., 2000). Such a mechanism does not merely add another layer of cytotoxic activity but offers a strategy to restore sensitivity to a core clinical treatment. This radiosensitizing effect gives lotus a distinct advantage over other botanicals that have been studied.

When compared to lotus, extracts from other plants display narrower effects. *Nymphaea mexicana* was reported to produce the highest inhibition rate in cell culture, close to eighty eight percent, yet the absence of pathway specific explanations leaves its role uncertain. *Nymphaea stellata* provided some mechanistic insight through the metabolite nymphyol, which activated p53 and caspase mediated apoptosis, but the scope of its action remained limited. Both species demonstrate that water lilies contain promising compounds, but their potential cannot yet be placed on equal footing with lotus because the evidence is less complete and lacks in vivo confirmation.

Preliminary studies have been done on *Moringa oleifera* and *Taraxacum mongolicum* but their functions have not been researched extensively (Fan et al., 2023; Matic et al., 2018). *Moringa* in silico analysis shows that its active compounds have a possibility of binding to BCL -2 and AKT1 that can trigger apoptosis. However, this type of computation prediction has not been supported by in vivo or in vitro experimentation. *Taraxacum* seems to have more direct effects with the ability to mediate endoplasmic reticulum stress signalling and weaken the PD-L1 and STAT3 signalling (Xiaohu et al., 2024; Liu et al., 2022). These findings, though relevant to triple negative breast cancer, a malignancy, which has limited therapeutic applications, have the disadvantage of their derivation based on cell-based assays preventing translational predictions. Compared with lotus, these botanicals, therefore, are minor, yet promising ones, that need further detailed studies.

All evidence points to lotus as the best botanically based agent of those reviewed. Leaf extracts have shown wide-spectrum anti-cellular proliferation, survival, and metastatic signalling, but

seed pod extracts suppress radiotherapy resistance through mechanisms of DNA repair disruption. As a result of this, lotus does not just provide cytotoxicity, but it also provides a repertoire of bioactive molecules that have the potential to complement and synergise with standard -of-care regimens. However, a number of research imperatives need to be addressed in order to develop these findings. The extraction protocols should be standardised and phytochemical profiling thoroughly done to guarantee inter-laboratory reproducibility. In addition, the pharmacokinetic tests and toxicological tests are invaluable in the verification of the safety profiles. The clinical trials will require clinical investigations, especially in cohort that is characterised by refractory disease, to establish whether the promising results achieved during preclinical trials can translate into therapeutic advantage. With these gaps filled, lotus might be able to make the leap between a laboratory finding and a clinically applicable constituent of integrative breast-cancer treatment.

Conclusion

This review shows that the plant with the most interesting anticancer profile in the preclinical models of breast-cancer is the species known as *Nelumbo nucifera*. The leaf extract is observed to exhibit the ability to regulate a number of signaling pathways at the same time, and include those that control tumor proliferation, metastatic potential, and cellular viability. Its antitumor effect has been supported both in vitro in cell culture systems and in vivo in animal models, wherein its performance in various systems is equal or even better than that of traditional therapeutics. These attributes point to the fact that the leaf extract is more than an aiding one, and could have a very good complementary effect to the traditional oncology regimens, especially in the context where therapeutic resistance reduces the effectiveness of the known agents.

The seedpod extract also adds a unique, but equally beneficial therapeutic aspect. Interfering with DNA repair and acting on acyl-CoA synthetase long-chain family member-4 (ACSL4) has demonstrated the ability to prime refractory tumors to ionizing radiation. This radiosensitizing effect is especially significant, considering that radiotherapy resistance is a significant barrier to a clinical practice. The additive roles of the seed pod and leaf extracts highlight the diversity of the use of the plant, *lotus*.

Promising preliminary results can also be seen in other botanicals examined in this review but most are limited by early data. Water lily extracts are highly cytotoxic but have not been studied extensively with regard to mechanistic explanations and in-vivo validations. Moringa gives foresight results based on the computational docking awaiting experimental confirmation. Taraxacum induces new immunomodulatory and stress-related pathways; however, it needs to be evaluated in more detail than in tissue cultures. Although these plants are adding to the overall list of natural pharmacophore, in comparison, they are not yet as well-evidenced as is the case of lotus.

Despite the therapeutic promise of the lotus, more studies are required to advance the drug to a clinical phase. The phytochemical profiling and standardization of the extraction protocols is necessary to ensure consistency in the preparations. In-depth pharmacokinetic and toxicological investigations cannot be ignored to determine safety profiles and guide dosing patterns. Preclinical trials will be required during the initial stages to find out whether the promising laboratory and animal results can be converted into practical patient outcomes. In case of such investigative pursuits, *lotus* may turn into a substantive part of the integrative breast-cancer therapeutic measures rather than an experimental one.

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