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PROGNOSTIC BIOMARKER OF INVASIVE BREAST CANCER ANALYSIS AND MOLECULAR INTERACTION WITH *Taxus sumatrana* PHYTOCOMPOUNDS

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Abstract

Invasive breast cancer remains a leading cause of cancer mortality, requiring reliable prognostic biomarkers and new therapeutic agents. *Taxus sumatrana* contains bioactive compounds with potential anticancer activity. This study aimed to identify poor prognostic biomarkers in invasive breast cancer and evaluate the molecular interactions between PGK1 and bioactive compounds from *T. sumatrana*. Gene expression analysis data was conducted by mining transcriptomic and Kaplan-Meier data from the UALCAN database to compare breast tumor and normal tissues and evaluated survival among 100 candidate genes. PGK1 was selected based on high expression and poor prognosis. Subsequently, 31 compounds of *T. sumatrana* from the KNApSAcK database were subjected to molecular docking against PGK1. PGK1 demonstrated significantly stronger expression in primary tumor tissues than normal tissues. This expression was associated with the poorest survival trend among analyzed biomarkers (TAGLN2, TUBA1B, and COX7B), indicating its prognostic relevance. taxinine B, tasumatrol X, and tasumatrol U were identified as promising compounds according to their favorable binding affinities toward the active site of PGK1, forming hydrogen bonds and hydrophobic interactions at key residues. PGK1 is a promising poor prognostic biomarker and therapeutic target in invasive breast cancer. Taxinine B from *T. sumatrana* may act as potential PGK1 inhibitors and merit further experimental validation.

Keywords: *Biomarker; Invasive breast cancer; Phytocompounds; Taxus sumatrana*

1. INTRODUCTION

Breast cancer remains one of the most significant global health threats and is the most frequently diagnosed cancer among women worldwide. In 2022, approximately 2.3 million new confirmed cases and almost 670,000 death cases were reported, highlighting the urgent need for improved diagnostic and therapeutic strategies (Freihat et al., 2025). Among its histopathological subtypes, invasive breast cancer is characterized by malignant epithelial cells that penetrate surrounding stromal tissues

and possess metastatic potential, which is leading to morbidity and mortality (Chang et al., 2017). Despite advances in treatments, the difference of prognosis is caused by molecular heterogeneity and treatment resistance (Cao et al., 2021; Zhu et al., 2021). Although several conventional biomarkers, including estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67, have been widely utilized for breast cancer classification and therapeutic guidance, these biomarker-defined subtypes demonstrate distinct outcomes and therapeutic responses, as well as differences in their global genomic and transcriptome profiles (Hu et al., 2023). Thus, identification of robust prognosis biomarkers remains crucial for precision oncology.

Invasive breast cancer cells undergo metabolic reprogramming to foster rapid proliferation, survival under hypoxic conditions, invasion, and metastasis. One major metabolic adaptation is the Warburg effect, in which cancer cells preferentially utilized aerobic glycolysis even in the presence of oxygen. This altered metabolic state is closely associated with tumor aggressiveness and resistance to therapy (Liu et al., 2024). Thus, metabolic-associated biomarkers can provide more dynamic and functional information regarding cancer progression compared with conventional receptor-based biomarkers alone.

Phosphoglycerate kinase 1 (PGK1), a key glycolytic enzyme, catalyzes ATP generation during glycolysis and contributes to angiogenesis, DNA repair, metastasis, and chemoresistance. Overexpression of PGK1 has been associated with worse prognosis in breast, liver, and endometrial cancer (P. Wang et al., 2023). In context of breast cancer, PGK1 has been discovered as a predictor of poor survival and prognostic biomarker of chemoresistance to paclitaxel treatment in breast cancer (Sun et al., 2015). The chemoresistance has been elaborated by He and colleagues, demonstrating that PGK1 upregulates autophagy, scavenges ROS, and inhibits ROS-stimulated apoptosis (He et al., 2019). These multifunctional roles suggest that PGK1 may serve not only as a metabolic marker but also as a potential therapeutic target in invasive breast cancer.

Natural products remain an essential source of anticancer agents. The genus Taxus is a well-known source of paclitaxel, the first-line single chemotherapeutic drug for breast, ovarian, lung, and head and neck cancers (Meng et al., 2025). In context of breast cancer, paclitaxel has been studied effectively in advanced or metastatic breast cancer, including triple-negative breast cancer (TNBC) (Slamon et al., 2001). Nevertheless, this anticancer agent must be combined with anti-HER2 agents such as trastuzumab and pertuzumab once incubating to HER2 positive breast cancer subtype (Tanaka et al., 2019). *Taxus sumatrana*, a less explored Southeast Asian species, contains diverse secondary metabolites with potential bioactivity (Novriyanti & Susilo, 2020). Moreover, this species of Taxus has been extensively studied to treat cancer cells (Wahyuni et al., 2024). Nevertheless, the inhibitory potential of this species' compounds on PGK1 remains unknown. Through molecular docking, we may predict and identify promising lead compounds on PGK1 structures. Therefore, this study aimed to analyze prognostic biomarkers of invasive breast cancer and predict binding affinity of *T. sumatrana* compounds on the worst prognostic biomarker protein structure through molecular docking.

2. METHODS

2.1 Prognostic Biomarker Analysis

The prognostic biomarker screening was performed using the UALCAN database (https://ualcan.path.uab.edu), an interactive web resource based on The Cancer Genome Atlast (TCGA) dataset. Initially, a heatmap of 100 candidate genes associated with invasive breast cancer was generated to identify genes with differential expression patterns between primary tumor and normal breast tissues. Then, the highly relevant genes were selected for further analysis such as gene expression from TCGA transcriptomic data and Kaplan-Meier survival rate to identify which gene is demonstrating the worst prognostic (Chandrashekar et al., 2017).

2.2 Taxus sumatrana Bioactive Compounds Identification and Structure Preparation

Taxus sumatrana phytochemical compounds name were retrieved from KNApSAck database (https://www.knapsackfamily.com/knapsack_core/top.php) (Afendi et al., 2012). A total of 31 compounds were collected, and their 3D chemical structures were downloaded from

the PubChem database in structure date file (SDF) format and converted into protein data bank (PDB) format using CACTUS online translator (https://cactus.nci.nih.gov/translate/).

2.3 Protein Structure Preparation

After determining PGK1 as the worst prognostic biomarker of invasive breast cancer, the crystal structure of PGK1 was obtained from the RCSB database (https://rcsb.org) under PDB ID 5NP8. Prior to docking, water molecules and non-essential ligands were eliminated in Biovia Disovery Studio (https://3ds.com) (BIOVIA, 2016). Polar hydrogen atoms and Kollman charges were assigned to the protein structure in Autodock tools (ADT) version 1.5.7 and converted to PDBQT format.

2.4 Molecular Docking Protocol

Molecular docking was performed using ADT version 1.5.7 (Morris et al., 2009). The docking grid box was centered on the co-crystallized ligand position with dimensions of 50 x 50 x 50 Å. Docking simulations were executed using the Genetic Algorithm with 50 runs, 200 population size, and default parameters for energy evaluations and mutation rates. The conformation was predicted using the Lamarckian Genetic Algorithm (Faisal et al., 2022; Faisal & Hariaji, 2026). Binding affinity values (kcal/mol) of all compounds were recorded and compared with the co-crystallized ligand of 5NP8.

2.5 Molecular Interactions Analysis

After the promising compounds were retrieved, we subjected each SMILES of lead compounds to predict their safety profile such as hepatotoxicity, neurotoxicity, nephrotoxicity, respiratory toxicity, cardiotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and clinical toxicity on ProTox online platform (https://tox.charite.de/protox3/) (Banerjee et al., 2024). Ultimately, molecular interactions between PGK1 with both Taxinine B and the co-crystallized ligand were visualized in two-dimensional figures.

3. RESULTS AND DISCUSSION

3.1 Prognostic Biomarker Identification

To identify potential prognostic biomarkers in invasive breast cancer, a heatmap of 100 candidate genes was generated by UALCAN online platform based on TCGA transcriptomic data. **Table 1** presented *p* value of overall survival, and the median day

survived patients of both high and low expressions from 100 genes candidate of invasive breast cancer. Moreover, we also generated heatmap of genes candidate in **Figure 1** and found PGK1, TAGLN2, COX7B, and TUBA1B showed markedly elevated expression in primary tumor tissues compared with normal breast tissues. These three genes were selected for further prognostic evaluation using Kaplan-Meier survival analysis.

Table 1. Gene expression of invasive breast cancer prognostic marker based on the survival rate from UALCAN database

Gene	Log rank P-value	High expression: Median survival (in days)	Low expression: Median survival (in days)
PGK1	0	2965	3959
LRP11	7.1e-06	2866	4267
OPN4	9.1e-06	2965	4456
MLLT4	3.86e-05	2911	6456
HCCS	5e-05	2965	4267
TAGLN2	5.51e-05	3472	3941
SATL1	6.6e-05	2911	4456
ADORA3	8.16e-05	3126	4267
SERPINA1	8.28e-05	7455	3472
ZIC5	8.49e-05	3461	3959
RAB3GAP2	9.58e-05	3262	4267
GARS	9.72e-05	3472	3945
LIMCH1	0.0001126	3126	4456
ATP5G3	0.0001129	3262	3941
IGSF9B	0.0001225	3126	4456
TCP1	0.000131	3462	4267
HBS1L	0.0001347	3409	4456
FAM127C	0.000137	3472	3959
BCLAF1	0.0001427	3262	6456
MCTS1	0.0001598	3873	3959
MRPL13	0.0001623	2965	4267
QPRT	0.0001704	3941	3959
UBA5	0.0001711	2965	4456
MOSPD1	0.0003963	3462	3959
ZDHHC9	0.0003998	3262	4267
GDI1	0.0004003	3462	4267
WWOX	0.0004084	3461	3959
MARS	0.0004085	3462	4267

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Table 1. Gene expression of invasive breast cancer prognostic marker based on the survival rate from UALCAN database (continued)

Gene	Log rank P-value	High expression: Median survival (in days)	Low expression: Median survival (in days)
AP3S1	0.0004106	3418	3959
TFPI2	0.0004232	7455	3669
H2AFV	0.0004293	3262	4267
SDC1	0.0004385	3409	3959
SLCO1A2	0.0004427	6593	3472
PROM2	0.0004738	3262	3959
APOBEC3D	0.0004786	7455	3736
TBPL1	0.0004839	3462	4267
NRK	0.000493	3262	4267
ALG9	0.0005064	3063	4456
MRO	0.0005081	3873	3959
SYS1-DBNDD2	0.0005094	2965	4267
NKX2-3	0.0005158	3063	3945
PLXNB3	0.0005191	3462	3959
ZNF485	0.0005242	3126	6593
FAM190A	0.0005274	3409	4456
VSIG8	0.0005558	6456	3941
FOXRED1	0.0005641	2965	3959
FAM127A	0.0005788	3941	3945
PDCD2	0.0005952	3926	6593
TMEM31	0.0006114	3472	3945
FUT3	0.0006162	3945	3941
RAB5B	0.000619	3262	4267
LOC441089	0.000641	2965	4456
TRERF1	0.0006643	3126	4267
FAM173B	0.0006714	2798	3959
CYC1	0.0006846	3736	3941
KIAA1024	0.0006875	3262	4456
ERCC6L	0.000705	3262	4267
C6orf138	0.0007062	3418	6456
MAP3K4	0.0007509	3418	6456
CST1	0.0007603	NA	3736
SCRN3	0.0007679	2798	4456
P4HA1	0.0007691	3418	4267
SPINT1	0.0007716	3262	3959
ATCAY	0.0008113	3418	4267
C2orf54	0.0008249	3941	3945
SQRDL	0.0008269	3063	4267
ABHD12	0.0008772	3126	3959
PDK3	0.0008898	3262	3959
APC2	0.0009041	3461	4267
PVRL4	0.0009086	3472	4267
PRRC1	0.0009182	2866	3959

Table 1. Gene expression of invasive breast cancer prognostic marker based on the

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survival rate from UALCAN database (continued)

Gene	Log rank P-value	High expression: Median survival (in days)	Low expression: Median survival (in days)
CDHR4	0.0009477	NA	3669
RACGAP1	0.0009478	3262	4267
RAET1G	0.0009485	3736	4267
LOC389332	0.0009572	3461	4267
LOC144438	0.000981	3262	4456
CLEC3A	0.0009958	3669	3959
COX7B	0.0010149	3063	3941
TM2D2	0.0010285	3418	6456
ZBTB11	0.00103	3669	3959
PXDNL	0.0010362	3462	4267
C7orf10	0.0011013	3462	3945

Figure 1. Heatmap of 100 gene expression patterns in invasive breast carcinoma (BRCA).

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Among them, PGK1 demonstrated the worst survival outcome, with a highly significant *p*-value of 0.000, indicating a strong association between elevated PGK1 expression and declined patient survival. In contrast, TAGLN2, COX7B, and TUBA1B showed weaker prognostic significance (see **Figure 2**). The overexpression of PGK1 fosters prior findings that glycolytic enzymes are frequently upregulated in aggressive tumors to fulfill upregulated metabolic demand. As a central ATP-producing enzyme, PGK1 may escalate breast cancer growth, migration, and therapy resistance (Fu et al., 2018; Sun et al., 2015; Yang & Han, 2026), shaping it a promising prognostic biomarker and therapeutic target in invasive breast cancer.

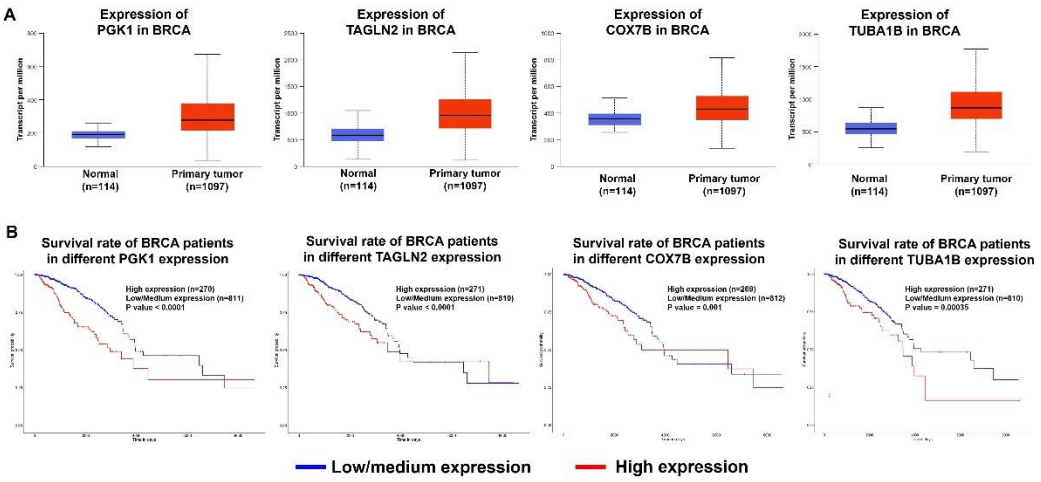

Figure 2. Expression and survival analysis of candidate biomarkers in BRCA **(A)** Gene expression analysis of PGK1, TAGLN2, COX7B, and TUBA1B in BRCA, and **(B)** Kaplan-Meier survival analysis of BRCA patients related to PGK1, TAGLN2, COX7B, and TUBA1B expression level.

3.2 Taxus sumatrana Compound Identification

A total of 31 phytochemical compounds of *Taxus sumatrana* were identified from the KNApSAck database. These compounds belong mainly to taxane diterpenoids, paclitaxel precursors, polyoxygenated taxane, and polyhydroxylated taxane. The genus *Taxus* is commonly known as the natural source of paclitaxel (taxol); hence, relevancy of *T. sumatrana* with breast cancer treatment effectivity is probably affected by its bioactive metabolites.

Most compounds identified from *T. sumatrana* are classified as taxane diterpenoids and paclitaxel-related metabolites, some of them have been studied regarding their anticancer

properties (Qayum et al., 2020; Shen et al., 2002; Yu et al., 2025). Particularly, paclitaxel primarily exert cytotoxic effects through microtubule stabilization and mitotic arrest (Chavez et al., 2019; Weaver, 2014). Moreover, taxane compounds were reported in influencing cancer metabolism and signaling pathways associated with glycolytic regulation (Oshiro et al., 2009; Premchandani et al., 2025). Inhibition of PGK1 according to prior study could suppress ATP production, reduce glycolytic flux, and disrupt the metabolic adaptability of breast cancer cells (Cui et al., 2024). It suggests that taxane-derived *T. sumatrana* may influence PGK1 activity or expression.

3.3 Molecular Docking Results

Molecular docking was carried out to predict the binding affinity of the 31 compounds toward PGK1 (PDB ID: 5NP8). Binding energy values indicate divergent levels of interaction, whereas more negative values represent stronger binding affinity. According to **Figure 3A**, among all screened compounds, taxinine B, tsumatrol X, and tasumatrol U exhibited more negative binding affinity values, indicating spontaneous binding toward the PGK1 active pocket. Meanwhile, the co-crystallized reference ligand showed the strongest binding affinity (approximately -8.8 kcal/mol).

Moreover, we predicted the top compounds safety profiles. According to **Figure 3B**, Taxinine B showed the most favorable safety profile, with lower predicted hepatotoxicity, neurotoxicity, nephrotoxicity, respiratory toxicity, and clinical toxicity than both tasumatrol X and tasumatrol U. Necessarily, taxinine B also exhibited a low probability of mutagenic and carcinogenic tendencies relative to the reference ligand. These findings indicate that Taxinine B combines promising bioactivity with acceptable drug-safety characteristics.

The superimposition analysis in **Figure 3C** revealed that Taxinine B occupied a binding region overlapping with the co-crystallized ligand, suggesting a similar inhibitory mechanism. Partial alignment within the ligand-binding pocket fosters the possibility that Taxinine B competitively interferes with substrate recognition or catalytic function of PGK1 such as GLY239, LYS220, and ALA215. In comparison, the reference ligand interacted with GLY214, GLY239, GLY313, LEU257, and PHE292. A prior study also revealed that Z57346765, a potent PGK1 inhibitor, formed hydrophobic interactions with LEU257 (He et al., 2024). Then, the shared interactions at LEU257, indicating that those residues were recognizably involved in inhibitor stabilization. Furthermore, western blot study demonstrated that LYS220 could be

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acetylated which is leading to PGK1 inactivity by disrupting the binding with its substrate (S. Wang et al., 2015).

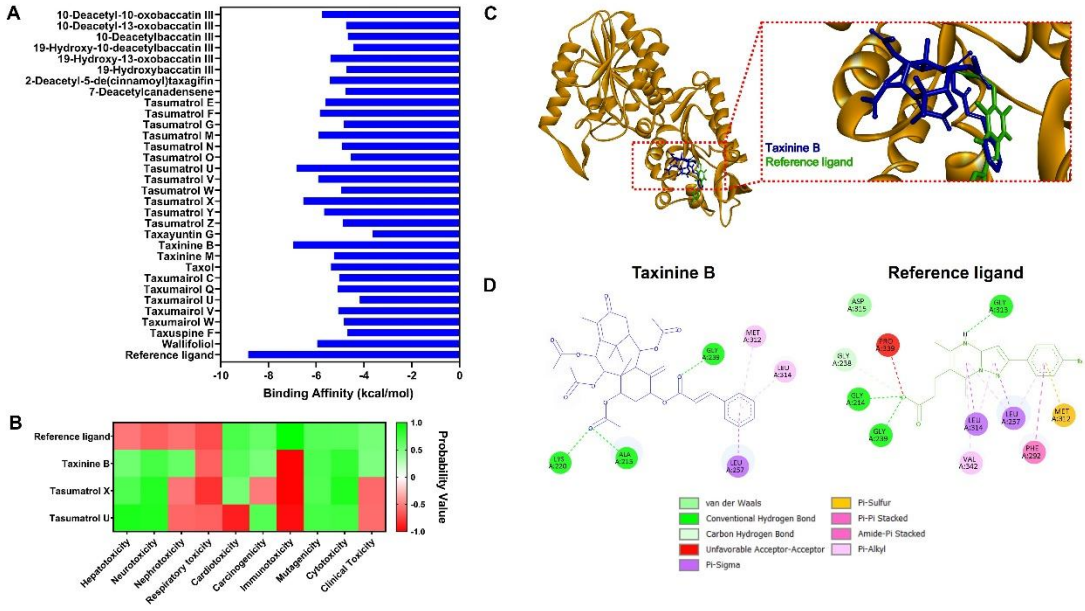

Figure 3. Virtual screening of *Taxus sumatrana* identified compounds, **(A)** Molecular docking results, **(B)** Toxicity screening, **(C)** Superimposition of Taxinine B and Reference ligand overlap on binding pocket of PGK1, **(D)** Molecular interaction of Taxinine B and Reference ligand with PGK1 residues.

4. CONCLUSION AND RECOMMENDATION

4.1 Conclusion

This study successfully predicted PGK1 as a significant poor prognosis biomarker in invasive breast cancer based on its elevated gene expression in primary tumor tissues and the most unfavorable survival outcomes from UALCAN analysis. These findings indicate that PGK1 plays an important role in breast cancer progression and may serve as a potential invasive breast cancer progression and may serve as potential therapeutic target. Molecular docking of 31 bioactive compounds from *Taxus sumatrana* revealed that taxinine B, tasumatrol U, and tasumatrol X showed the strongest binding affinities toward PGK1. Among them, taxinine B demonstrated the most favorable overall profile due to its strong binding interaction, overlapping binding mode with the reference

ligand, and acceptable predicted toxicity. Therefore, taxinine B may serve as a promising natural lead compound for developing PGK1-targeted therapy against invasive breast cancer.

4.2 Recommendation

Further studies are recommended to validate the inhibitory activity of taxinine B against PGK1 through *in vitro* enzymatic assays, breast cancer cell line experiments, and apoptosis or proliferation studies. In addition, molecular dynamics simulation should be carried out to confirm the stability of the PGK1-taxinine B complex under physiological conditions. Future *in vivo* studies are also necessary to evaluate pharmacokinetics, toxicity, and anticancer efficacy. Moreover, structural modifications of taxinine B may be explored to improve potency, selectivity, and drug-likeness for future therapeutic development.

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