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Network Pharmacology Analysis of Black Turmeric (*Curcuma caesia* Roxb.) for Diabetic Nephropathy: Exploring Potential Therapeutic Targets

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ABSTRACT: Diabetes mellitus is a non-communicable disease with a high prevalence that has the potential to cause chronic complications, such as diabetic nephropathy (ND). Diabetic nephropathy is characterized by microalbuminuria, decreased glomerular filtration rate, and the risk of end-stage renal failure. Conventional treatment with oral hypoglycemic drugs often causes side effects such as hyperkalemia and impaired heart function. This indicates the need for alternative therapies with high effectiveness, low toxicity, and affordable costs. This study explores the potential of black turmeric as a therapeutic agent for diabetic nephropathy through an in-silico approach. The active compounds of black turmeric were analyzed for their pharmacokinetics using SwissADME based on Lipinski's rules. The target proteins of the compounds were obtained through SwissTargetPrediction and compared with ND-encoding proteins from GeneCards using Venny 2.1. Specific proteins were analyzed for protein-protein interactions through STRING and visualized with pharmacological networks using Cytoscape. In-depth analysis was carried out to identify biological pathways through KEGG and molecular activity using WebGestalt. The results showed that black turmeric has 123 specific target proteins for ND, with EGFR and STAT3 as core proteins that play a role in regulating apoptosis, inflammation, and insulin sensitivity. Curcumin showed significant activity on the AGE-RAGE and FoxO pathways, which are relevant for the treatment of ND. This study provides initial insight into the potential of black turmeric as an alternative therapy for diabetic nephropathy.

Keywords: Black turmeric; diabetic nephropathy; network pharmacology

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INTRODUCTION

Non-communicable diseases (NCDs) are the cause of death of around 41 million people each year. Diabetes mellitus is one of the non-communicable diseases that have increased, specifically from 6.9% to 8.5%, based on data from the Ministry of Health in 2023. Diabetes is a group of metabolic diseases characterized by increased glucose levels exceeding normal limits (hyperglycemia) due to damage to insulin secretion, insulin function, or both (ADA, 2022). Indonesia is the only country in Southeast Asia included in the list of the top 10 countries with the highest number of people living with diabetes in 2019, ranking 7th with a total of 10.7 million people (Kemenkes RI, 2023).

Diabetes mellitus is a top priority for controlling non-communicable diseases. This is because uncontrolled DM can cause chronic complications. One of the chronic microvascular complications is diabetic nephropathy (DN). The risk of developing diabetic nephropathy begins with albuminuria, progressing from microalbuminuria to macroalbuminuria. Microalbuminuria is considered an early marker of DN and a predictor of cardiovascular disease (Aldukhayel, 2017). Diabetic nephropathy is characterized by progressive excretion of abnormal albumin through urine of 30-300 mg/day and a decrease in the glomerular filtration rate (eGFR) to <60ml/minute/ 1.73m2 (Thomas et al., 2020). Diabetic nephropathy is the primary cause of end-stage kidney damage resulting from high glucose levels in the body. Prevention of complications in DM can be controlled using Oral Hypoglycemic Drugs (OHO) of the sulfonylurea group, glinide, biguanide, thiazolidinedione, acarbose, and insulin injections. Treatment with OHO can cause various side effects, one example is that sulfonylurea drugs can cause nausea, diarrhoea, vomiting, headaches, and hypoglycemia (Costello et al., 2024). The combination of oral sulfonylurea and ACE/ARB drugs in DN patients has a risk of side effects such as hyperkalemia, and the combination with ET-1 can increase the risk of heart failure (Samsu, 2021).

New therapeutic agents through the use of herbal preparations that are effective, relatively cheaper, with low side effects and low toxicity. Black turmeric is a native Indonesian plant that can be widely found across the country, making it a readily accessible resource for natural therapy development. One of the plants with antidiabetic activity is black turmeric (*Curcuma caesia* Roxb.). This plant contains active compounds such as ar-turmerone, (Z)-ocimene, ar-curcumene, 1,8-cineole, Elemene, borneol, bornyl acetate, and curcumin as its main components (Pandey, 2022). The curcumin content in black turmeric has anti-tumour, antioxidant, anti-inflammatory and antidiabetic effects (Baghel et al., 2013). Curcumin has been shown to have practical applications in the management of hyperglycemia, type 1 and type 2 diabetes, diabetic neuropathy, diabetic nephropathy, and pancreatic beta cell damage (Malik et al., 2021). The function of curcumin is involved in several molecular signalling pathways, including nuclear factor kappa B (NF-κB), PPARγ, and free fatty acid pathways. The mechanism of action of the antidiabetic effect of curcumin, a component of black turmeric *(Curcuma caesia* Roxb), can suppress inflammation caused by cytokines such as MCP, IL-6, and TNF-α, and also reduce NF-κB activity. This can lead to a decrease in blood sugar levels, particularly when there is increased beta cell function in insulin secretion and enhanced insulin sensitivity to insulin receptors (Malik et al., 2021).

In silico studies are computational studies that serve as a precursor to drug development, examining the interaction of molecular stages (Moradi et al., 2022). Analysis of absorption, distribution, metabolism, and excretion (ADME) is used as the primary

screening to determine the fate of a drug in the body (Flores-Holguín et al., 2021). Network pharmacology is employed to elucidate the complex pharmacological processes between compounds through biological pathways, thereby predicting the core target protein of a compound (Kim et al., 2023). This background prompted researchers to conduct an in silico test of black turmeric as a preliminary study of an alternative treatment for diabetic nephropathy. This study aims to provide initial information on the prediction of black turmeric's ability as an alternative treatment for diabetic nephropathy.

METHODS

Tools and materials

The tools used in this study are hardware in the form of an Acer Aspire A314-2140WH laptop with an AMD APU A4-9120 processor e 8GB RAM SSD 256 windows 11. The software used is Microsoft Office 2021, cytoscape 3.10.2 and cyto Hubba. The websites used are pubchem PubChem (nih.gov), SwisADME SwissADME, genecard GeneCards - Human Genes | Gene Database | Gene Search, SwisTargetPrediction SwissTargetPrediction, Venny 2.1 Venny 2.1.0 (csic.es), string database STRING: functional protein association networks (string-db.org), KEGG pathway KEGG: Kyoto Encyclopedia of Genes and Genomes, and webgestalt WebGestalt (WEB-based GEne SeT AnaLysis Toolkit).

The main ingredients needed in this study are active compounds from black turmeric obtained from the results of Sahu et al (2016) research using GC-MS. . The nine compounds of black turmeric content obtained are Camphor (PCID: 2537), Curcumin (PCID: 969516), Ocimen (PCID: 6436627), Cineole (PCID: 2758), Elemene (PCID: 6918391), Borneol (PCID: 64685), bornyl acetate (PCID: 64428), Curcumen (PCID: 91753507), and Turmerone (PCID: 558173) (Sahu et al., 2016).

Research Procedures

Screening of active compounds in black turmeric

Structure compound active obtained use PubChem (nih.gov) Then done screening pharmacokinetics through SwissADME. The results then done screening based on rule lipinski as rule general screening pharmacokinetics candidate drug new orally.

Criteria used that is Molecular Weight (MW) < 500 g/mol, Hydrogen Bond donor (HBD) < 5, Hydrogen Bond acceptors < 10, Log-P < 5 (Abdul-Hammed et al., 2022), Polar refraction (MR) 62.17 cm3/mol to 131.57 cm3/mol, and Topology Polar surface area (TPSA) 20 to 130 A (Abdullah et al., 2021).

Target protein analysis and comparison with diabetic nephropathy coding proteins

Target protein of every compound can found through the database on the website https://www.swisstargetprediction.ch/ with use *canonical smiles* from the PubChem website (nih.gov). The collection of protein targets focuses on human species and is restricted to mark trust >0 hope Can specify the desired target (Oh et al., 2021). Coding protein diabetic nephropathy that has obtained through GeneCards - Human Genes | Gene Database | Gene Search with restrictions mark trust >1. Comparison between the target protein compound and the coding protein diabetic nephropathy is acquired with Venny 2.1.0 website help (csic.es). Intersection results between both of them is a specific target protein compounds in disease diabetic nephropathy. Specific targets then stored and arranged then done analysis interaction between proteins (PPI) using the STRING website : functional protein association networks (string-db.org). The role of analysis this for get

activity of proteins with other proteins as well as protein activity against body man (Lestariningrum et al., 2024).

Formation of the pharmacological network

Formation of Network pharmacology using Cytoscape software 3.10.1 with entered results, findings, plant-compounds, target-compounds, and target-activities in Excel. Adjusting node1, node2, and attributes from every node makes it easier for Cytoscape in the analysis and visualisation of network pharmacology results. Analysis of 10 proteins with activity best obtained through processed core protein results is performed using the StringDB website, then saved in the appropriate file format (TSV) with the Cytoscape file format. CytoHubba will analyse to get 10 proteins with the best activity.

Analysis of core target protein activity

The core target proteins were re-analyzed for activity through the WebGestalt website (WEB-based GEne SeT AnaLysis Toolkit). The results of this analysis are the biological process (BP), molecular function (MF), and cellular component (CC) classifications of the core proteins. Protein signaling in the human body was also analyzed using the KEGG pathway.

RESULT AND DISCUSSION

Screening of bioactive components as well as pharmacokinetic screening of compounds

Results of pharmacokinetic profile analysis with the help of the SwissADME website are shown in Table 1. Pharmacokinetic analysis of oral drugs has several established standards; in this study, we employed the Lipinski rule as a benchmark. Several pharmacokinetic variants, which adhere to Lipinski's rules, such as molecular weight, Log P, acceptors, and hydrogen donors, showed promising results. The compound element e was found to have results that exceeded the Lipinski rule limit on Log P, which was 4.65. The condition of this compound enables it to easily penetrate the lipid bilayer membrane, resulting in excessive activity (Daina et al., 2017). Lipinski's rule has a tolerance of 2 inappropriate parameters; therefore, in this case, all compounds can be continued in the following research process (Daoui et al., 2021).

Table 1. Analysis profile pharmacokinetics compound turmeric black

Compound	Formula Form	Molecular Weight	Log P	Acceptor Hydrogen	Hydrogen Donor	Molar Reactivity	TPS	Lipinski
Camphor	C10H16O	152.23	2.37	1	0	45.64	17.07	+
Curcumin	C21H20O6	368.38	3.03	6	2	102.80	93.06	+
Ocimen	C10H18O	154.25	2.68	1	0	48.72	9.23	+
Cineole	C10H18O	154.25	2.67	1	0	47.12	9.23	+
Elements	C15H24	204.35	4.65	0	0	70.42	0.00	Log P
Borneo	C10H18O	154.25	2.38	1	1	46.60	20.23	+
Bornyl acetate	C12H20O2	196.29	3.21	2	0	60.13	26.30	+
Curcuma	C15H22O	218.33	3.77	1	0	70.88	17.07	+
Turmerone	C15H22O	218.33	3.63	1	0	70.88	17.07	+

Target protein analysis and intersection with diabetic nephropathy coding proteins

Using the GeneCards website - Human Genes | Gene Database | Gene Search, 4,144 proteins were identified as having potential coding disease associations with diabetic nephropathy. Screening mark trust more from 1 yields 3,819 potential proteins big in coding diabetic nephropathy. A total of 255 protein compounds were compared to find proteins with specific targets in diabetic nephropathy. Specific proteins were identified in compounds neryl acetate and ocimen, with a total of 52 target proteins. No specific protein was found, so that compound was eliminated. The amount of specific protein in turmeric that affects diabetic nephropathy consists of 123 protein codes, as shown in Figure 1.

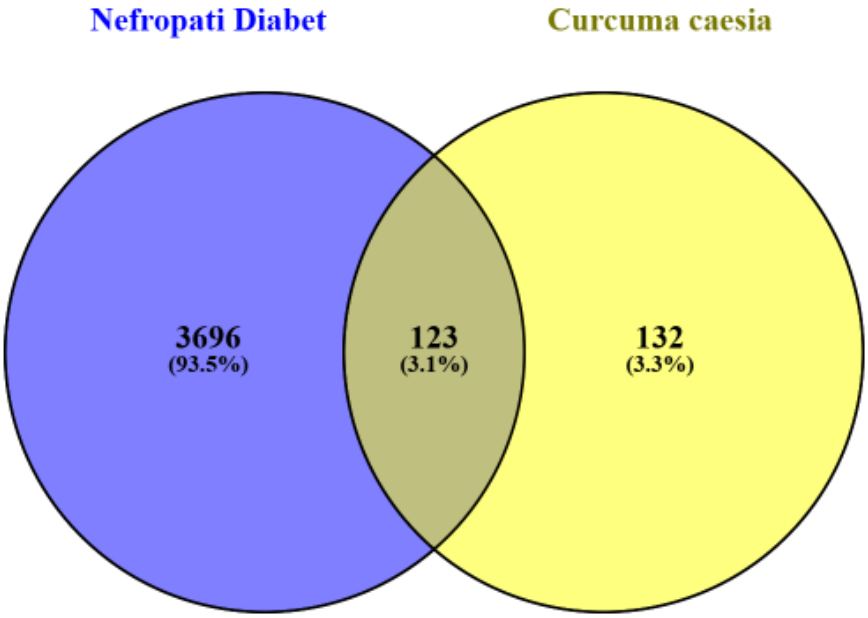

Figure 1. Intersection target protein against diabetic nephropathy coding protein

Interaction between proteins obtained through the STRING website: functional protein association networks (string-db.org), shown in Figure 2. The interaction produces 123 nodes with an average node value of 15.9, 980 edges, and a local cluster coefficient value of 0.515. The large number of interactions between proteins opens up the possibility of a potential treatment in black turmeric plants. (Soleymani et al., 2022). PPI exhibits a stable association in a protein complex that contributes to the structural organisation of the cell (Rochette et al., 2015). Four pathways are associated with diabetic nephropathy signals: "AGE-RAGE signalling pathway in diabetic complications" (hsa04933), "Renin-angiotensin system" (hsa04614), "FoxO signalling pathway" (hsa04068), and "Longevity regulating pathway" (hsa04211). The results of the comparison between specific target proteins and four diabetic nephropathy pathways indicate that the core protein of black turmeric may serve as a therapeutic option for diabetic nephropathy.

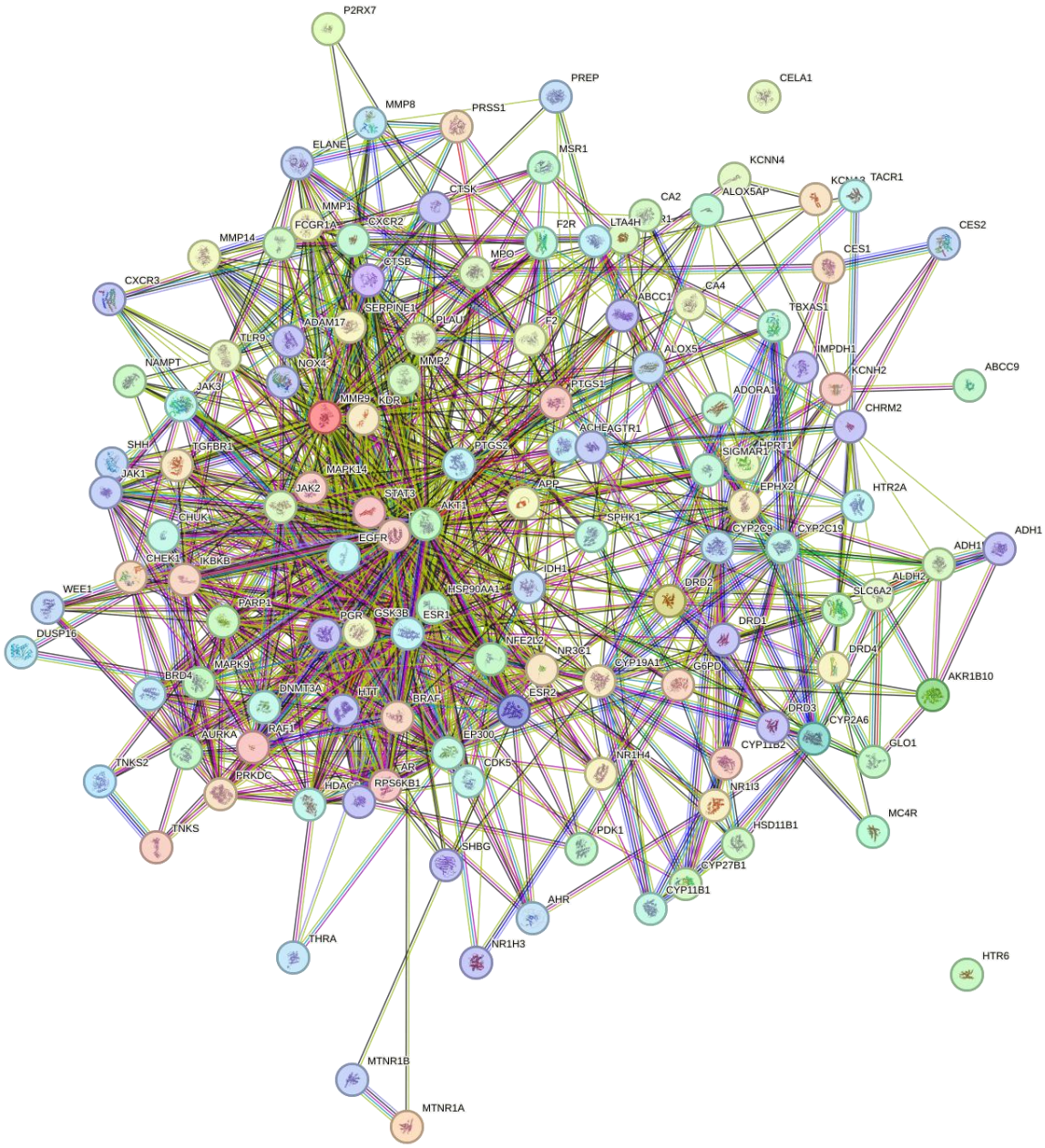

Figure 2. Protein interaction between specific target proteins

Analysis of the formation of the pharmacological network

The pharmacological network of black turmeric against diabetic nephropathy is visualised in Figure 3. Black turmeric is visualised as a green circle in the middle of the image, representing a plant with potential. The active compound of black turmeric is visualised as a green hexagon surrounding the plant as a therapeutic agent. Specific proteins are visualised as red components, as proteins that can interact with black turmeric compounds. The "Longevity regulating pathway" pathway (hsa04211) was not identified in this study; therefore, it was excluded. The three main pathways of diabetic nephropathy

development are visualised as light green boxes for reference in identifying the core target protein of this study. The analysis results identified 18 Core Proteins, including MAPK14, EP300, STAT3, EGFR, CHUK, MAPK9, RAF1, BRAF, IKBKB, TGFBR1, AKT1, AGTR1, PREP, MMP2, SERPINE1, NOX4, JAK2, and and BCL2.

The core target is visualised as a red triangle shape, representing a protein that directly contributes to the treatment of diabetic nephropathy using black turmeric. The results of the interaction between core proteins are based on 10 proteins with the highest interaction, as determined using CytoHubba, which is illustrated in Figure 4, visualised from red to yellow. Epidermal growth factor receptor (EGFR) and Signal transducer and activator of transcription 3 (STAT3) have the highest number of interactions, at 16. Inhibitor of NF-kappa-B kinase (IKKβ) and B-Raf (BRAF) are proteins with the lowest number of interactions, specifically 9.

Epidermal growth factor receptor (EGFR) is a derivative of the ErbB family, which is included in the tyrosine kinase receptor superfamily. EGFR can be found in the glomerulus (Sheng et al., 2021). EGFR is one of the genes that contribute to the development of diabetic neuropathy, regulating cell proliferation and cell survival (Chen et al., 2015). The pathogenesis of diabetic nephropathy is related to the activation of EGFR by high glucose, which accelerates kidney injury (Tung et al., 2018). The presence of hemodynamic disorders in diabetic nephropathy associated with nitric oxide can be reduced by inhibiting EGFR activity (Sheng et al., 2021). Li et al.'s (2018) research demonstrates the benefits of inhibiting EGFR blockade in a mouse trial with diabetic nephropathy. This blockade can inhibit immune cell infiltration and oxidative stress, while also increasing islet cell autophagy to maintain pancreatic beta cells and enhance insulin circulation (Li et al., 2018).

Saik and Klimton (2020) identified 10 genes (PTEN, THBSQ, GSK3B, HSP90AA1, EGF, MAPK1, TP53, EGFR, and STAT3) that were experimentally associated with GV (Saik & Klimontov, 2020). Hu et al. (2024) demonstrated the presence of STAT derivative activity in immune cell infiltration in the body, although not as pronounced as TNF (Hu et al., 2024). STAT 3 functions to increase the activity and resistance of pancreatic beta cells, thereby enhancing insulin sensitivity. STAT3 is associated with damage to podocytes, tubular cells, and the retina in diabetes, which is caused by the activation of both the cytokine response and the apoptotic response. STAT3 inhibition is known to inhibit cell apoptosis and suppress the development of diabetic nephropathy in mice tests (Hou et al., 2021).

Analysis of core target protein activity

Molecular function (MF) analysis shows that gene activity is at the molecular level (Aleksander et al., 2023). The green diagram in Figure 5 shows that black turmeric has the highest significant "protein binding " activity with 18 activities. Ion binding has an activity of 13, "nucleotide binding" and "transferase activity" have the same number of activities, namely 11. Biological progress (BP) is a molecular activity that works in conjunction with IMF to influence specific molecular targets (Aleksander et al., 2023). BP analysis of the target protein identified six significant "metabolic processes," 18 activities, and five processes with the same value. The results of the analysis are shown in the red diagram in Figure 5. A cellular component (CC) is a component or location that serves as the target for MF and BP activities (Aleksander et al., 2023). CC analysis in the blue diagram in Figure 5 shows that "nucleus and membrane" has the highest activity with 15 activities, followed by "cytosol" and "membrane-enclosed complex".

Kyoto Encyclopedia of Genes and Genomes (KEGG) is a cellular knowledge database that contains a collection of molecular activities used for functional orthology mapping (Kanehisa, 2019; Kanehisa et al., 2022). Pathways in KEGG mapping are manually curated to establish molecular relationships within biological systems, which are organised into several categories (Kanehisa et al., 2023). KEGG is a database that features an information system comprising pathways, BRITE, and modules, which are the focus of research (Kanehisa et al., 2022). Figure 6 presents the results of the KEGG pathway analysis, with the most significant finding being the Pancreatic Cancer pathway, which has an enrichment ratio of 48,473. Pathways in cancer are the lowest pathways with an Enrichment Ratio value of 10,792. AGE-RAGE signalling pathway in diabetic complications has an Enrichment Ratio value of 44,883. The FoxO signalling pathway is a key pathway in the development of diabetic nephropathy, with an enrichment ratio of 33,662. The renin-angiotensin system, after re-analysis, does not have a direct pathway in the treatment of diabetic nephropathy using black turmeric. Further research is needed to confirm the potential of black turmeric as an alternative treatment for diabetic nephropathy. The AGE-RAGE signalling pathway plays a crucial role in diabetic kidney disease by promoting oxidative stress and chronic inflammation, which contribute to the progression of kidney damage. Targeting this pathway offers a promising strategy to reduce oxidative injury and inflammation, potentially slowing the advancement of diabetic kidney disease and related age-associated renal dysfunction (Wu et al., 2021).

These findings align well with previous studies demonstrating the therapeutic potential of turmeric and its active compound curcumin in diabetic nephropathy. Consistent with Nugroho et al. (2019), who reported that turmeric can prevent oxidative stress and renal damage in diabetic rats, our study highlights key molecular targets, such as EGFR and STAT3, involved in pathways linked to kidney injury. Similarly, clinical studies by Hendre et al. (2022) and Vanaie et al. (2019) demonstrated that turmeric supplementation improved kidney function markers and reduced proteinuria in diabetic patients, supporting the relevance of turmeric as an adjuvant therapy. Moreover, the antifibrotic effects observed by Lu et al (2017) through curcumin's modulation of inflammatory pathways further reinforce the mechanistic basis of our network pharmacology results. The novelty of our study lies in identifying specific core targets and signalling pathways through a systematic network pharmacology approach, providing a more detailed understanding of black turmeric's potential mechanisms against diabetic nephropathy.

This comprehensive insight paves the way for targeted experimental validation and clinical translation, marking a significant advancement in exploring black turmeric as a promising alternative treatment. Experimental validation through in vitro and in vivo studies is necessary to confirm the therapeutic effects and safety of black turmeric compounds. Future research should focus on laboratory experiments to verify the identified targets and pathways, followed by clinical trials to evaluate the efficacy and safety in patients with diabetic nephropathy. Additionally, exploring synergistic effects with current treatments could provide a more comprehensive understanding of black turmeric's therapeutic potential

CONCLUSION

Pharmacokinetic screening of black turmeric revealed that most compounds meet Lipinski's criteria, except for a few elements. Target protein analysis identified 123 proteins

related to diabetic nephropathy, with EGFR and STAT3 as key targets involved in the AGE-RAGE and FoxO pathways. These findings suggest that black turmeric has potential as an alternative therapy for reducing kidney damage and improving cellular function in diabetic nephropathy. However, this study is limited by its reliance on in silico analysis, which may not fully capture the complexity of biological systems.

AUTHOR CONTRIBUTION

ZQA: Responsible for generating concepts or ideas, designing the study, conducting the literature search, and preparing the manuscript.
MF: Contributed to generating concepts or ideas, designing the study, performing the literature search, analyzing data, and preparing the manuscript.
TW: Involved in generating concepts or ideas, designing the study, conducting the literature search, and analyzing data.
LDR: Contributed to performing the literature search, analyzing data, and preparing the manuscript

CONFLICT OF INTEREST

None to declare

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