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Network Pharmacology of Swietenolide from *Swietenia mahagoni* Jacq.: Putative Mechanisms Against Leukemia

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ABSTRACT

Leukemia is a type of cancer that can affect people of all ages and genders, and its cause is not yet known. This is exacerbated by an increasing trend, meaning that existing treatments are inadequate, therapy resistance, resulting in negatively impact for patients. The use of natural products can be a solution to this problem due to their multitarget effects. The use of swietenolide as a bioactive phytochemical from *Swietenia mahagoni* Jacq. can be used as an anti-leukemic agent. This study aims to explore the mechanism of swietenolide with target proteins as a treatment for leukemia using a network pharmacology approach. A predictive network depicting the relationship between swietenolide with leukemia was designed based on information collected from databases, namely Swiss Target Prediction (STP) version 2019, and DisGeNET version 2025. All databases accessed in October 2025. Identified overlapping targets related to both swietenolide with leukemia were crossed with information on biological processes (BPs) and molecular/signaling pathways using the ShinyGO and Cytoscape software. For the result, genes obtained from STP and DisGeNet, 111 and 438 genes, respectively, with the following results overlapping targets between swietenolide and leukemia gene targets produced 20 genes, with AKT1 showing the highest degree centrality score from the protein-protein interaction analysis results. Gene ontology from all genes showed biological processes related to apoptosis-multiple species and acute myeloid leukemia. AKT1 emerged as the top hub; AKT/mTOR signaling is implicated in Acute Myeloid Leukemia (AML) pathobiology. Inhibition of AKT1 expression is a key target that can reduce the proliferation and migratory activity of AML cells. As a result, this study successfully predicted the mechanism of action of swietenolide from mahogany seeds (*Swietenia mahagoni* Jacq.) using a network pharmacology analysis approach.

Keywords:
Swietenolide; *Swietenia mahagoni*; Network Pharmacology; AKT1; mTOR pathway; Acute Myeloid Leukemia

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1. Introduction

Leukemia is a type of cancer that affects the bone marrow and blood, causing the body to produce too many abnormal white blood cells. These cells can make the body

produce fewer healthy blood cells. This can lead to a range of complications, such as anaemia, bleeding disorders and a weakened immune system. The exact causes are unclear, but genetic mutations, radiation, chemicals and infections are associated with it [1]. The incidence and mortality rates of leukemia are also showing an upward trend, as more people are being diagnosed each year [2]. The findings indicate that current treatment regimens are inadequate, therapy resistance, resulting in negatively impact for patients. Therefore, there is need for safe and targeted therapeutic treatments, one of which is the use of natural products. Effect of phytochemicals from natural products as anticancer can be mediated by a variety of mechanisms, including apoptosis, modulation of the immune system and inhibition of angiogenesis [3].

Mahogani seed, from the mahogany (*Swietenia mahagoni* Jacq.), contains bioactive compounds like limonoids, flavonoids, and triterpenoids. It has shown potential anticancer effects against leukemia with multi-target approaches by inducing apoptosis, inhibiting cell growth, and modulating immune responses. Studies suggest its extracts affect cancer cell pathways through oxidative stress regulation, cell cycle arrest, and activation of apoptotic signals, making it a promising adjunct therapy for leukemia that requires further research to clarify its molecular targets and optimize efficacy [4]. Swietenolide is a plant-derived natural compound as marker of *Swietenia mahagoni* Jacq. that has been explored for its potential anticancer and specifically anti-leukemic effects. Medicinal plants and their bioactive compounds, such as swietenolide, have shown promise in cancer treatment due to their cytotoxicity toward leukemic cells and ability to induce apoptosis, inhibit proliferation, and modulate key signaling pathways involved in cancer progression.

One approach to elucidating the mechanism of swietenolide as an anti-leukemic agent is through network pharmacology analysis. Network pharmacology was proposed to predict the multiple interactions among structure from drugs with multiple targets from specific diseases [5], [6]. The present study aims to elucidate the mechanism of swietenolide, a biologically active phytochemicals from *Swietenia mahagoni* Jacq., as an anti-leukemic agent that targets multiple proteins and molecular pathways. This will be achieved by employing network pharmacology and bioinformatics tools.

2. Methods

Analysis of Swietenolide by Network Pharmacology

Overall, the design experiment of this research can be divided into two main topics; target predictions, and network analysis. All research procedures were conducted using the web-database in October 2025.

Potential targets of Swietenolide

Canonical SMILES of swietenolide from ChEMBL (https://www.ebi.ac.uk/chembl/) was used as the keyword in that database. Swietenolide target was obtained from SwissTargetPrediction (http://www.swisstargetprediction.ch) selected with human species. For the result, all genes with score probability were obtained then reduplicated and subjected to further analysis. UniProtKB (https://www.uniprot.org/) was used to standardize the nomenclature used and only human gene criteria were included.

Related targets of Leukemia

Related targets of leukemia were obtained from two databases, namely cBioPortal (https://www.cbioportal.org/); DisGeNet (https://www.disgenet.org). The keywords used were "Leukemia"; “Acute Myeloid Leukemia”; ”Lympoid Leukemia”. For the result, all genes were obtained then reduplicated and subjected to further

analysis. UniProtKB (https://www.uniprot.org/) was used to standardize the nomenclature used and only human gene criteria were included.

Overlapping Swietenolide and Leukemia targets and PPI network analysis

Target genes of swietenolide each overlapping with the leukemia gene targets using a Venn diagram using InteractiVenn (https://www.interactivenn.net/index2.html) [7]. Protein-protein interaction (PPI) network analysis using STRING (https://string-db.org/) and visualized with Cytoscape (ver. 3.10.0) and CytoHubba for determine the gene ranking based on Degree Centrality from largest to smallest.

Pathway and biological process enrichment analysis

Platform ShinyGO version 0.85 (http://bioinformatics.sdstate.edu/go/) is used for clustering and analyzing the Gene Ontology (GO) function, Kyoto Encyclopedia of Genes and Genomes (KEGG) mapping and visualization clustering tool. The species used is human, with FDR cutoff criteria of 0.05 and a pathway to show for 20.

3. Results and Discussion

Swietenia mahagoni (West Indian mahogany) exhibits diverse pharmacological effects, including, antidiabetic [8], anti-inflammatory, hepatoprotective [9], and antioxidant, antimicrobial, anticancer activities [10]. The activity of a plant is correlated with its phytochemical content. Swietenolide is a limonoid compound with the structure shown in **Figure 1** with InChlKey DTWMLACXVXYHJD-IPJXLRNBSA-N from PubChem database, which is a marker compound in mahogany seeds (*Swietenia mahagoni* Jacq.) [11].

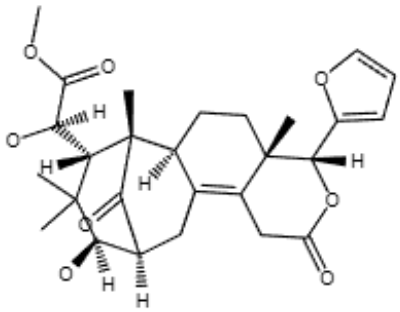


Figure 1. Structure of swietenolide

Swietenolide has been reported to have potent anticancer effects. The ethyl acetate fraction of mahogany seeds has an anticancer effect on T47D breast cancer [12]. Furthermore, the isolation of swietenolide from chloroform extracts of mahogany seeds has an anticancer effect on human colon carcinoma [13]. The mechanism of action of swietenolide in several types of cancer can provide a framework for the development of anticancer drugs, especially for leukemia. The mechanism of action of a drug can be predicted using a network pharmacology analysis approach, which utilises the structure of drug candidates with disease-causing gene targets using a representative database. Network pharmacology analysis accelerates mechanism of action prediction using a disease target gene-structure approach, thereby accelerating the development of new drug candidates that are more targeted and precise in their interaction with the cause of

the disease. Therefore, this study conducted a network pharmacology analysis of swietenolide from mahogany seeds (*Swietenia mahagoni* Jacq.) in leukemia.

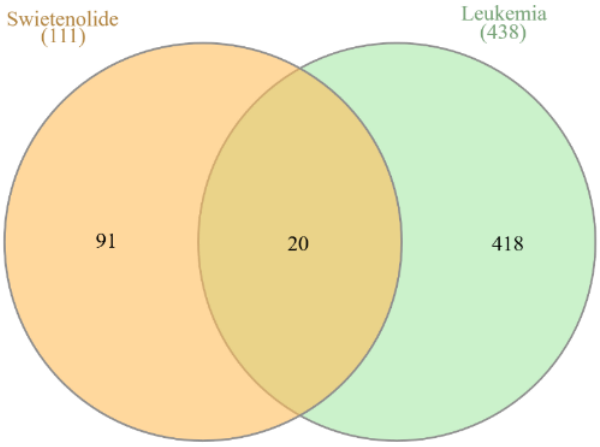


Figure 2. Venn diagram of overlapping gene targets

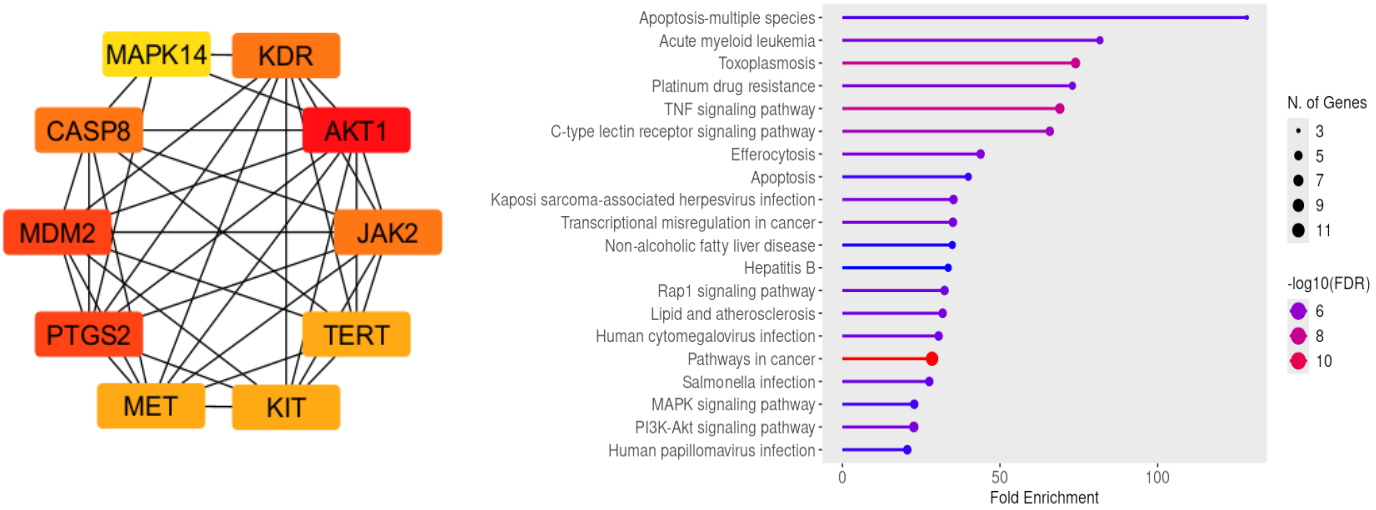
For the results, The STP gene targets from SMILES swietenolide and the target genes from the Cbioportal and Disgenet databases were obtained as 111, 115, and 492, respectively. After duplication and validation, the total number of human genes in swietenolide and leukaemia were obtained as 111 and 438, respectively. Network pharmacology analysis of swietenolide as an anti-leukemic agent obtained 20 gene targets from the overlapping results shown in **Figure 2**.

Table 1. Result of overlapping genes with Degree scores and Disease Specificity Index (DSI) scores

Rank	Gene Name	Degree Scores	DSI
1	AKT1	16.0	0.35
2	MDM2	12.0	0.36
2	PTGS2	12.0	0.31
4	CASP8	9.0	0.41
4	KDR	9.0	0
4	JAK2	9.0	0.36
7	MET	8.0	0.34
7	KIT	8.0	0.33
7	TERT	8.0	0.33
10	MAPK14	5.0	0.44

From **Table 1**, the top 10 gene targets were obtained based on the degree scores. The degree score is a quantitative measure of the importance of a gene within a protein-protein interaction (PPI) network. It is calculated by determining the total number of direct connections of the gene to other genes or proteins. Higher degree scores indicate that the gene has a greater influence on other genes. On the other hand, DSI shows the number of diseases that a gene or variant can cause. A high DSI indicates a gene or variant associated with a narrow set of diseases, while a low DSI suggests a broader range of associated diseases. In addition, protein-protein interactions of all target genes obtained were performed using CytoHubba with degree centrality parameters in

Cytoscape software. The degree centrality parameter was selected because it provides a comprehensive overview of how significantly a gene influences in hub-genes based on the analysis network used [14]. The results show that the gene AKT1 is strongly influenced by the effect of swietenolide on the leukaemia gene. This enables the gene to become a target for action by swietenolide, a potential anti-leukemic drug.



(a) **(b)**

Figure 3. (a) Protein-protein interaction (PPI) network of 10 tops hub gene targets, colored from red (higher degree) to yellow (lower degree) ; **(b)** GO /KEGG enrichment

The results of the degree centrality analysis on all target genes can be shown in **Figure 3a**, nodes are colored from red (higher degree) to yellow (lower degree) being AKT1, MDM2, PTGS2, CASP8, KDR, JAK2, MET, KIT, TERT, MAPK14, respectively. Furthermore, enrichment analysis was performed using gene ontology to determine the mechanism of all target genes, as shown in **Figure 3b**. All target genes obtained can be concluded to have functions in apoptosis-multiple species and acute myeloid leukemia. This proves that the predicted targets of swietenolide are indeed in line with the targets of leukemia. KEGG analysis of the AKT1 protein is located in the mTOR signalling pathway as the mechanism for the occurrence of Acute Myeloid Leukemia (AML), as shown in **Figure 4**.

In cases of AML patients, there is overexpression dan knockdown insulin receptor (INSR) that makes INSR facilitates the transition of cells from the G1 phase to the S phase, thus promoting the growth of AML cells. Moreover, INSR has been observed to upregulate vimentin and N-cadherin expression, thereby enhancing cell invasion and migration. Integration of the data on gene expression and its interactive analysis has revealed a correlation between the expression of the AKT1 gene and that of the INSR. However, it is also evident that the level of AKT1 expression is inversely proportional to the prognosis of AML patients. AKT1 has a critical function related to cell regulation, particularly cell apoptosis, autophagy regulation, and protein synthesis [15], [16]. Therefore, inhibition of AKT1 expression is a key target that can reduce the proliferation and migratory activity of AML cells.

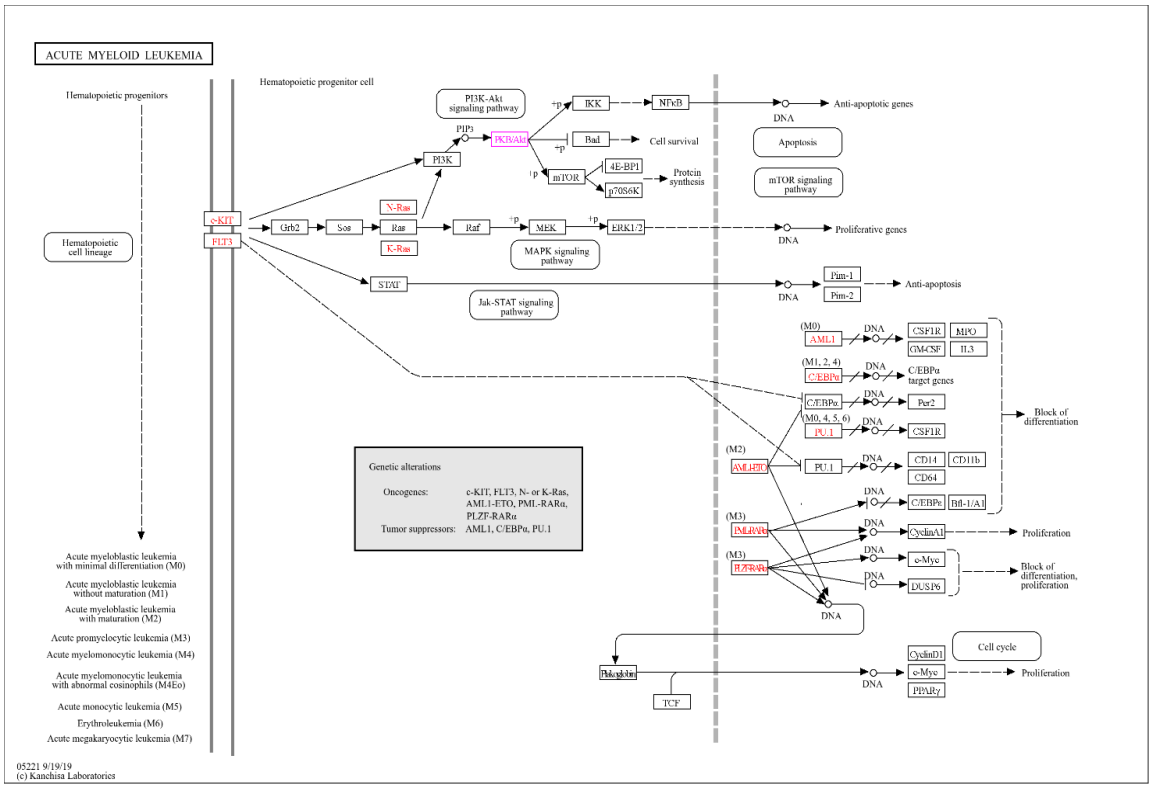


Figure 4. KEGG mapping analysis of AKT1

These findings correlate with the activity of swietenolide in mahogany seeds, which has been empirically and scientifically proven to be antidiabetic, with a mechanism of increasing apoptosis in insulinoma cell line (INS-1) cells, thereby promoting β-cell regeneration [8], [17], [18]. This analogy can also occur in cases of AML, where white blood cells improvement is expected. In other study, in silico study of *Swietenia macrophylla* on cancer, including AML, found that it has similar binding interactions with Venetoclax, a B-cell lymphoma inhibitor (BCL-2). However, the study did not specifically discuss swietenolide as an anti-leukemia agent [19].

Based on the network pharmacology analysis that has been conducted, the mechanism of action of swietenolide as an anti-leukemic agent is through the inhibition of AKT1 expression, which is the main target of leukemia treatment, so that swietenolide from mahogany seeds (*Swietenia mahagoni* Jacq.) can be a promising candidate for anti-leukemic agent. The mechanistic predictions can be validated with molecular docking and molecular dynamics in order to consolidate the predictions of the interrelationships between swietenolide and the AKT1 target gene for leukemia. However, due to limitations in this study, this was not carried out. The findings of this study indicate that further research is necessary in order to conduct in vivo and in vitro testing on swietenolide, a substance found in mahogany seeds, with a view to investigating its potential use as an anti-leukemic agent.

4. Conclusion

This network pharmacology analysis shows that AKT1 within PI3K/AKT/mTOR could be a target for swietenolide to change the pathways involved in leukemia. These are computational predictions that need to be confirmed using

molecular docking and molecular dynamics, as well as in vitro and in vivo AML models experiments (such as gene expression, phospho-AKT readouts, and viability/apoptosis).

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Conflicts of Interest:
The authors declare no conflict of interest regarding the publication of this paper.

References

[1] T. Patel and T. Bill, "Understanding leukemia and its clinical significance," *J. Appl. Biotechnol. Bioeng.*, vol. Volume 12, no. Issue 1, pp. 29–37, Mar. 2025. Available: https://medcraveonline.com/JABB/JABB-12-00381.php

[2] S. M. Syame, S. M. Mohamed, E. A. Elgabry, Y. A. A. Darwish, and A. S. Mansour, "Chemical characterization, antimicrobial, antioxidant, and cytotoxic potentials of *Swietenia mahagoni*," *AMB Express*, vol. 12, no. 1, p. e0325937, Jun. 2022. Available: https://doi.org/10.1186/s13568-022-01406-w

[3] P. C. Situmorang, S. Ilyas, S. E. Nugraha, R. A. Syahputra, and N. M. A. Nik Abd Rahman, "Prospects of compounds of herbal plants as anticancer agents: a comprehensive review from molecular pathways," *Front. Pharmacol.*, vol. 15, p. 1387866, Jul. 2024. Available: https://doi.org/10.3389/fphar.2024.1387866

[4] C. Cotoraci, A. Ciceu, A. Sasu, E. Miutescu, and A. Hermenean, "The Anti-Leukemic Activity of Natural Compounds," *Molecules*, vol. 26, no. 9, p. 2709, May 2021. Available: https://doi.org/10.3390/molecules26092709

[5] L. A. Usman *et al.*, "Network pharmacology analysis of phytochemicals in targeting cancer: A systems biology approach.," *J. Clin. Oncol.*, vol. 43, no. 16_suppl, Jun. 2025. Available: https://doi.org/10.1200/JCO.2025.43.16_suppl.e15130

[6] B. Wang *et al.*, "Insights into the mechanism of Arnebia euchroma on leukemia via network pharmacology approach," *BMC Complement. Med. Ther. 2020 201*, vol. 20, no. 1, pp. 322-, Oct. 2020. Available: https://doi.org/10.1186/s12906-020-03106-z

[7] H. Heberle, G. V. Meirelles, F. R. da Silva, G. P. Telles, and R. Minghim, "InteractiVenn: a web-based tool for the analysis of sets through Venn diagrams," *BMC Bioinformatics*, vol. 16, no. 1, p. 169, May 2015. Available: https://doi.org/10.1186/s12859-015-0611-3

[8] Sukardiman and M. Ervina, "The recent use of *Swietenia mahagoni* (L.) Jacq. as antidiabetes type 2 phytomedicine: A systematic review," *Heliyon*, vol. 6, no. 3, p. e03536, Mar. 2020. Available: https://doi.org/10.1016/j.heliyon.2020.e03536

[9] D. Roy *et al.*, "A Review on Phytochemical Studies and Biological Activities of *Swietenia mahagoni*," *Hum. Journals Rev.*, vol. 26, no. 1, pp. 422–434, 2022, Available: www.ijppr.humanjournals.com

[10] S. M. Syame, S. M. Mohamed, E. A. Elgabry, Y. A. A. Darwish, and A. S. Mansour, "Chemical characterization, antimicrobial, antioxidant, and cytotoxic potentials of *Swietenia mahagoni*," *AMB Express 2022 121*, vol. 12, no. 1, pp. 77-, Jun. 2022. Available: https://doi.org/10.1186/s13568-022-01406-w

[11] Ministry of Health, *Farmakope Herbal Indonesia*, II. Jakarta: Ministry of Health, Republic of Indonesia, 2017. Available:

https://farmalkes.kemkes.go.id/2020/08/farmakope-herbal-indonesia-edisi-ii-tahun-2017-3/

[12] D. Tohir, P. E. Wuyung, and R. Farida, "Anti-Cancer activity of *Swietenia mahagoni* seed extract in ethyl acetate-induced breast cancer cell T47D," *AIP Conf. Proc.*, vol. 2243, p. 020030, Jun. 2020. Available: https://doi.org/10.1063/5.0005908

[13] P. C. Pal, S. Nag, D. Jyothi, S. Das, K. Das Saha, and U. P. Singh, "Swietenolide isolated from Swietenia macrophylla King in Hook seeds shows in vitro anti-colorectal cancer activity through inhibition of mouse double minute 2 (MDM2) homolog," *Nat. Prod. Res.*, vol. 38, no. 12, pp. 2097–2104, Jun. 2024. Available: https://doi.org/10.1080/14786419.2023.2233045

[14] C. H. Chin, S. H. Chen, H. H. Wu, C. W. Ho, M. T. Ko, and C. Y. Lin, "cytoHubba: identifying hub objects and sub-networks from complex interactome," *BMC Syst. Biol.*, vol. 8, no. Suppl 4, p. S11, Dec. 2014. Available: https://doi.org/10.1186/1752-0509-8-s4-s11

[15] L. Lin *et al.*, "INSR/AKT1 axis promotes cells proliferation and migration in acute myeloid leukemia," *Biochim. Biophys. Acta - Mol. Basis Dis.*, p. 168132, Dec. 2025. Available: https://doi.org/10.1016/j.bbadis.2025.168132

[16] C. Evangelisti *et al.*, "Autophagy in acute leukemias: A double-edged sword with important therapeutic implications," *Biochim. Biophys. Acta - Mol. Cell Res.*, vol. 1853, no. 1, pp. 14–26, Jan. 2015. Available: https://doi.org/10.1016/j.bbamcr.2014.09.023

[17] J. Duan *et al.*, "Swietenine and swietenolide from Swietenia macrophylla king improve insulin secretion and attenuate apoptosis in H 2 O 2 induced INS-1 cells," *Environ. Toxicol.*, vol. 37, no. 11, pp. 2780–2792, Nov. 2022. Available: https://doi.org/10.1002/tox.23636

[18] J. Duan *et al.*, "Swietenine improved the progression of diabetic nephropathy through inhibiting ferroptosis via activating Akt/GSK-3β/Nrf2 signaling pathway," *J. Ethnopharmacol.*, vol. 349, p. 119981, Jun. 2025. Available: https://doi.org/10.1016/j.jep.2025.119981

[19] B. M, H. P, A. Kumar B, A. Kumar Reddy C, and P. Kumar P, "In Silico Modelling Studies to Identification of Lead Compounds from Swietenia Macrophylla Against Cancer," *J. Neonatal Surg.*, vol. 14, no. 25s, pp. 1045–1059, 2025. Available: https://www.jneonatalsurg.com/index.php/jns/article/view/6627