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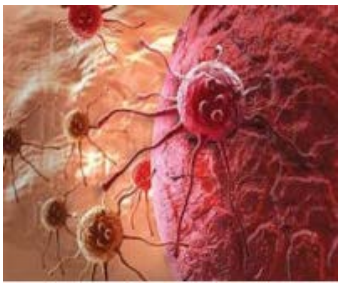

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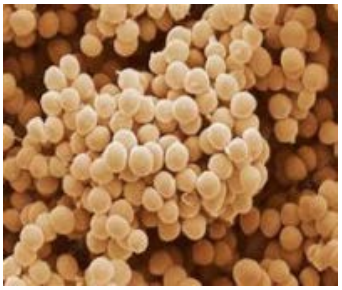

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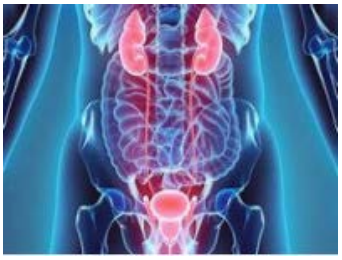

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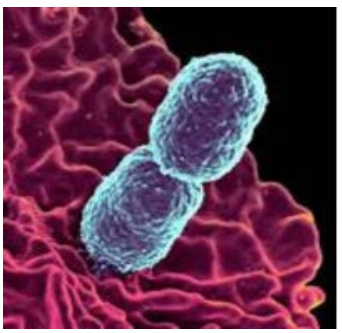

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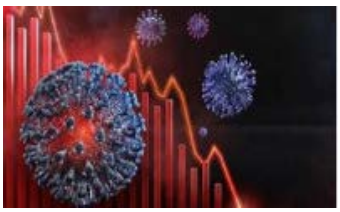

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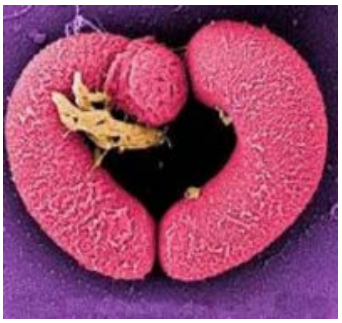

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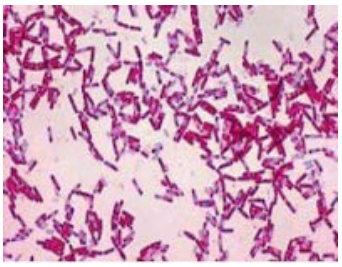

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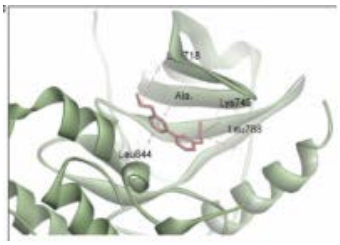

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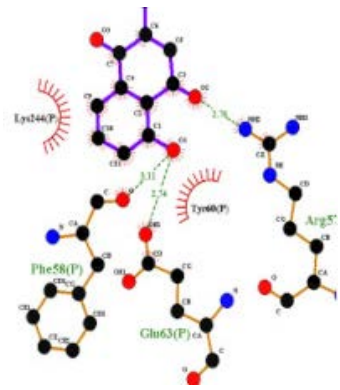

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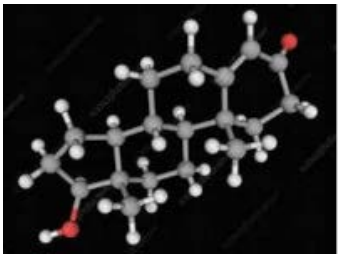

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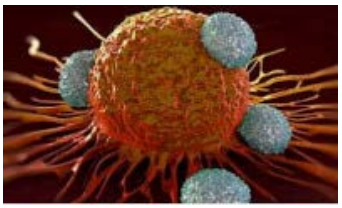

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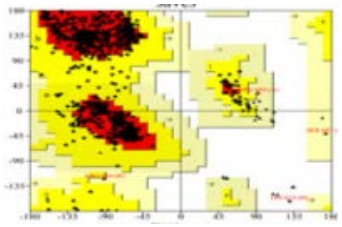

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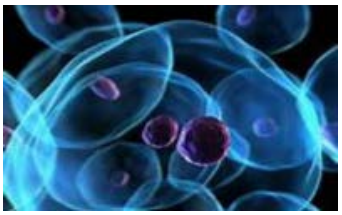

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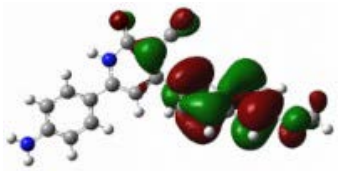

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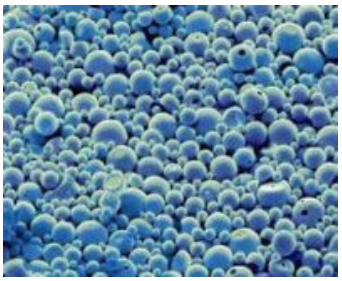

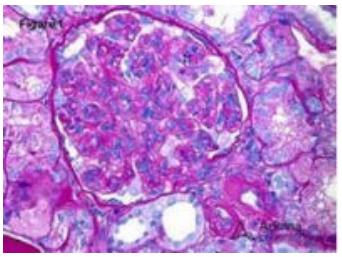

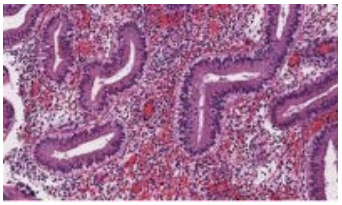

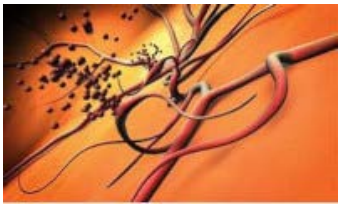

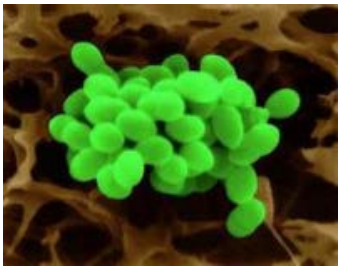

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Original Research Article

Molecular Cascade of Neolignan as A Natural Anti-Diabetics Agent: A Bioinformatics Approach

Yustina S. Hartini, Brigitta A. Maharani, Kadek A. Widyantara, Bakti W. Saputra, Dewi Setyaningsih, Agustina Setiawati*

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ABSTRACT

In cases of chronic diabetes, hyperglycemia triggers the activation of various molecular pathways. To control hyperglycemia in diabetic patients, anti-diabetic agents should precisely target these specific molecular pathways or elaborate on protein targets within the molecular cascade. However, it's important to note that anti-diabetic medications often come with significant side effects, including the risk of hypoglycemic coma and potential liver and kidney complications. Therefore, the inclusion of medicinal plants with anti-hypoglycemic properties continues to be crucial for diabetes management.

Neolignan, a biosynthesis product of the shikimate pathway in plants, has previously shown *in vitro* anti-diabetic activity. This study was designed to identify neolignan's multiple molecular targets and its molecular cascade for inhibiting diabetes. The researchers mined online databases for genes related to diabetes and hyperglycemia, as well as genes affected by neolignan. The Venn diagram result of these genes was further utilized to figure out a network of protein-protein interaction and gene clustering.

In summary, the study identified proteins targeted by neolignan, which include IGFR-1, EGFR, the inflammatory cytokine TNF-α, the chaperone protein Hsp90, as well as various downstream signaling molecules such as MAPK8, SCR, PI3K, and JAK1. These proteins work in concert during neolignan treatment to support its anti-diabetic activity. This research provides an initial glimpse into the molecular mechanisms of neolignan in diabetes treatment.

***Keywords*:** Neolignan, gene targets, diabetes, bioinformatics.

Introduction

Globally, diabetes mellitus increased fourfold over the past three decades and currently ranks as the ninth most common cause of mortality.[1] The prevalence is rapidly increasing and is now recognized as a major contributor to cardiovascular disease.[2] Two main categories of diabetes are distinguished: type 1 diabetes mellitus (T1DM), which results from the complete absence of insulin secretion, and type 2 diabetes (T2D). Type 2 diabetes is the most prevalent, constituting over 90% of all diabetes cases, and it has reached the status of a global pandemic.[1] The widespread occurrence of diabetes mellitus and its associated complications presents a significant and pervasive global health hazard.[1,3] Maintaining strict glycemic control can effectively deter the initiation and progression of complications associated with diabetes.[4]

Type 2 diabetes mellitus (T2DM) stands as the most widespread metabolic condition, marked by persistent high blood sugar levels and a limited reaction of peripheral tissues to insulin in the bloodstream, which leads to insulin resistance.[5] Elevated levels of sugar in the blood, referred to as hyperglycemia, play a central role in the development of complications associated with diabetes.

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In cases of long-term diabetes, hyperglycemia sets off the activation of various biochemical pathways, which include the hexosamine biosynthetic pathway, protein kinase C, the sorbitol–aldose reductase pathway, and mitogen-activated protein kinases (MAPKs).[6,7] Furthermore, hyperglycemia results in an increased expression of growth factors and cytokines such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), insulin-like growth factor (IGF), platelet-derived growth factor, and tumor necrosis factor-α (TNF-α).[8,9] Reactive oxygen species (ROS) have a critical role in orchestrating these processes and activating intracellular signaling and transcription pathways, with nuclear factor kappa B (NF-kB) and MAPKs playing significant roles.[10] Thus, some anti-hyperglycemic agents work by inhibiting the activity of α-glucosidase enzymes located in the small intestine. It converts oligosaccharides and disaccharides into monosaccharides, a crucial step for the absorption of nutrients in the gastrointestinal system.[11] Therefore, to control hyperglycemia in diabetes patients, the anti-diabetic agent should precisely address those molecular pathways of diabetes, or elaborate protein targets in the molecular cascade.

Treatment approaches for diabetes have advanced in recent decades. Nevertheless, anti-diabetic medications come with significant side effects, including the risk of experiencing a coma as a result of low blood sugar levels and potential liver and kidney complications.[12] The World Health Organization (WHO) advises incorporating medicinal plants into food for managing DM.[13,14] In developing countries, at least four billion people utilize medicinal plants to address metabolic conditions like DM.[14,15,16] Different medicinal plants or plant extracts that include chemical components such as flavonoids, alkaloids, phenolic compounds, terpenoids, saponins, and phytosterols have shown effectiveness in treating complications associated with diabetes. This efficacy can be linked to their ability to improve chronic high blood sugar levels, reduce oxidative stress, and influence various metabolic processes that play a role in the development of diabetic complications.[11] Hence, the inclusion of medicinal plants with anti-

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hypoglycemic properties continues to be crucial for diabetes management. Scientific studies have demonstrated their effectiveness in reducing blood sugar levels, as evidenced by both pre-clinical and clinical research.[17,18] One of the natural compounds exhibiting anti-diabetics activity is neolignan which exists in various plants.[2] Neolignan from *Viburnum macrocephalum* inhibited α-glucosidase, comparable with acarbose, a commercial anti-diabetic agent.[19] Neolignan-containing plant extract, *Piper crocatum*, inhibited *in vitro* α-glucosidase and α-amylase enzyme.[20] The impeded activity of α-glucosidase disrupts the absorption of carbohydrates in the intestine, with a rapid onset of action but relatively low effectiveness.[21] Neolignans linked to 2-styryl-1,3-dioxane at 8-9' containing *Torreya yunnanensis* inhibited *in vitro* phosphodiesterase 9A (PDE9A) activity which plays a crucial role in insulin secretion.[22] Thus, neolignan-containing extract of the leaves of *Eugenia sonderiana* has shown remarkable effectiveness in both *in vitro* and *in vivo* for decreasing blood glucose levels and enhancing diabetic conditions through the inhibition of amylase and glucosidase activity, as evidenced in studies involving diabetic mice.[23] Thus, neolignan's ability to impair hyperglycemia may elaborate other molecular mechanisms. Therefore, the comprehensive molecular pathway mechanisms of neolignan for impeding the progression of diabetes are interesting to investigate.

This study offered a comprehensive molecular mechanism based on bioinformatics analysis. We extracted genes related to diabetes from Pubmed (www.ncbi.nlm.nih.gov), OMIM (www.omim.org), and GeneCard (www.genecard.org). Thus, this study utilized both STITCH and STRING to obtain the direct and indirect protein interfered with by neolignan. A protein-protein interaction (PPI) network was constructed from the affected genes from Venn diagram. This study found that 96 of 100 genes interfered with by neolignan are diabetes-related genes in which epithelial Growth Factor Receptor (EGFR) and Insulin Growth Factor Receptor (IGF-1R) are recognized as the top interfered genes by neolignan. Thus, the protein-protein interaction (PPI) network was constructed to determine neighborhood information, shortest path, distance, and modularity of interacting proteins. The PPI network was validated by high-throughput experiments, including *in vitro*, *in vivo*, and *in silico* methods[24]. Thus, this study ranked the most influence genes with MCC (Maximal Clique Centrality), an algorithm to form an interlinked cluster, and DMNC (Density Maximal Neighborhood Centrality) quantifies centrality by considering the distance from a node to its neighboring nodes.[25,26]

Furthermore, the use of protein-ligand docking, and simulation techniques has significantly applied to identify the identification of new medications for diabetes. There were previous molecular docking studies employed AutoDock 4.2 with Lamarckian Genetic Algorithm (Lamarckian GA), and Molecular Operating Environment (MOE) software to determine RMSD value, binding energy, and S-score as the parameters. [27-29] A study by Arief *et al.* (2021) conducted molecular docking of peptides from *M. charantia* against SGLT1, DPP IV, and GLUT2.[28] While other studies applied α-amylase, β-glucosidase, and pancreatic lipase.[29] This study used AutoDock 4.2 to explore neolignan's ability to bind to diabetic-related proteins. We found that neolignan bound to both EGFR and IGF-1R with the lowest energy binding of -6.64 and -6.84 kcal/mol mostly through Van der Waals interaction. Instead of those two targets having similar protein downstream targets such as PI3K and AKT, other genes related to hyperglycemia and reactive oxygen species; HIF1A. Another neolignan downstream target is MAPKs, a protein kinase in glucose homeostasis, which is also targeted by metformin, a commercial anti-diabetic.[30-32] Moreover, neolignan targets TNF-α, a proinflammatory cytokine playing an important role in developing insulin resistance if it is overexpressed in myocytes and adipocytes. Since it is targeted by metformin and piolglitazone,[33] neolignan may be a promising agent for diabetes therapy. In summary, our study has revealed a range of molecular pathways that involve diverse targets, including growth factor and insulin growth factor receptor, cytokine, and hypoxia, all of which play a role in influencing anti-diabetics activity.

Materials and Methods

Data Minning and Collection

Proteins and genes that are involved in diabetes, hyperglycemia, and insulin resistance were mined from an online database, Pubmed (www.ncbi.nlm.nih.gov), OMIM (www.omim.org), and GeneCard (www.genecard.org). Afterward, proteins and genes targeted directly and indirectly from Neolignan were screened from www.stitch.embl.de. The genes affected by Neolignan in diabetes, hyperglycemia, and insulin resistance were determined using a Venn diagram (www.interactivenn.net).

Protein-protein Interaction (PPI) Network and Gene Clustering Construction

Using www.string-db.org we got protein-protein interaction (PPI) network. The PPI network was analyzed using Cytoscape 3.9.1 (https://cytoscape.org/) and STRING-DB v11.5 (https://string-db.org/) software, generating the top 15 genes using the MCC and Degree algorithm from the Cyto-Hubba plugin. The bioinformatics analysis employed a computer with Intel(R) Core (TM) i3-1005G1, CPU@ 1.20GHz, RAM 4GB.

Molecular Docking

The IGF-1R and EGFR proteins were sourced from rcsb.org. Using BIOVIA Discovery Studio 2021, the ligand was extracted from IGF-1R (PDB ID: 2OJ9) and EGFR (PDB ID: 7U9A), while AutodockTools 1.5.7 (www.scripps.edu) was employed for control docking.[34] Unlike the ligand, which underwent Gasteiger charges, the protein was protonated and assigned Kollman charges. The central coordinates of the grid box for IGF-1R were x = 5.708, y = -7.753, and z = 20.645. Correspondingly, for EGFR, these coordinates were x = 52.045, y = 0.217, and z = 23.279. Grid point spacing for the grid box was set at 0.375 with a 40 x 40 x 40 number of grid points. Docking was performed using AutoDock-GPU The Lamarckian Genetic Algorithm (LGA) was run for 1000 iterations.[35] The cumulative free energy of binding included various components such as final van der Waals forces, hydrogen bonding, intermolecular energy, electrostatic interactions, desolvation, final total internal energy, the energies of the unconstrained system, and torsional freedom. A docking configuration was considered valid if the Root Mean Square Deviation (RMSD) between initial and post-docking poses did not exceed 2.0[36]. Visualization of docking poses was executed using BIOVIA Discovery Studio 2021. For the new ligand (neolignan), preparation and docking were conducted following the same parameters as control dockings, utilizing PubChem (https://pubchem.ncbi.nlm.nih.gov/). The molecular docking was conducted in computer with computer with AMD Ryzen 3 3300, RAM DDR4 16 GB, and Nvidia GTX 1650.

Results and Discussion

Neolignan is a phenolic compound derived from plants through the shikimate acid biosynthesis pathway, displaying diverse chemical structures and a range of biological activities (Figure 1a). There are 22,287 genes involved in diabetes, hyperglycemia, and insulin resistance, as well as 100 genes associated with neolignan. Based on Venn diagram analysis, there are 96 neolignan-related genes connected to diabetes, hyperglycemia, and insulin resistance (Figure 1b). Through protein interaction (PPI) networks, genes BCAT1, CETP, IMPDH1, IMPDH2, and SLC27A1 are identified separately from the pool of 96 genes (Figure 1c). Using the Cytoscape application, gene interactions are measured in terms of degree using MCC and DMNC algorithms, resulting in the top 15 ranks for each algorithm (Figure 2). The MCC data, comprising the top 10 ranks, are extracted and discussed in Table 1.

The study was further carried out by conducting molecular docking between Neolignan and the top 10 genes, resulting in the identification of Insulin-Like Growth Factor 1 Receptor (IGF-1R) and Epidermal Growth Factor Receptor-1 (EGFR1). Neolignan interacts with IGF-1R with a binding energy of -6.84 kcal/mol through 7 hydrophobic interactions at Leu975, Val983, Ala1001, Lys1003, Met1049, Met1112, Met1126, as well as Van der Waals interactions at Gly978,

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Ser979, Phe980, Gly981, Thr1004, Phe1017, Val1033, Glu1050, Leu1051, Met1052, Asp1123, Thr1127. Another interaction of neolignan with EGFR1 results in slightly weaker binding energy of -6.64 kcal/mol through hydrophobic interactions at Leu718, Ala743, Lys745, Leu788, Leu844, and Van der Waals interactions at Val726, Ile744, Glu762, Met766, Ile789, Thr790, Gln791, Leu792, Met793, Pro794, Gly796, Thr854, Asp855 (Table 2). In conclusion, the genes capable of interacting with Neolignan are IGF-1R and EGFR1. The results of the molecular interactions of neolignan docking onto the active sites of IGF-1R and EGFR1 can be visualized in both 2D and 3D forms in Figure 3.

Neolignan binds to IGF-1R and EGFR1, which both of them predict to activate Insulin Receptor Substrate 1 (IRS1) in the cytoplasm domain by phosphorylation (Figure 4). The activated IRS1 then phosphorylates PI3K, a downstream protein of IRS1, which then activates Akt, leading to the metabolic function of insulin. [37] Activated Akt is responsible for translocating GLUT4 transporter from cytoplasm to plasma membrane, resulting in glucose intake to the cell and lowering glucose blood level.[37] However, a study by Cong and colleagues showed that Akt not only can promote the translocation of GLUT4 but is also likely to have a substantial physiological role in insulin-triggered glucose uptake.[38] Moreover, neolignan also demonstrates to modulate SRC which is responsible for the cell survival effect downstream.[39] In kidney cells, SRC has been implicated in diabetic kidney fibrosis, by activating activator protein-1 (AP-1), then resulting in the accumulation of extracellular matrix (ECM), which is accountable for the development of renal diabetic fibrosis in fibroblast cells.[39,40] Moreover, SRC plays a role in β-pancreas cell survival.[39]

Interestingly, several studies have reported that inflammatory cytokines have played a pivotal role in diabetes pathogenesis, one of them is TNF-α which elevates glucose uptake by activating Janus Kinase 1/2 (JAK1/2).[41] Neolignan exhibits TNF-α and JAK1/2 activation, resulting in the activation of the Signal transducer and activators of transcription (STAT5) translocation to the nucleus to activate gene target transcription, for instance, Insulin Growth Factor (IGF) (Figure 4).[42] The activation of JAK2, resulting from TNF-α binding to its receptor exhibited the release of Hsp90 from β-pancreas cell.[43] Modulating inflammatory processes in a general sense, especially regulating inflammatory cytokines, like neolignan, could offer potential benefits in both preventing and treating diabetes[43]. Additionally, it could open up new avenues for therapeutic targets aimed at preventing and managing complications associated with diabetes.[37]

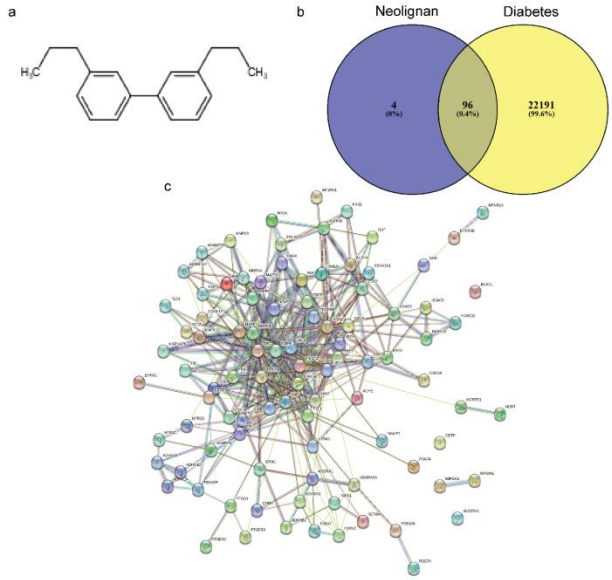

Figure 1: Neolignan's top target genes and proteins related to diabetes. a. Neolignan's structure, b. Venn diagram of neolignan and diabetes interfered genes, c. Protein-protein interaction (PPI) network of the intersecting genes.

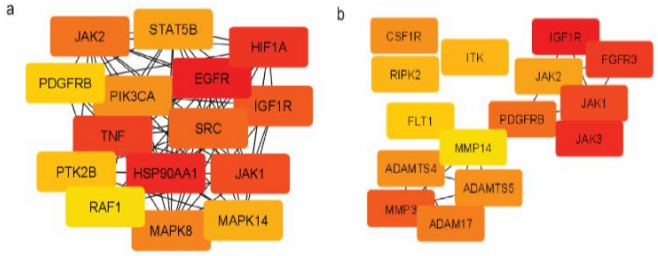

Figure 2: The clustering of the top 15 genes related to diabetes according to MCC (a) and DMNC algorithm (b) in CytoHubba.

Table 1: Top 10 proteins network interaction ranked by MCC algorithm

No	Gene symbol	Gene/Protein name	Biological function related to diabetes
1	EGFR1	Epidermal Growth Factor Receptor-1	Initiate various cell signaling and transcription factors, leading to the onset of multiple cellular and tissue reactions that play a role in the advancement of Diabetic Kidney Disease.[44]
2	HSP90AA1	Heat Shock Protein HSP 90-Alpha	An autoreactive peptide segment known as P277 is generated from HSP60 or HSP65 and discharged alongside insulin from pancreatic β-cell.[44,45]
3	HIF1A	Hypoxia-Inducible Factor 1-Alpha	In a shortage of iron or oxygen, the HIF-1α protein builds up. It then binds with HIF-1β to form a dimer, which attaches to hypoxia response elements (HREs). This action enables the regulation of gene expression.[46]
4	IGF-1R	Insulin-Like Growth Factor 1 Receptor	The tyrosine kinase type receptor for Insulin-like Growth Factor-1 (IGF-1). This binding harmonizes protein, carbohydrate, and fat metabolism. In skeletal muscle, it elicits an insulin-sensitizing effect and lowers blood glucose.[42]
5	JAK1	Janus Kinase-1	JAK1 serves as a substrate for the creation of PTPN2, a protein that

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			plays a role in controlling the apoptosis (cell death) of pancreatic β-cells when exposed to inflammatory cytokines. [47]
6	TNF	Tumor Necrosis Factor	Regulate Insulin action, and as a pro-inflammatory mediator which is involved in the advancement of insulin resistance and the development of type II diabetes mellitus.[43]
7	PI3KCA	Phosphatidylinositol 3-Kinase	Downstream effectors of Insulin Receptor Substrate-1 (IRS-1), which lead Akt activation in signaling pathway. [37]
8	MAPK8	Mitogen-activated protein kinase 8	Activated by cytokines binding receptor, then induces phosphorylation and dimerization of STAT1, followed by its translocation to the nucleus, are key steps in the process of regulating the transcription of numerous genes.[44,48,49]
9	SRC	Proto-Oncogene Tyrosine-Protein Kinase SRC	In Src, the activation of kinase activity is encouraged by phosphorylation at Tyr416, whereas phosphorylation at Tyr527 leads to deactivation. Src contributes to the development of diabetic nephropathy (DN) through various mechanisms, such as influencing mesangial cell proliferation, inducing apoptosis in renal tubular cells, and triggering the activation of other pro-fibrotic signaling pathways like EGFR and MAPK.[40,50,51]
10	JAK2	Janus Kinase 2	Within pancreatic β-cells, the binding of IFN-γ to its receptor initiates the phosphorylation and dimerization of STAT1 through the action of JAK1/2, subsequently leading to its translocation into the cell nucleus. [37,52]

Table 2: Molecular Docking Results of Neolignan with IGF-1R and EGFR

Target Protein	Binding Energy (kcal/mol)	Hydrophobic residues	Van der Waals residues
IGF-1R	-6.84	Leu975, Val983, Ala1001, Lys1003, Met1049, Met1112, Met1[1]26	Gly978, Ser979, Phe980, Gly981, Thr1004, Phe1017, Val1033, Glu1050, Leu1051, Met1052, Asp1123, Thr1127
EGFR	-6.64	Leu718, Ala743, Lys745, Leu788, Leu844	Val726, Ile744, Glu762, Met766. Ile789, Thr790, Gln791, Leu792, Met793, Pro794, Gly796, Thr854, Asp855

High levels of glucose within cells, along with situations involving low oxygen (hypoxia) and the presence of reactive oxygen species (ROS), lead to the activation of the Hypoxia-Inducible Factor 1-Alpha (HIF1α) protein.[53] Hypoxia-inducible factors (HIFs) are involved in the development of β cell dysfunction and diabetes, and their stability is compromised by hyperglycemia, leading to impaired responses to hypoxia.[54] In diabetes, both insulin resistance and deficiency are linked to the destabilization of the HIF protein, resulting in the inability to protect cells from hypoxia.[54] The excessive generation of reactive oxygen species (ROS) in the mitochondria is a key factor in the onset of complications associated with diabetes.[53] Furthermore, recent research has highlighted the additional detrimental role of hypoxia in diabetes. A prior study has shown that the overproduction of ROS is a consequence of impaired responses to hypoxia, primarily due to the inhibition of hypoxia-inducible factor-1 (HIF-1) caused by high blood sugar levels (hyperglycemia).[53] Thus, a deficiency in HIF-1α has been linked to a decline in the function and survival of β cells, it is probable that the glucose-induced reduction in enhancing the stability of the HIF-1α protein could lead to a faster decline in β cell function and hasten the development of diabetes.[54] Neolignan affects HIF-1α which may reverse impaired hypoxia responses under hyperglycemia conditions, resulting in normalized diabetic conditions.[46] Moreover, neolignan thus interferes with Heatshock protein 90 (Hsp90), a molecular chaperone, which has previously been demonstrated to be essential for maintaining the stability and proper functioning of HIF-1α. When direct physical interaction between HIF-1α and Hsp90 is disrupted, HIF-1α undergoes efficient ubiquitination.[44,45] This ultimately results in its degradation through the proteasome pathway, independent of oxygen levels.[46]

In summary, the study identified proteins targeted by neolignan, which include IGFR-1, EGFR, inflammatory cytokine TNF-α, chaperone protein Hsp90, as well as various downstream signaling molecules such as MAPK8, SCR, PI3K, and JAK1. These proteins work orchestrated during neolignan treatment to support its anti-diabetic activity. This research provides an initial glimpse into the molecular mechanisms of neolignan in diabetes treatment.

Conclusion

Based on bioinformatics analysis, neolignan affects a range of proteins, including EGFR, the inflammatory cytokine TNF-α, the chaperone protein Hsp90, and several downstream signaling molecules such as MAPK8, SCR, PI3K, and JAK1. These proteins collaborate in a coordinated manner during neolignan treatment to enhance its effectiveness in combating diabetes. This funding provides fundamental data to investigate *in vitro* and *in vivo* activities of neolignan as a prospective novel anti-diabetic agent.

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Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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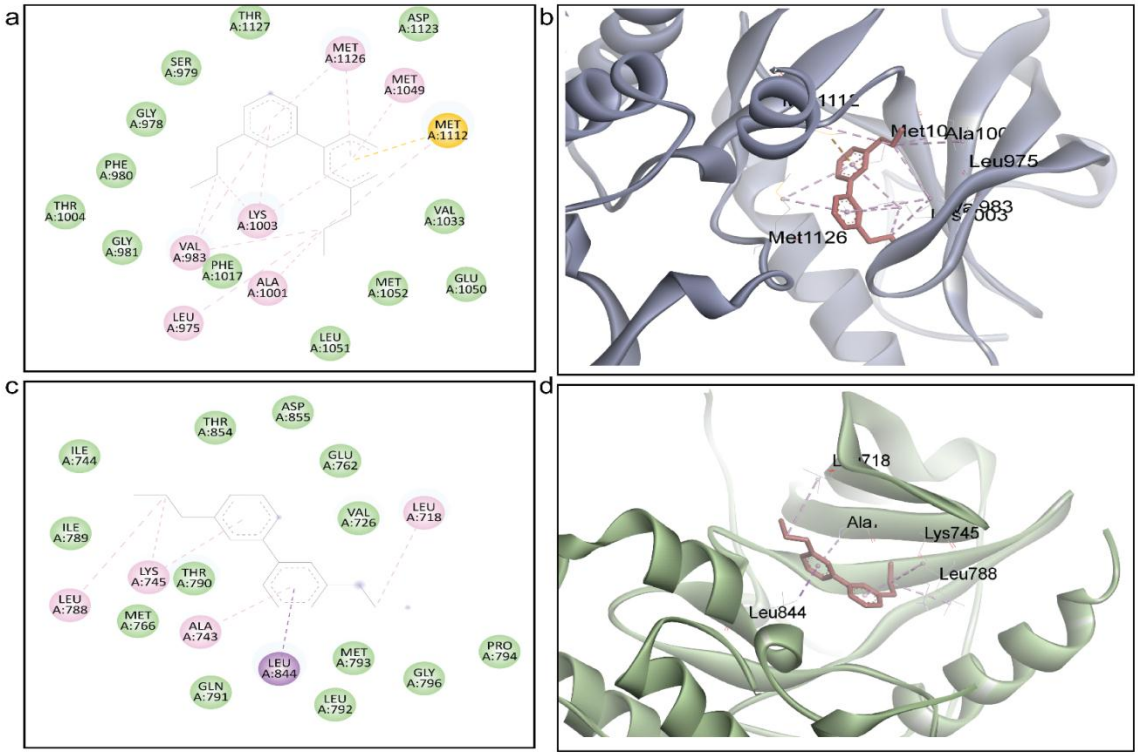

Figure 3. The binding poses of neolignan at IGF-1R binding pocket in 2D view (a), and 3D view (b); and at EGFR binding pocket in 2D view (c), and 3D view (d). Yellow, red, and white indicated carbon, oxygen, and hydrogen atoms. The green, pink, orange, and purple represent Van der Walls, alkyl/pi-alkyl, pi-sulfur, and pi-sigma.

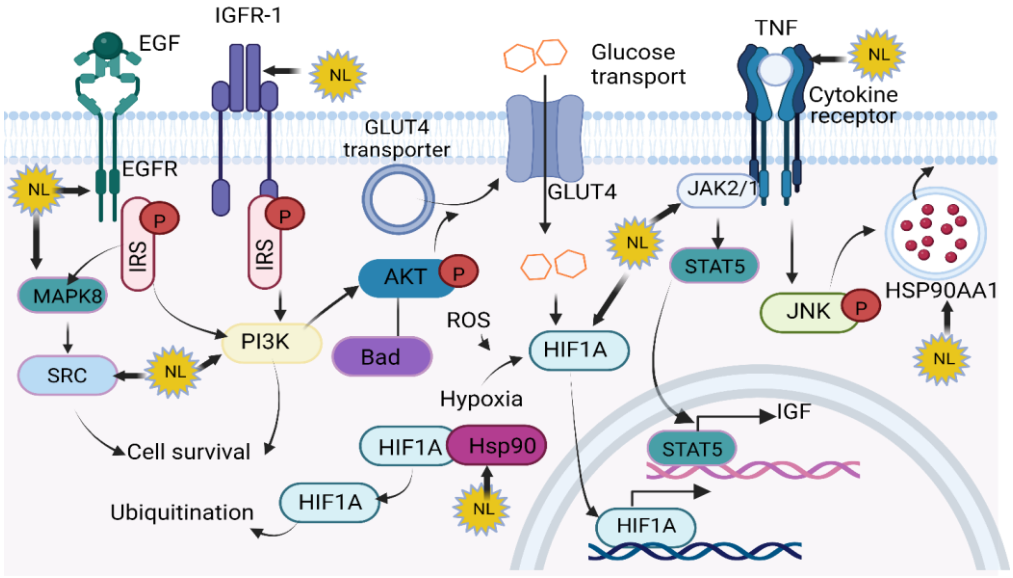

Figure 4: Molecular cascade of neolignan in diabetic disease.

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