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Network Pharmacology of Ki Encok (*Plumbago zeylanica* Linn) Plant as A Treatment for Osteoarthritis

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Abstract: One of the plants in Indonesia used by the community to treat gout or Osteoarthritis (OA) is the Ki Encok plant (*Plumbago zeylanic*a Linn). However, it is currently unknown what active substances play a role in the therapy process for gout or OA and what the pathway is. This study aimed to predict the pharmacological mechanism of the active content of Encok leaves against OA disease. This study used an in silico experimental test. The content of active plant substances was extracted from IMPPAT and KNAPSACK. Then, the target proteins of all these active substances were searched for, including target proteins involved in OA disease, through the GeneCards database. Common targets were then analyzed using the STRING database. Pathways involved in OA therapy by *P. zeylanica* Linn were analyzed using Gene Ontology. The active *substances P. zeylanica* plant are 52 components with 163 protein targets. Proteins involved in the pathogenesis of OA were found to be 5,394 proteins. Common targets were found to be 100 proteins. After being analyzed based on degree, the top 10 common targets that may play a role are ALB, TNF, INS, AKT1, TP53, IL6, PPARG, ESR1, HIF1A, and JUN. The active compounds contained in *P. zeylanica* with target proteins that match OA are D-glucose, vanillic acid, beta-stigmasterol, isoorientin, and lupeol.

Keywords: network pharmacology, osteoarthritis, *Plumbago zeylanica*

Abstrak: *Salah satu tanaman di Indonesia yang dimanfaatkan oleh masyarakat untuk mengatasi encok atau Osteoarthritis (OA) adalah tanaman Ki Encok (Plumbago zeylanica Linn). Namun, saat ini belum diketahui zat aktif apa yang berperan dalam proses terapi encok atau OA serta bagaimana jalur metabolismenya. Tujuan penelitian ini adalah untuk memprediksi mekanisme kerja farmakologi kandungan aktif daun encok terhadap penyakit OA. Penelitian ini menggunakan uji eksperimen in silico. Kandungan zat aktif tanaman disarikan dari IMPPAT dan KNAPSACK lalu dicari protein target dari semua zat aktif tersebut. Protein target yang terlibat dalam penyakit OA dicari melalui database GeneCards. Protein target lalu dianalisis dengan STRING database. Jalur metabolisme yang terlibat dalam terapi OA oleh P. zeylanica dianalisis dengan Gene Ontology. Zat aktif tanaman P. zeylanica sebanyak 52 komponen dengan target 163 protein. Protein yang terlibat dalam patogenesis OA ditemukan sebanyak 5.394 protein. Protein target yang ditemukan sebanyak 100 protein. Setelah dianalisis berdasarkan jumlah interaksi antara protein yang satu dengan protein lain d idapatkan 10 protein target teratas yang mungkin berperan yaitu ALB, TNF, INS, AKT1, TP53, IL6, PPARG, ESR1, HIF1A, dan JUN. Senyawa aktif yang terkandung dalam P. zeylanica dengan protein target yang sesuai dengan OA adalah D-glucose, vanillic acid, beta-stigmasterol, isoorientin, dan lupeol.*

Kata kunci: *network pharmacology, osteoarthritis, Plumbago zeylanica*

INTRODUCTION

Osteoarthritis (OA) is a chronic joint disease that often occurs due to degeneration of joint cartilage and causes pain, disability in movement, loss of joint function, decreased quality of life, and economic burden (Coaccioli *et al*. 2022). This disease is often found in women aged 60-74 (Muhyi *et al*. 2023). In addition, obesity is also often found in OA sufferers (Syifaa *et al*. 2022).

One of the treatments for OA is to use non-steroidal anti-inflammatory drugs (NSAIDs) such as sodium diclofenac and piroxicam. NSAIDs work by inhibiting the enzyme cyclooxygenase, which causes inflammation in the joints. The side effects of

NSAIDs, if consumed for a long time, are gastrointestinal disorders such as stomach bleeding (Magni *et al*. 2021). Therefore, it is necessary to find alternative drugs that can help reduce joint inflammation and provide milder side effects or even none.

One of the plants in Indonesia that is used by the community to treat OA is the Ki Encok leaves. The function of this plant is that the leaves paste applied to the skin of body parts that experience joint pain or rheumatism, so this plant is called the Rheumatism Leaf plant (Santoso 2022). The Latin name for this plant is *Plumbago zeylanica* Linn. The active components of *P. zeylanica* in the leaves have not been studied much compared to the roots. The active substances contained in the *P. zeylanica* leaf include 1-Undecanol, Hexanedioic acid, bis (2-ethylhexyl) ester, Tributyl acetylcitrate, Dodecyl acrylate, Phytol, Decyl propanoate, Dodecyl dodecanoate, Lauric acid (dodecanoic acid), Dibutyl decanedioate, Lupeol, Beta-sitosterol, and Plumbagin (Purwoko *et al*. 2022). Beta-sitosterol is known to have an angiogenesis inhibiting effect on joint synovial membranes which can inhibit joint swelling (Qian *et al*. 2022). Lauric acid has been studied to have anti-inflammatory activity in previous in vitro and in vivo studies (Mustafa *et al*. 2025). Previous study in animal model of rheumatoid arthritis showed that ethanol extract of *P. zeylanica* root reduced serum levels of inflammatory biomarkers and expression of the enzyme cyclooxygenase 2 (Das *et al*. 2025).

However, it is currently unknown what active substances play a role in the therapy process for gout or Osteoarthritis and what the pathway is. This study aimed to identify the network pharmacology between the target protein of active substances contained in PZ and the protein involved in OA and analyze the pathway.

MATERIALS AND METHOD

Step 1. Identify active compounds of *Plumbago zeylanica*

Identification of the active substance content of the P. *zeylanica* plant was carried out through the Indian Medicinal Plants, Phytochemistry, and Therapeutics (IMPPAT) database (https://cb.imsc.res.in/imppat/basicsearch/phytochemical) accessed on January 22, 2025 and KNAPSACK (https://www.knapsackfamily.com/knapsack_core/top.php) accessed on January 04, 2025.

Step 2. Identify Target Proteins

The target protein of each active compound of *Plumbago zeylanica* was searched through the IMPPAT database (https://cb.imsc.res.in/imppat/basicsearch/phytochemical). The target protein involved in OA was searched in the Genecards database (https://www.genecards.org/) accessed January 23, 2025. The target proteins of the active compounds and a list of proteins involved in OA disease were submitted into a Venn diagram application (http://bioinformatics.psb.ugent.be/webtools/Venn/).

Step 3. Network Analysis

Proteins in the intersection area (common target) were analyzed for their network using the STRING database (https://string-db.org/). The parameters used in the use of STRING are Homo sapiens organisms, Network type: complete STRING network, Score: Highest confidence interaction (0.9), and FDR stringency medium 5 percent. Search for the top 10 proteins based on degree centrality (DC), closeness centrality (CC), and betweenness centrality (BC) using the CytoHubba application installed in the Cytoscape application. The cut-off value for DC is 3, for CC, 0.01, and for BC, 0.044.

Step 4. Gene Ontology

The Gene Ontology database identifies pathways involving overlapping common targets (https://geneontology.org/).

Hardware

This research was conducted with hardware in the form of a laptop with the Macbook Air system model specifications with Apple M2 Chip, 8-core CPU, 8-core GPU, 16-core Neural Engine, 8-gigabyte RAM, and macOS Sequoia. The software used is STRING 12.0 (https://string-db.org/), Cytoscape 3.10.3, and CytoNCA 2.1.6.

RESULT AND DISSCUSION

The results of the identification of the active substance content of the *P. zeylanica* plant from the IMPPAT and KNAPSACK databases were 52 components. The target proteins of the 52 components were collected from the IMPPAT database and Herbal Ingredients' Targets Platform (HIT 2.0) database as many as 185 proteins (Table 1). After removing the duplicate proteins, 163 proteins were obtained. Proteins involved in the pathogenesis of OA were found as many as 5,394 proteins from the GeneCards database.

The target proteins that overlap in the Venn diagram in Figure 2 are 100 proteins. The one hundred proteins were then analyzed using the STRING Cytoscape application to see protein-protein interactions (Figure 1). In the STRING analysis process, the VEGFA protein cannot be found in the software, so it cannot appear in the protein-protein interactions.

The screening results using CytoCNA based on the degree with a cut-off value of 3 obtained the top 10 common target proteins (Table 2). The ALB protein holds the highest Degree and BC scores.

Data filtering was performed to obtain the top 10 targets of *Plumbago zeylanica* in OA, namely ALB, TNF, INS, AKT1, TP53, IL6, PPARG, ESR1, HIF1A, and JUN (Table 2). ALB has the highest DC

Table 1. Active substance content of *Plumbago zeylanica* L. and prediction of its target protein.

No	Active Substances	Target Proteins
1	Ficusin	KCNC1, SOD1, MAOA, DCLRE1B, MAOB, UPP2
2	Seselin	-
3	Isoorientin	AKT1, NFE2L2
4	Isovitexin	-
5	Glycine	AHCY, F9, HSPA8, IFNG, APOB, BHMT2, BHMT, ABR, CASP3 CHDH, SLC6A13, SLC6A12, F8, TLR4, MTHFR, ALDH7A1
6	L-Tryptophan	-
7	1-Methyl-beta-carboline	MAOB, DBI
8	Xanthyletin	-
9	Droserone	-
10	Plumbagin	MAPK1, DHODH, CDKN1A, NR0B2, MAPK3, SOD1, AKT1, UGT1A1, NFE2, SLC2A4, UGT1A10, UGT1A9, SRC, MAPK8, UGT1A7, UGT1A8, CXCR4, TOP2B, TOP2A
11	beta-Sitosterol	APOE, ABCG5, ABCB11, ICAM1, ABCG8, CYP7A1, CASP3, SREBF1, SREBF2, DHCR24
12	beta-Stigmasterol	SLCO1B1, ABCG5, ABCG8, IL8, ABCA1, TNF, IL10
13	alpha-Amyrin	-
14	beta-Amyrin	-
15	Lupeol	TP53, MITF, CTNNB1, PTEN
16	Lupeol acetate	-
17	Taraxasterol	PTGS2
18	Quercetin 3-O-alpha-L-rhamnoside	CYP1B1, AKR1B1, CYP3A4, RPS6KA3, CYP1A1, RPS6KA1
19	Isoaffinetin	-
20	Neoechinulin A	-
21	3-O-beta-D-Glucopyranosyl sitosterol	-
22	Isoshinanolone	-
23	Friedelanol	-
24	Xanthoxyletin	-
25	3,3'-Biplumbagin	-
26	Chitranone	-
27	Elliptinone	-
28	Isozeylanone	-
29	Maritinone	-
30	Calendol	-
31	3'-O-beta-Glucopyranosyl plumbagic acid	-
32	3'-O-beta-Glucopyranosyl plumbagic acid methyl ester	-
33	5-Methoxyseselin	-
34	Suberosin	NFATC3, RELA
35	2,5-Dimethyl-7-hydroxychromone	-
36	Androsta-1,4-diene-3,17-dione	-
37	Plumbagic acid	-
38	Isozeylanone	-

Table 1. Active substance content of *Plumbago zeylanica* L. and prediction of its target protein (**Continued**)

No	Active Substances	Target Proteins
39	Plumbazeylanone	-
40	(2,2'-Binaphthalene)-5,5',8,8'-tetrone, 1,1'-dihydroxy-6,6'-dimethyl-	-
41	3-Chloro-5-hydroxy-2-methylnaphthalene-1,4-dione	-
42	Zeylanone	-
43	5-Hydroxy-8-(4-hydroxy-7-methyl-5,8-dioxonaphthalen-1-yl)-2-methylnaphthalene-1,4-dione	-
44	Methylnaphthazarin	F2, NQO1, F9, GGCX, PROC, PROS1
45	D-Glucose	CEACAM1, ESR1, MAPK1, HMOX1, NFKBIA, GLA, RETN, TGFB1, NAMPT, SERPINE1, GCK, CCL2, MAPK14, MOGS, INS, G6PC, IL6, SMAD2, MAPK3, TREH, LCT, SI, NNT, SLC2A9, PPARGC1A, G6PC3, TP53, AKT1, GJA1, HK2, HK3, AGL, ALB, TNFRSF11B, NOS3, CKB, LALBA, INSR, IRS1, PRKCB, CEBPB, GAA, IL8, GLB1, B4GALT2, CASP3, ADPGK, LEP, GBA, PKM, SLC2A2, GSK3B, GANC, NR1I2, GANAB, ACACA, PRKAA1, HKDC1, FN1, RAC1, FAM3B, MAP3K5, MAPK8, SOD2, JUN, PRKAA2, VEGFA, IRS2, SLC2A5, TBC1D4, GBA2, FOXO1, B4GALT1, PDX1, PC, NUPR1, SLC2A11, SLC2A7, RELA, HK1, CEBPD, PRKCA, SLC2A1, CEBPA, MGAM
46	D-Fructose	-
47	((1S,5R,6S)-5-(Benzoyloxy)-1,6-dihydroxy-2-oxocyclohex-3-en-1-yl)methyl benzoate	-
48	Indole-3-carboxaldehyde	AOX1, XDH
49	Vanillic acid	PPARG, TYR, CEBPA, CA3, HIF1A, NOS3, TYRP1
50	4-Hydroxybenzaldehyde	ALDH5A1
51	Cinnamic acid	HAL, TYR, ADIPOQ, UGT1A10, UGT1A7, UGT1A8, KDM1A, UGT1A3, RCOR1
52	7-Hydroxy-2,5-dimethyl-4H-1-benzopyran-4-one	-

score, BC, and CC value compared to other targets. A higher CC means that ALB has a good position in the protein network, and a high BC means that ALB functions well as a mediator of information between common target proteins in the network. A protein degree value 75 indicates that 75 other common target proteins can interact with ALB (Chen *et al*. 2019).

Molecularly, knee OA is divided into four stages: pre-OA, early OA, progressive OA, and end-stage OA. The cytokine TNF is involved in the early process of knee OA and the progression stage of knee OA (Lv *et al*. 2021). TNF protein likely plays a vital role in the inflammatory process of OA. Serum TNF increased in mice induced with monosodium iodoacetate to become OA compared to normal mice. Administration of TNF alpha inhibitors to OA mice showed a decrease in Mankin scores, inhibited inflammatory cell infiltration, and reduced bone destruction in joints and cartilage (Li *et al*. 2018). IL-6 and IL-17 work synergistically with IL-1β and TNF-α in inducing the release of inflammatory mediators in joint tissue affected by OA (Stefik *et al*. 2021).

Human serum albumin encoded by the ALB gene creates a conducive environment for infiltrating, maintaining, and differentiating stem cells in the knee joint. In addition, serum albumin is also thought to be involved in the anti-inflammatory prostaglandin pathway involving Cyclooxygenase 2 (Sheridan 2018).

The AKT1 gene is involved in the PI3K/AKT/mTOR signaling pathway. This pathway experiences increased activity in the cartilage cells of OA patients and OA mice. Continuous activation of the Akt pathway causes the accumulation of reactive oxygen species and stimulates chondrocyte aging. Chondrocyte aging is one of the characteristics of OA (Xie *et al.* 2019).

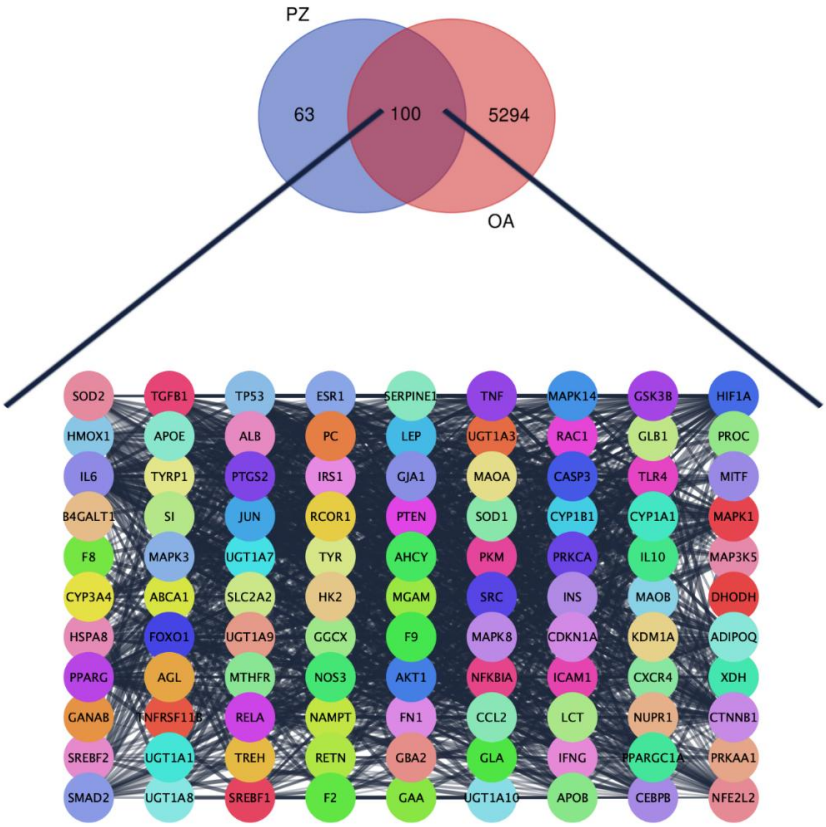

Figure 2. Venn diagram between the active ingredient content of *P. zeylanica* leaves and its predicted target proteins. The intersection shows 100 proteins (common target). The circular image at the bottom is the network between the 100 common target proteins.

Table 2. Scores of the Top 10 *Plumbago zeylanica* linn targets for OA

UniProt ID	Node	Active substance in PZ	Degree	BC	CC
P02768	ALB	D-glucose	75.0	836.0439	0.8640777
P01375	TNF	Beta-stigmasterol D-glucose	69.0	401.52747	0.8165138
P01308	INS	D-glucose	69.0	220.49315	0.8165138
P31749	AKT1	Isoorientin Plumbagin D-glucose	69.0	242.41028	0.8165138
P04637	TP53	D-glucose Lupeol D-glucose	69.0	362.08475	0.8165138
P05231	IL6	D-glucose	68.0	251.94061	0.8090909
P37231	PPARG	Vanilic acid D-glucose	66.0	248.99127	0.79464287
P03372	ESR1	D-glucose	60.0	240.8512	0.7542373
Q16665	HIF1A	Vanillic acid	59.0	104.075584	0.7478992
P05412	JUN	D-glucose	58.0	137.63188	0.7416667

BC= betweenness centrality; CC= closeness centrality

Table 3. Gene ontology enrichment pathway involving common target proteins

No	Pathway	Count	Gene Name
1	AMPK signalling	10	IRS1, AKT1, SREBF1, ADIPOQ, PPARG, PRKAA1, RELA, FOXO1, XDH, PC
2	Acute inflammatory response	12	B4GALT1, TNF, UGT1A1, F2, F8, PPARG, NUPR1, CEBPB, RETN, FOXO1, NOS3, NFKBIA

The INS gene encodes the Insulin protein, which is not directly involved in the occurrence of OA. Human chondrocytes show functional insulin receptors (Rosa *et al*. 2011). Type 2 Diabetes Mellitus disease, which shows Insulin resistance, causes loss of insulin receptor sensitivity to Insulin. This is thought to cause a decrease in the survival and differentiation process of chondrocytes, resulting in OA progression (Malaguarnera *et al*. 2012).

Apoptosis positively correlates with the severity of cartilage damage and matrix thinning in human osteoarthritis tissue specimens. Freshly isolated chondrocytes from human OA cartilage show morphological evidence of apoptosis, clear cytoplasmic cell surface spots, altered nuclear shape, apoptotic bodies, and parallel loss of atomic volume. This is not found in chondrocytes from regular donors (Musumeci *et al*. 2015). One of the proteins that can trigger the activation of the internal apoptosis pathway through Caspase-3 is the p53 protein encoded by the TP53 gene (Xu-Chang *et al.* 2019).

The ESR1 gene encodes the estrogen receptor alpha (ERα) protein. A study found ERα levels in damaged cartilage in OA patients and OA model mice decreased significantly compared to normal cartilage. The experimental animal model with the ESR1 gene damaged showed an increase in several molecular markers of aging OA chondrocytes (Wang *et al.* 2022).

Peroxisome proliferator-activated receptor gamma (PPARγ) is a transcription factor encoded by the PPARG gene. This transcription factor, when activated, forms a heterodimer with the retinol X receptor and then binds to a specific reaction element, thereby increasing the expression of the target gene. Western blotting and qRT-PCR tests showed decreased PPARγ protein regulation in knee cartilage damaged by OA. This protein regulates chondrocyte apoptosis through the mitochondrial caspase-3 pathway (Yuan *et al*. 2024).

The HIF1A gene encodes the transcription factor hypoxia-inducible factor-1 alpha. This transcription factor responds to decreased cellular oxygenation in tissues (Warbrick & Rabkin 2019). If there is a decrease in oxygenation, HIF1A will change metabolism from oxidative to glycolysis. In addition, HIF1A plays a role in increasing the synthesis of the cytokine IL-1β, a pro-inflammatory cytokine. Things that induce HIF1A expression in chondrocytes are catabolic stress, IL-1β, and oxidative stress (Zeng *et al.* 2022).

The AP-1 transcription factor subunit gene or Jun proto-oncogene (JUN) has decreased expression in OA mice induced by ACLT and aging chondrocytes (Xie *et al*. 2023). Aging chondrocytes cause OA by destroying extracellular matrix homeostasis (Xie *et al*. 2021).

The active compounds contained in Plumbago zeylanica with target proteins that correspond to OA are D-glucose, vanillic acid, beta-stigmasterol, isoorientin, and lupeol (Table 2).

CONCLUSION

Plumbago zeylanica contains some active compounds that have shown good potential for acting as a treatment for osteoarthritis. Future in vivo studies can determine the interactions between D-glucose, vanillic acid, beta-stigmasterol, isoorientin, lupeol, and Osteoarthritis-related proteins ALB, TNF, INS, AKT1, TP53, IL6, PPARG, ESR1, HIF1A, and JUN.

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