

In Silico Study of *Ficus deltoidea* as Adjuvant to Tamoxifen Targeting CYP2D6

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DOI: 10.29322/IJSRP.16.03.2026.p17120

<https://dx.doi.org/10.29322/IJSRP.16.03.2026.p17120>

Paper Received Date: 25th February 2026

Paper Acceptance Date: 26th March 2026

Paper Publication Date: 30th March 2026

Abstract: Breast cancer is the most common cancer diagnosed in women and the second most common cause of death from cancer among women worldwide. Hormonal therapy with tamoxifen is the primary option for estrogenic receptor-positive patients. However, tamoxifen's effectiveness could be significantly influenced by drug metabolism through the CYP2D6 enzyme. The concomitant use of drugs that inhibit this enzyme can decrease the conversion of tamoxifen to its active metabolite, Endoxifen, thereby reducing therapeutic efficacy. *Ficus deltoidea*, a native Indonesian plant, is known to possess antioxidant and antiproliferative properties and may be potentially developed as an adjuvant in cancer therapy.

Objective: This study aimed to evaluate the potential of *Ficus deltoidea* as an adjuvant in enhancing the effectiveness of tamoxifen on CYP2D6 using molecular docking study.

Methods: Protein target was CYP2D6; bioactive compounds from the *Ficus deltoidea* plant, such as Baicalin, Isovitexin, Nicotiflorin, Apigenin, Izalpinin, Kaempferol, and Episappanol in pdb format.

Molecular docking was done using Autodock Vina. **Results:** *Ficus deltoidea* molecular docking analysis showed that Baicalin, Isovitexin, and Nicotiflorin could bind to CYP2D6 with respective ΔG values of -9.74 kcal/mol, -9.47 kcal/mol, and -8.17 kcal/mol. Baicalin and Isovitexin contain hydrogen bonds with the greatest activity with CYP2D6 on Asp 301, Ser 304, Gln 244, Ala 209 for Baicalin on Ser 304, Asp 301, Leu 208, Thr 375, Arg 221 for Isovitexin. Nicotiflorin formed hydrogen bonds with CYP2D6 at Ser 304, Leu 121, Ala 209, and Gln 244.

Conclusion: These findings highlight the synergistic potential of *Ficus deltoidea* in enhancing tamoxifen efficacy through the CYP2D6 enzyme, underscoring the need to evaluate drug-herb and drug-drug interactions in breast cancer treatment.

Keywords: Breast cancer, Tamoxifen, CYP2D6, *Ficus deltoidea*

INTRODUCTION

Breast cancer is the most common cancer diagnosed in women and the second most common cause of death from cancer among women worldwide. A complex interplay of multiple factors, including age, genetics, environment, and reproductive history, and unknown factors, causes breast cancer. The risk of breast cancer increases with older age and is most common in post-menopausal women. Genetics and heritable factors play an important role in the development of breast cancer. A first-degree family history of breast cancer significantly increases breast cancer risk. Potentially modifiable factors, including obesity, alcohol consumption, smoking, physical inactivity, and replacement hormonal therapy, have all been associated with increased breast cancer risk.[1]

Treatment includes surgery, radiation, chemotherapy, and immunotherapy, which are used in combination to treat breast cancer, depending on the stage and type of tumors. Improvements in these treatment modalities have resulted in significant improvements in overall survival and patient-reported outcomes. First-line medications used to treat Breast cancer that the FDA has approved, like Raloxifene, Soltamox, and Tamoxifen, have shown some significant results. For example, Tamoxifen is a medication used to treat breast cancer because of its sensitivity to estrogen-positive breast cancer [2]. However, long-term treatment for patients with Tamoxifen also shows some side effects, including anxiety, bone density loss, joint pain, fatigue, and even depression [5].

To fix the condition, most healthcare professionals recommend polypharmacy therapy, including the usage of medications for anxiety and depression in breast cancer patients. However,

Tamoxifen is a prodrug and needs to be converted to the active metabolite, Endoxifen, by the CYP2D6 enzyme. Co-administration of Tamoxifen with the CYP2D6 inhibitor drug is a hindrance to the metabolism of Tamoxifen. As a result, the effectiveness of the treatment significantly decreased.[4]

Previous research has shown that the use of herbal medicine as adjuvant therapy for breast cancer is a desirable choice of treatment for the long term and is promising to achieve a better outcome. Their effectiveness is also reported to decrease toxicity in use and reduce the recurrence of resistance to hormonal targeting anti-cancer agents. Such uses are due to their antioxidant and anti-inflammatory properties, immunomodulatory properties, and ability to induce anti-proliferative and anti-apoptotic effects on these cancer cells. For example, the biochemical properties and pharmacokinetics of Ginseng, Gallic, Green tea, Flaxseed, Turmeric, and Black Cumin. These well-known herbs are commonly used in traditional medicine as adjuvants in breast cancer therapy [3].

Investigating potent natural compounds from plants with high biological activity is an ongoing process. *Ficus deltoidea* Jack (FD) is one of the most well-known and widely appreciated plants. Many studies have been published on the plant's biological properties, including antioxidant activity, anti-inflammatory activity, effect on microorganisms, effect on the endocrine system, anti-hypertensive activity, aphrodisiac activity, wound healing activity, and anticancer activity. In traditional medicine, the plant's leaves and syconia are used to cure a wide variety of ailments, including itchiness, diarrhea, cancer, sexual dysfunction, age-related issues, malaria, anxiety, pain, constipation, fever, diabetes, tooth pain, and tooth decay. *In vitro* and *in vivo* studies showed the effectiveness of the leaves against breast cancer cell lines.[7]

Research related to FD and CYP2D6 or CYP26 inhibitors is still limited. In this study, we will analyze the potential of *Ficus deltoidea* in breast cancer treatment through a molecular docking study. By targeting enzyme CYP2D6 with some bioactive compounds of *Ficus deltoidea* to know how much they bind to the target enzyme CYP2D6 and how FD contributes to Tamoxifen metabolism, which can lead to a breakthrough in breast cancer treatment.

LITERATURE REVIEW

2.1 Tamoxifen and CYP2D6 enzyme interaction

Tamoxifen is a selective estrogen receptor modulator (SERM)

widely used in hormone receptor-positive breast cancer. Its therapeutic efficacy depends on metabolic activation by the cytochrome P450 enzyme CYP2D6, which converts Tamoxifen into its active metabolite, Endoxifen. However, co-administration of CYP2D6 inhibitors, such as certain SSRIs, can significantly reduce this conversion, leading to suboptimal treatment outcomes. Studies have shown that patients with poor CYP2D6 metabolizer status or those taking CYP2D6 inhibitors have lower plasma levels of endoxifen and poorer clinical responses.[5][6]

Tamoxifen Metabolic Pathway

2.2 *Ficus deltoidea*: A Phytochemical Powerhouse

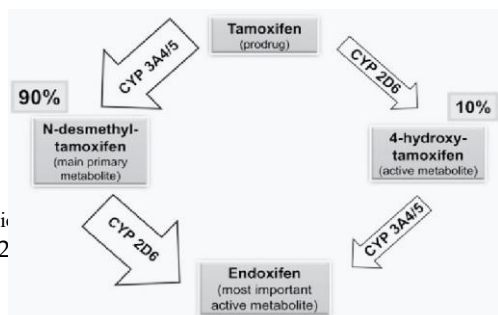
Ficus deltoidea, a traditional medicinal plant native to Southeast Asia, has gained attention for its diverse pharmacological properties. It contains bioactive compounds like flavonoids such as vitexin, isovitexin, Baicalin, Nicoflorin, and kaempferol, etc, derivatives, which exhibit antioxidant, anti-inflammatory, and anticancer activities. Studies have explored the potential of FD in breast cancer treatment. One study published in the *Journal of the Indonesian Medical Association* discusses the anticancer properties of *Ficus deltoidea* leaves, which contain flavonoids, saponins, tannins, steroids, and terpenes compounds known for their anticancer effects. The study highlights how patients often seek natural-derived treatments due to the side effects of conventional therapies like chemotherapy and radiation.[8][9]

2.3 Molecular Docking in Drug Discovery

Molecular docking is a computational method that predicts the preferred orientation of a ligand when bound to a protein target. It helps estimate binding affinity and interaction profiles, making it a powerful tool in structure-based drug design. It provided a comprehensive overview of docking algorithms, scoring functions, and their applications in virtual screening and lead optimization. Docking studies involving CYP2D6 enzymes have shown that ligand binding can be influenced by hydrophobic interactions and coordination with the heme group, which is critical for accurate modeling.[10]

2.4 Natural Products as Adjuvants in Cancer

The integration of natural compounds as adjuvants in cancer therapy is a growing field. These compounds can modulate drug metabolism, enhance efficacy, and reduce side effects. For instance, flavonoids have been shown to influence cytochrome P450 activity, either by inhibition or induction, depending on their structure. This dual role opens the possibility of using *Ficus deltoidea* compounds to either bypass or complement CYP2D6-mediated metabolism, especially in patients with compromised enzyme activity.[9]



2.5 Gaps and Opportunities

Ficus deltoidea has demonstrated promising anticancer and metabolic regulatory effects; its role as an adjuvant to Tamoxifen, particularly in the context of CYP2D6 inhibition, remains underexplored. In silico studies can bridge this gap by

modeling interactions between *Ficus deltoidea*'s bioactive compounds and protein targets like CYP2D6. This approach may uncover novel mechanisms of synergy and pave the way for integrative breast cancer therapy.

Ligand in pdpqt

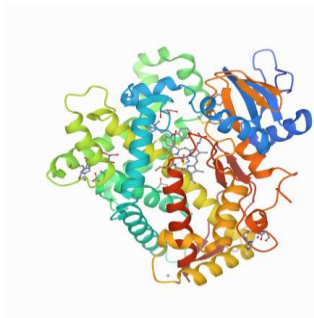
METHODOLOGY

3.1 Research Design

Molecular docking is a computational technique that predicts the interaction between two molecules—typically a small ligand (such as a drug) and a macromolecule (such as a protein or DNA). It helps scientists understand how drugs bind to their targets and how effective they might be in treating diseases. If the focus is on whether the drug binds to the targeted protein and the value of the binding affinity.

3.2 Participants/Sample

Protein target was *CYP2D6*, whose structure from PubChem. Ligands are bioactive compounds from *Ficus deltoidea* plant, such as *Baicalin*, *Isovitexin*, *Nicotiflorin*, *Apigenin*, *Izalpinin*, *Kaempferol*, and *Episappanol* in pdb format.



CYP2D6 - cytochrome P450 family 2

subfamily D member 6 (gene/pseudogene)

(human)



3.3 Data Collection

In this study, the grid box dimensions include 40x40x40, 50x50x50, and 60x60x60. However, only the grid box dimension 50x50x50 is used. In other words, among these three grid box dimensions. The center grid box in 40x40x40 is -11,9 kcal/mol, RMSD Reference Å 0,33 kcal/mol, and Inhibition Constant (nM) 1,61kcal/mol, while in grid box 50x50x50 with center grid box of -12 kcal/mol, RMSD Referene A 0,31 kcal/mol, and Inhibition Constant (nM) 1,61 kcal/mol, although in grid box 60x60x60, Center grid box is -12, 00 kcal/mol, RMSD reference 0,35 kcal/mol and Inhibition Constant (nM) 1,61 kcal/mol. Which means the grid box 50x50x50, with the least or most negative binding energy(ΔG) (kcal/mol), is likely to be more sensitive when binding. The energy binding at the Center grid box is -12.00 kcal/mol, RMSD Reference A is about 0.31 kcal/mol, and the Inhibition Constant is 1.61 kcal/mol, indicating that the grid box best used is 50x50x50. See Table 1.

3.4 Data Analysis

Binding Energy (ΔG) indicates the strength of interaction between ligand and receptor. The energy is released when the ligand binds to the receptor. Lower (more negative) values suggest stronger binding affinity. Compare across multiple ligands to identify the most promising candidate. Ligands are bioactive compounds from *Ficus deltoidea* plant, such as *Baicalin*, *Isovitexin*, *Nicotiflorin*, *Apigenin*, *Izalpinin*, *Kaempferol*, and *Episappanol* in pdb format.

Docking Score is a numerical value generated by the docking software (e.g., AutoDock, Glide). Often correlates with binding energy but may include additional scoring functions. Use it to rank compounds in virtual screening.

Interaction Analysis is used to visualize hydrogen bonds and hydrophobic interactions. Focus on interactions with active site residues or catalytic domains.

Table1. Grid Box Validation

Dimensi Grid Box	ΔG (kcal/mol)		
	40x40x40	50x50x50	60x60x60
CYP2D6 (PDB ID: 4WNT)			
Center Grid Box			
x-Center = 8.787	-11.9	-12.00	-12.00
y-Center = 35.803			
z-Center = -76.67			
RMSD References Å	0.33	0.31	0.35
Inhibition Constant (nM)	1.61	1.61	1.61

Table 2. Result of Molecular Docking Study of Biocompounds of *F.deltoidea* on CYP2D

Compounds	Binding energy (kcal/mol)	Constant Inhibition (Ki)	Residue with Hydrogen bond
5-Methyl Kaempferol	-7.33	4.24 uM	Asp 301, Ala 209, Ser 304
Apigenin	-7.86	1.74 uM	Leu 121, Asp 301, Ala 209
Baicalin	-9.74	72.91 nM	Asp 301, Ser 304, Gln 244, Ala 209
Episappanol	-7.41	3.67 uM	Glu 216, Gln 244, Asp 301, Ser 304
Isovitexin-3"-O-glucopyranoside	-9.47	114.65 nM	Ser 304, Asp 301, Leu 208, Thr 375, Arg 221
Izalpinin	-7.70	2.28 uM	Asp 301, Ser 304
Kaempferol 3-O- β -D-glucuronopyranosyl methyl ester	-7.46	3.40 uM	Asp 301
Nicotiflorin	-8.17	1.02 uM	Ser 304, Leu 121, Ala 209, Gln 244
Pachypodol	-7.88	1.67 uM	Gln 244, Ser 304
Rhamnazin	-7.67	2.37 uM	Asp 301, Ser 304
Skulcaflavon 1	-8.36	741.85 nM	Glu 216, Asp 301, Ser 304

RESULT AND DISCUSSION

See Table 2. According to the results of *Ficus deltoidea* molecular docking analysis, Baicalin, Isovitexin, and Nicotiflorin could bind to CYP2D6 with respective ΔG values of -9.74 kcal/mol, -9.47 kcal/mol, and -8.17 kcal/mol. Baicalin contains a hydrogen bond with the greatest activity with CYP2D6 on Asp 301, Ser 304, Gln 244, Ala 209 for Isovitexin on Ser 304, Asp 301, Leu 208, Thr 375, Arg 221. In addition, Nicotiflorin forms hydrogen bond with CYP2D6 on Ser 304, Leu 121, Ala 209, and Gln 244.

These results suggest that *Ficus deltoidea* compounds may enhance tamoxifen's metabolism or bypass CYP2D6 inhibition, potentially reducing side effects and increasing the effectiveness of the drug.

This finding aligns with previous studies on *Ficus deltoidea*'s anticancer properties due to its bioactive compounds.[7][9]

However, this study only focuses on in silico analysis, which may require further validation in vitro and vivo studies.

CONCLUSION

These findings highlight the synergistic potential of *Ficus deltoidea* in enhancing tamoxifen efficacy through the CYP2D6 enzyme and underline the need to evaluate drug-herb and drug-drug interactions in breast cancer treatment.

APPENDIX

To conduct this study, a computer with the necessary software is required.

ACKNOWLEDGMENT

"This article has been funded with support of the Kemitraan Negara Berkembang (KNB) Scholarship from Ministry of Higher Education, Sciences, and Technology of Republic of Indonesia on behalf of the Government of the Republic of Indonesia. This Publication reflects the view only of the author, and the Ministry of Higher Education, Sciences, and Technology of the Republic of Indonesia cannot be held responsible for any use which may be made of the information contained therein."

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