INTISARI

Neuropati perifer diabetik (DPN) adalah komplikasi umum diabetes yang menyebabkan kerusakan saraf progresif, nyeri kronis, dan disabilitas. Pengobatan saat ini terutama menawarkan peredaan gejala, menyoroti kebutuhan akan agen terapeutik baru. Andrografolid, lakton diterpen bioaktif dari *Andrographis paniculata*, dilaporkan memiliki sifat anti-inflamasi, antioksidan, dan neuroprotektif, menjadikannya kandidat potensial untuk terapi DPN.

Differentially expressed genes (DEGs) neuropati perifer diabetik diidentifikasi menggunakan paket DESeq2 yang diterapkan pada data gabungan dari GSE193571 dan GSE148059. Analisis KEGG *pathways* dan *Gene Ontology* dilakukan untuk mengeksplorasi *pathways* biologis terkait dan mengidentifikasi protein target. *Hub genes* diidentifikasi dengan mengiriskan DEG neuropati perifer dan DEG andrografolid, serta melakukan analisis interaksi protein-protein menggunakan 11 metode analisis topologi *plugin* CytoHubba pada Cytoscape. *Molecular docking* menggunakan PLANTS dilakukan untuk mengevaluasi afinitas pengikatan andrografolid terhadap protein yang dikode oleh *hub genes*, dibandingkan dengan ligan referensi, substrat endogen, dan senyawa obat pembanding.

Analisis *pathways enrichment* DEG neuropati perifer diabetik mengungkapkan hubungan signifikan antara remodeling matriks ekstraseluler, pensinyalan AGE–RAGE, pensinyalan kalsium, RNA non-koding, dan *phospholipase D* dengan neuropati perifer diabetik. Kami menggunakan *phospholipase D2* dan *matrix metalloproteinase* 9 sebagai target *molecular docking* karena 2 protein ini mempengaruhi *pathways* signifikan hasil analisis Analisis KEGG *pathways* dan *Gene Ontology*. *Hub genes* yang digunakan untuk menemukan target *molecular docking* adalah *BCL2*, *CCNB1*, *CDK1*, *CDK2*, *PPARG*, *TGFBR2*, *BRCA1*, *EZH2*, dan *AURKB*. Hasil pengurutan *hub genes* berdasarkan *log2FoldChange* dan p *adj* memberikan beberapa gen yang layak

diteliti lebih lanjut. Gen-gen tersebut adalah *TGFBR2*, *PPARG*, *BCL2*, *CCNB1*, *CDK1*, dan *AURKB*.

Molecular docking menunjukkan interaksi yang kuat dari andrografolid terhadap *phospholipase D2* (-84,05603) dan *b-cell lymphoma* 2 (-72,03838), dengan rata-rata *docking score* lebih tinggi dari ligan referensi. Kesimpulan yang dapat diambil adalah andrografolid dapat digunakan sebagai terapi potensial DPN karena kemampuannya dalam mempengaruhi ekspresi *hub genes* dan berinteraksi dengan protein *phospholipase D2 dan b-cell lymphoma 2*.

Kata Kunci: **neuropati perifer diabetik, andrografolid, *molecular docking, hub genes, differentially expressed genes***

ABSTRACT

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes that causes progressive nerve damage, chronic pain, and disability. Current treatments primarily offer symptom relief, highlighting the need for new therapeutic agents. Andrographolide, a bioactive diterpene lactone from Andrographis paniculata, has been reported to possess anti-inflammatory, antioxidant, and neuroprotective properties, making it a potential candidate for DPN therapy.

Differentially expressed genes (DEG) in diabetic peripheral neuropathy were identified using the DESeq2 package applied to combined data from GSE193571 and GSE148059. KEGG pathway and Gene Ontology analysis were performed to explore related biological pathways and identify target proteins. The hub genes were identified by overlapping DPN DEG and andrographolide DEG, and performing protein-protein interaction analysis using 10 topology analysis methods of CytoHubba plugin in Cytoscape. Molecular docking using PLANTS was performed to evaluate the binding affinity of andrographolide to the protein encoded by the hub gene, compared to the reference ligand, native ligand, and drug compound.

Enriched pathway analysis revealed significant associations with extracellular matrix remodeling, AGE-RAGE signaling, calcium signaling, non-coding RNA, and phospholipase D. We used Phospholipase D2 and matrix metalloproteinase 9 as molecular docking targets because they affect significant pathways in DPN. The key genes used to find the molecular docking targets were BCL2, CCNB1, CDK1, CDK2, PPARG, TGFBR2, BRCA1, EZH2, and AURKB. Molecular docking showed strong interactions of andrographolide with phospholipase D2 (-84.05603) and b-cell lymphoma 2 (-72.03838), with docking scores mean higher than the reference ligand. The results of ranking hub genes based on log2FoldChange and p adj provide several genes worthy of further investigation. These genes are TGFBR2, PPARG, BCL2, CCNB1, CDK1, and AURKB.

We conclude that andrographolide can be used as a potential therapy for DPN due to its ability to influence the expression of hub genes and interact with phospholipase D2 and b-cell lymphoma 2.

Keywords**: **diabetic peripheral neuropathy, andrographolide, molecular docking, hub genes, differentially expressed genes