Targeting Immune Dysregulation in COVID-19 with Type 2 Diabetes Mellitus: Phytocompound Interactions from *Phaleria macrocarpa* via Network Pharmacology Approach

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Abstract. Patients with type 2 diabetes mellitus (T2DM) tend to experience worse clinical outcomes when infected with SARS-CoV-2. The hyperinflammatory state associated with diabetes contributes to immune dysregulation during COVID-19 infection, often triggering a cytokine storm that exacerbates disease severity. *Phaleria macrocarpa* (mahkota dewa) fruit is known to possess bioactivities, including antioxidants, anti-diabetic, antiviral, anti-inflammatory, and immunomodulatory properties. This study aims to explore the potential interactions between *P. macrocarpa* phytochemicals and immune-related proteins associated with COVID-19 and T2DM using a network pharmacology approach. HPLC was further used to analyze selected compounds from the *P. macrocarpa* extract and fractions identified by LC-HRMS, aiming to isolate target-specific compounds. The target proteins were retrieved from the GeneCards and OMIM databases, while the structures of the compounds were obtained from PubChem and KNApSAcK. Cytoscape was employed to construct the protein-protein interaction (PPI) networks. The interactions between *P. macrocarpa* phytochemicals and the predicted target genes were visualized, followed by enrichment analysis using Metascape. The results showed that a total of six compounds, including phalerin, khellin, tridemorph, glycetin, L-α-palmitin, and navenone A, were found to interact with 27 nodes of protein targets associated with the immune response in COVID-19 patients with T2DM. In conclusion, these targets play key roles in modulating immune function through antiviral defense, interferon-mediated responses, and toll-like receptor pathways.

Keywords: Hyperglycemia, Immune Response, Interferon, Phalerin, Toll-like Receptor.

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1 Introduction

Diabetes mellitus (DM) is a chronic metabolic disease characterized by high blood glucose levels (hyperglycemia) [1]. Type 2 diabetes mellitus develops due to the reduced cellular sensitivity to insulin, leading to insulin resistance and relative insulin deficiency. Major risk factors for type 2 diabetes mellitus (T2DM) include obesity, family history and a sedentary lifestyle [1–3]. According to the International Diabetes Federation (IDF), Indonesia ranks fifth globally in terms of diabetes cases, with 19.5 million sufferers in 2021, and is projected to rise to 28.6 million by 2045 [4].

Patients with type 2 diabetes mellitus (T2DM) exhibit poorer clinical outcomes in the presence of infections. In the last Coronavirus Disease 2019 (COVID-19) pandemic, patients with diabetes who were infected had a poor prognosis. Although COVID-19 has been declared endemic, patients with comorbid DM must remain cautious. Infection with SARS-CoV-2 in patients with T2DM can trigger inflammatory responses that exacerbate insulin resistance and lead to elevated blood sugar levels, thereby worsening disease severity. Chronic inflammation enhances the immune and inflammatory responses, leading to the overproduction of cytokines, chemokines, and apoptosis, which play a significant role in the pathogenesis of hyperglycemia. The interaction between inflammatory cytokines and hyperglycemia is an essential factor in the development of multi-organ damage and increased mortality in hospitalized COVID-19 patients [5,6]. Under hyperglycemic conditions, the activity of lactate dehydrogenase (LDH) increased due to the accumulation of HIF-1α. LDH plays a role in modulating the inflammatory immune response, by inhibiting the retinoic acid-induced I-like receptor (RLR) gene receptor by directly binding to the mitochondrial domain of antiviral signaling transmembrane proteins. This can reduce IFN production and viral clearance.

Furthermore, the hyperglycemic environment promotes immune dysfunction. In diabetic COVID-19 patients, hyperinflammation often occurs which can lead to a cytokine storm, causing lung injury and acute respiratory distress syndrome (ARDS) [7]. Cytokine storms in severe COVID-19 cases can be life-threatening and are characterized by excessive production of inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-17, tumor necrosis factor-alpha (TNF-α), and monocyte chemotactic protein-1 (MCP-1) [8]. Thus, it calls for the discovery of treatments to modulate the dysregulation in cytokine storms. One of the treatment candidates known to possess immunomodulatory activity is *Phaleria macrocarpa* [9,10].

P. macrocarpa (mahkota dewa) belongs to the *Thymelaceae* family and is a widely used traditional medicinal plant in Indonesia. It has been empirically used to treat various diseases such as cancer, diabetes, rheumatism, and hypertension [11,12]. Studies have confirmed the safety profile of *P. macrocarpa* through in vitro and in vivo studies. *P. macrocarpa* extract contains bioactive compounds such as flavonoids, saponins, tannins, alkaloids, and glycosides. Previous studies have reported that *P. macrocarpa* exhibits bioactivity, including antioxidant, antimicrobial, anti-diabetic, anti-hypercholesterolemic, anti-proliferative, anti-hypertensive, anti-inflammatory, and immunomodulatory effects [13]. Nonetheless, the interaction of the main bioactive compound with

the proteins related to the dysregulation of the immune system in COVID-19 patients with T2DM remains unknown. Network pharmacology has been effectively utilized to identify potential active components for quality control in traditional medicine preparations, primarily by identifying target genes and predicting their functions based on the chemical constituents listed in existing databases for each herb [14]. Therefore, this study aims to explore the potential interactions between *P. macrocarpa* phytochemicals and immune-related proteins associated with COVID-19 with T2DM using a network pharmacology approach, to reveal the possible mechanism of action of *P. macrocarpa* in hyperinflammatory conditions.

2 Materials and Methods

2.1 Liquid Chromatography High Resolution Mass Spectrometry (LC-HRMS) Analysis of *Phaleria macrocarpa*

LC-HRMS was performed using Thermo Scientific™ Vanquish™ UHPLC Binary Pump with a Q Exactive™ Hybrid Quadrupole-Orbitrap™ HRMS. The chromatographic separation was carried out on an Accucore Phenyl-Hexyl column (100 × 2.1 mm ID x 2.6 μm), maintained at 40 °C with a flow rate of 0.3 mL/min. The ethanol extract and fractions of *P. macrocarpa* (5-10 mg) were dissolved in 1 mL of MS-grade water, methanol, or acetonitrile. The mobile phases consisted of 0,1% formic acid in water (A) and 0,1% formic acid in acetonitrile (B). The gradient elution began with 5% mobile phase B, increased gradually to 90% over 16 minutes, maintained at 90% for 4 minutes, and then returned to 5% B over the next 25 minutes. The injected sample volume was 3 μL. MS analysis was performed using positive electrospray ionization (ESI) mode, with a capillary voltage of 3,30 kV and a capillary temperature of 320 °C, and a scan range of 66.7-1.000 m/z. Data were acquired in Full MS/DDMS2 TOP N mode [15]. The composition of the detected compounds was analysed using Compound Discoverer™ 3.2, and compound classification was determined based on its chemical profiles using mzCloud™ and ChemSpider [16,17].

2.2 Databases for network pharmacology

The network pharmacology model was constructed by collecting and screening information on bioactive compounds, target genes and disease genes from multiple databases. The selected compounds identified through LC-HRMS analysis of *P. macrocarpa* extract and fractions were further analyzed using HPLC to focus on specific target compounds. The Canonical Simplified Molecular Input Line Entry System (SMILES) representations of these compounds were retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/), KNApSAcK (http://www.knapsackfamily.com) [18]. The SMILES were then input into the SWISS Target (http://www.swisstargetprediction.ch/) to identify potential protein targets of *P. macrocarpa* constituents. Only human (*Homo sapiens*) target proteins were retrieved, with protein IDs cross-referenced against UniProt IDs to ensure accuracy. To determine the

disease-related target genes, searches were conducted using OMIM (https://www.omim.org/) and GeneCards (https://www.genecards.org/) employing the following keywords: 'COVID19' AND 'Diabetes Mellitus Type 2' AND 'Hyperinflammatory' AND 'Innate Immunity' AND 'Cellular Immunity' AND 'Humoral Immunity' [14,19].

2.3 Target Protein Prediction

A network of identified compounds, target genes, and associated pathways was generated in Cytoscape (version 3.10.2) by integrating compound-gene and gene-pathway interactions. The protein-protein interaction (PPI) network of the collected target genes was constructed in the STRING platform (https://string-db.org/), restricting the organism to *Homo sapiens* and applying the maximum interaction confidence threshold (0,900) to retain only the most strongly supported interactions, thereby minimizing false positives and ensuring network robustness for subsequent analyses [14].

2.4 Enrichment Analysis

Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis were performed to identify the functional roles and biological pathways associated with the target genes [20]. GO terms were classified into molecular functions, biological processes, and cellular components. Analyses were conducted using the Metascape web tool (htttps://metascape.org/) [21].

2.5 Pharmacokinetic Profile Prediction

The pharmacokinetic profile and drug-likeness were evaluated based on Lipinski's rule of five using SwissADME (http://www.swissadme.ch/index.php) [18]. These rules provide guidelines for assessing drug bioavailability, with a focus on the Absorption, Distribution, Metabolism, Excretion (ADME) profile [22]. An overview of the study workflow is presented in Fig. 1.

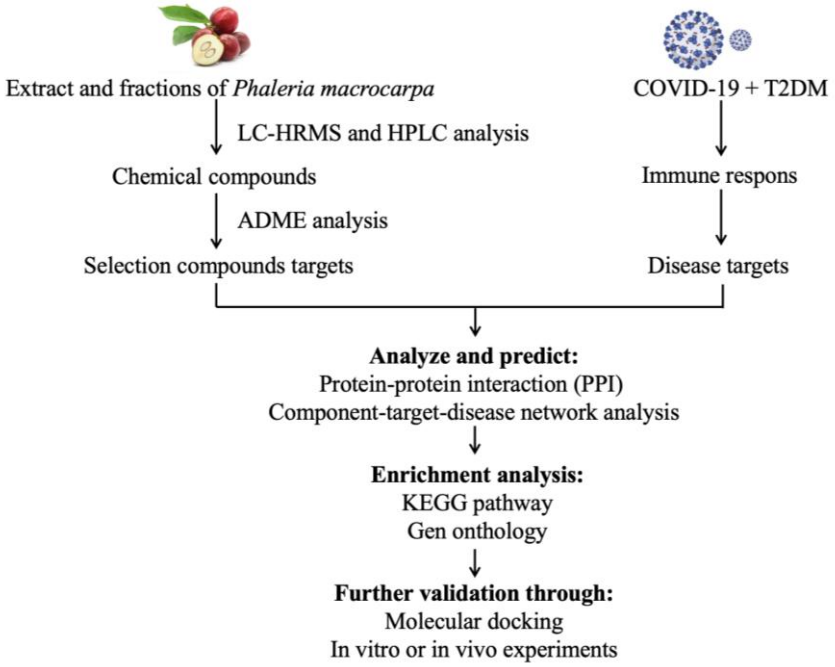

Fig. 1. Overview of study workflow

3 Results

3.1 Result of LC-HRMS Analysis

Out of Out of 643 compounds detected by LC-HRMS, 24 compounds from the extract and fractions of *P. macrocarpa* are presented in Table 1. Targeted HPLC analysis further confirmed the presence of phalerin and mangiferin, as shown in Fig. 2a and 2b.

Table 1. Compounds identified from extract and fractions of *P. macrocarpa* by LC-HRMS.

Compound	Formula	RT (min.)	Calc. m/z	Error PPM (<5 ppm)
L-α-PALMITIN	$C_{19}H_{38}O_4$	14,334	330,2763	-2,03
Khellin	$C_{14}H_{12}O_5$	5,271	260,0681	-1,43
(±) Muscone	$C_{16}H_{30}O$	14,326	238,2295	-0,69
Stearamide	$C_{18}H_{37}NO$	15,501	283,2877	0,46
Capsi-amide	$C_{17}H_{35}NO$	14,756	269,2719	0,01
Anomalin A	$C_{14}H_{10}O_6$	6,015	274,0479	0,59
Pectolinarigenin	$C_{17}H_{14}O_6$	10,234	314,0792	0,45
2,5,6,8-Tetrahydroxy-2-methyl-2,3-dihydro-4H-benzo[g]chromen-4-one	$C_{14}H_{12}O_6$	5,89	276,0635	0,38
2,2,6,6-Tetramethyl-1-piperidinol (TEMPO)	$C_9H_{19}NO$	8,947	157,1468	0,71
Benzaldehyde	C_7H_6O	5,695	106,0422	3,31

p-cymene	$C_{10}H_{14}$	6,746	134,1096	0,3
(2E,4Z,12E)-1-(1-Piperidinyl)-2,4,12-octadecatrien-1-one	$C_{23}H_{39}NO$	16,142	345,3028	-1,11
Navenone A	$C_{15}H_{15}NO$	10,446	225,1154	0,04
Glycitein	$C_{16}H_{12}O_5$	10,058	284,0687	0,63
Erucamide	$C_{22}H_{43}NO$	16,569	337,3341	-1,19
Acridine-9(10H)-thione	$C_{13}H_9NS$	11,8	211,0457	0,77
Tridemorph	$C_{19}H_{39}NO$	15,885	297,303	-0,57
1-(14-methylhexadecanoyl) pyrrolidine	$C_{21}H_{41}NO$	16,724	323,3182	-1,83
24-methylenecycloartanol	$C_{31}H_{52}O$	19,143	440,4017	-0,3
Coumarin	$C_9H_6O_2$	8,705	146,0367	-0,44
Stigmasterol	$C_{29}H_{48}O$	19,06	412,37022	-0,71
Mahkoside A	$C_{20}H_{22}O_{10}$	4,817	422,12096	-0,8

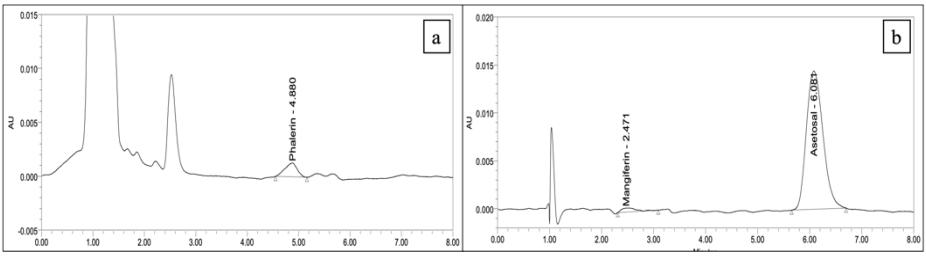

Fig. 2. Targeted HPLC analysis of selected compounds detected in the extract and fractions of *P. macrocarpa*: (a) phalerin and (b) mangiferin.

3.2 Assessment of Drug-Likeness and Pharmacokinetics Profile

Table 2 presents the profiles of the selected compounds, including an assessment of their drug-likeness based on Lipinski's Rule of Five, and pharmacokinetic profiles – commonly referred to as absorption, distribution, metabolism and excretion (ADME), which are influenced by the physicochemical properties and lipophilicity of the compounds. In this study, a total of 24 compounds were evaluated. Among these, mangiferin exhibited two violations of Lipinski's Rule of Five, indicating potential limitations in its oral bioavailability and suggesting it may not be an optimal candidate for oral drug development. Based on Lipinski's criteria, compounds may have poor oral bioavailability if two or more of their criteria are violated [23].

Table 2. Drug-likeness prediction of identified phytochemicals in *P. macrocarpa*.

Compound	MW (g/mol)	GI Abs	B B B	CYP Substance					Lipinski Violation
				1A2	2C19	2C9	2D6	3A4	
Phalerin	422.38	Low	-	-	-	-	-	-	1
Mangiferin	422.34	Low	-	-	-	-	-	-	2
L-α-PALMITIN	330.50	High	√	-	-	-	√	-	0

Khellin	260.24	High	√	√	-	√	-	√	0
(±) Muscone	238.41	High	√	-	-	√	-	-	0
Stearamide	283.49	High	√	√	-	-	-	-	1
Capsi-amide	269.47	High	√	√	-	-	-	-	0
Anomalin A	274.23	High	-	√	-	-	√	√	0
Pectolinarigenin	314.29	High	-	√	-	-	-	-	0
2,5,6,8-Tetrahydroxy-2-methyl-2,3-dihydro-4H-benzo[g]chromen-4-one	276.24	High	-	-	-	-	-	-	0
2,2,6,6-Tetramethyl-1-piperidinol (TEMPO)	157.25	High	-	-	-	-	-	-	0
Benzaldehyde	106.12	High	√	-	-	-	-	-	0
p-cymene	134.22	Low	√	-	-	-	√	-	1
(2E,4Z,12E)-1-(1-Piperidinyl)-2,4,12-octadecatrien-1-one	345.56	Low	√	-	-	-	√	-	1
Navenone A	225.29	High	√	√	-	-	-	-	0
Glycitein	284.26	High	-	√	-	-	√	√	0
Erucamide	337.58	Low	-	√	-	-	-	-	1
Acridine-9(10H)-thione	211.28	High	√	√	√	-	-	-	0
Tridemorph	297.52	High	√	√	-	-	√	-	0
1-(14-methylhexadecanoyl) pyrrolidine	323.56	High	√	√	-	-	-	-	1
24-methylenecycloartanol	440.74	Low	-	-	-	-	-	-	1
Coumarin	146.14	High	√	√	-	-	-	-	0
Stigmasterol	412.69	Low	-	-	-	√	-	-	1
Mahkoside A	422.38	Low	-	-	-	-	-	-	1

3.3 Screening of Target Genes and Development of Protein-Protein Interaction Networks

A total of 784 predicted target genes were identified for 24 compounds from *P. macrocarpa*. As depicted in Fig. 3, the resulting interaction network included 531 nodes and 1968 edges. In contrast, a total of 332 potential disease–related target genes associated with COVID-29 and T2DM were obtained from the OMIM and GeneCard databases, with the organism restricted to *Homo sapiens*. The PPI network of the intersecting target genes, consisted of 108 nodes and 403 edges (see Fig. 4).

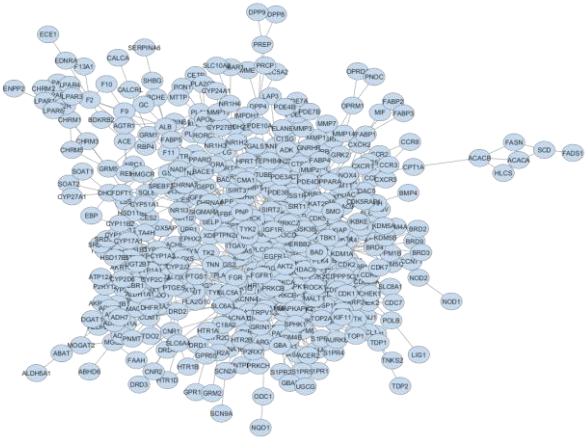

Fig. 3. Visualization of 784 target proteins associated with 24 compounds from *P. macrocarpa* using Cytoscape

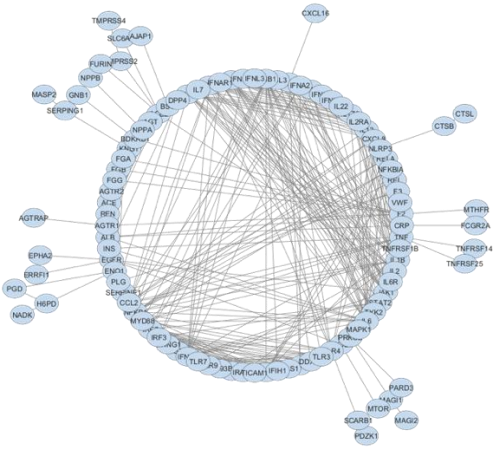

Fig. 4. Protein-protein interaction network linked to the immune response in COVID-19 with T2DM at a 90% confidence level.

The prediction was performed by integrating two networks: the target gene network of *P. macrocarpa* compounds and the PPI networks associated with disease pathogenesis. The merged network was analyzed and visualized using Cytoscape, which facilitates the identification of key overlapping targets and their interactions. Clustering analysis using ClusterOne identified 27 nodes, which were then determined using CytoHubba. The nodes included UNC93B1, TBK1, MYD88, IRF7, IFNL2, IRF3, IFNL3, IFIH1, IFNL1, OAS1, IFNA2, TLR7, IFNAR2, TLR9, TYK2, TLR3, STAT2, IFNA1, IFNLR1, DDX58, IFNAR1, TLR8, TICAM1, ISG15, IFNB1, IRAK4, JAK1 (Fig. 5 and Table 3).

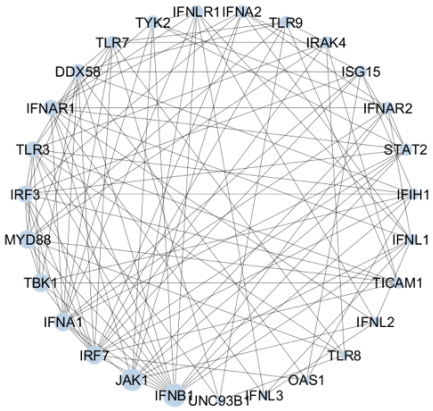

Fig. 5. Results of a 27-node cluster utilizing ClusterOne.

Table 3. Potential therapeutic targets of *P. macrocarpa* against COVID-19 with T2DM.

Target Name	Gene ID	Target Name	Gene ID	Target Name	Gene ID
IFNB1	P01574	DDX58	O95786	STAT2	P52630
JAK1	P23458	IFNLR1	Q8IU57	TICAM1	Q8IUC6
IRF7	Q92985	TLR7	Q9NYK1	IFNL1	Q8IU54
MYD88	Q99836	IFNA2	P01563	IFIH1	Q9BYX4
TBK1	Q9UHD2	TYK2	P29597	IFNL2	Q8IZJ0
IFNA1	P01562	IRAK4	Q9NWZ3	TLR8	Q9NR97
IRF3	Q14653	TLR9	Q9NR96	IFNL3	Q8IZI9
IFNAR1	P17181	IFNAR2	P48551	OAS1	P00973
TLR3	O15455	ISG15	P05161	UNC93B1	Q9H1C4

3.4 Enrichment Analysis

Enrichment analysis was performed using the Metascape platform. Based on GO annotation, the study identified a total of 358 biological processes, 27 cellular components, 43 molecular functions associated with the target genes, and 56 KEGG pathway, as illustrated in Fig. 6.

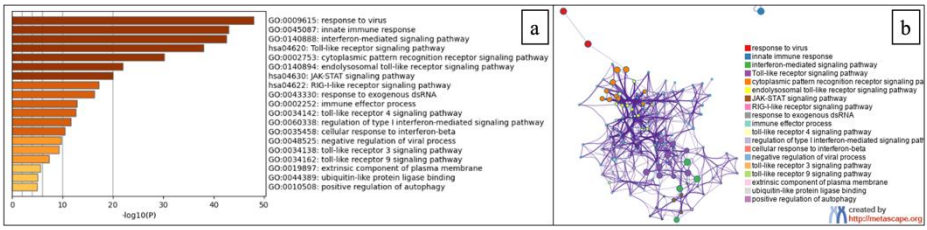

Fig. 6. Enrichment network analysis using GO and pathways (a) Darker colors represent more significant pathways (lower p-value); (b) Node color indicate cluster membership, and edge thickness reflects the similarity score.

The relationship between the active compounds of *P. macrocarpa*, their predicted target proteins, and the immune-related pathways involved in the immunological response to COVID-19 with type 2 diabetes mellitus (T2DM) is illustrated in Fig. 7.

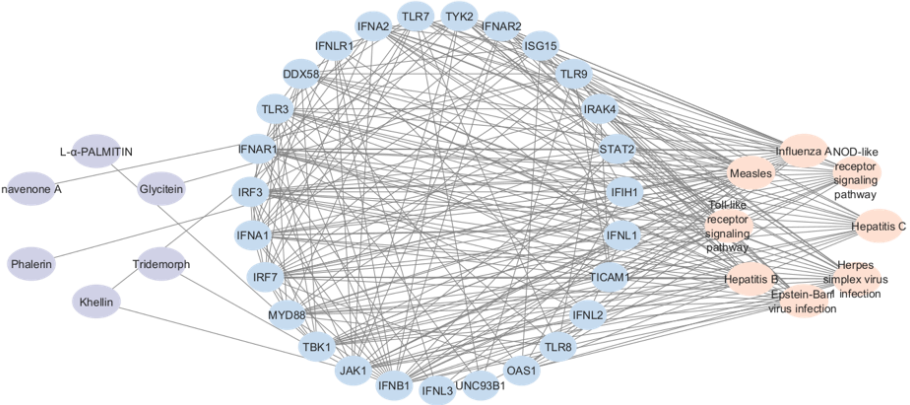

Fig. 7. Pharmacological network analysis

4 Discussion

Network pharmacology represents a holistic approach that integrates computational algorithms and virtual simulation to predict interactions with multiple targets. This methodology is extensively applied in uncovering potential targets within complex traditional medicine formulation [24]. The intersection analysis identified a protein targeted explicitly by the constituents of *P. macrocarpa*. A total of six compounds, such as phalerin, khellin, tridemorph, glycetin, L-α-palmitin, and navenone A were found to interact with 27 nodes of the target protein associated with the immune response in COVID-19 with T2DM. The target genes are primarily related to defense responses to viruses, interferon-mediated signaling pathways, cellular responses to viruses, toll-like receptor signaling pathways, and type 1 interferon-mediated signaling pathways.

In this study, the target genes within the network play key roles in modulating the immune response. Myeloid differentiation primary response protein (MYD88) is a critical adaptor molecule in innate immunity that mediates signaling of Toll-like receptors (TLRs) and interleukin-1 receptors (IL-1Rs)-specifically through TLR4, TLR7, and TLR8-while TRIF is associated with TLR 3 and TLR 4 [25]. It has been specifically implicated in the recognition of SARS-CoV-2 RNA. This cascade ultimately activates NF-Kβ, promotes cytokine production (IL-1, IL-6 and TNF-α), and initiates inflammatory responses [25,26]. MYD88 also enhances IL-8 transcription and contributes to IL-18-mediated signaling.

Interleukin-1 receptor-associated kinase 4 (IRAK4) is a gene target of phalerin, a serine/threonine-protein kinase that is essential in triggering innate immune response against foreign pathogens. Involved in TLR and IL-1R signaling pathways [27]. It is rapidly recruited by MYD88 to the receptor signaling complex upon TLR activation, forming the Myddosome together with IRAK2. Phosphorylates initially IRAK1, thus stimulating the kinase activity and intensive autophosphorylation of IRAK1. Inhibition of IRAK1 and IRAK4 has demonstrated significant efficacy in attenuating various inflammatory diseases [27–29]. Accordingly, modulation of IRAK activity represents a promising therapeutic strategy for managing inflammatory conditions.

The interferon lambda (IFNL) cytokine family is produced during the early stages of infection and is widely recognized for its antiviral properties and overall beneficial role in host defense [30]. IFNL1, IFNL2, and IFNL3 have antiviral, antitumor and immunomodulatory activities. IFNL2 binds a heterodimeric class II cytokine receptor composed of IL10RB and IFNLR1. This receptor activation triggers the JAK/STAT signaling pathway, leading to the induction of interferon-stimulated genes (ISGs), which are essential for establishing an antiviral state [31]. JAK1 is a tyrosine kinase of the non-receptor type, involved in the IFN-α, -β, and -γ signaling pathway. JAK-1-driven activation of the JAK/STAT pathway contributes to the cytokine storm in severe COVID-19. Modulating this pathway offers a targeted strategy to control hyperinflammation [32].

The strength of this study lies in its comprehensive approach, using a network pharmacology method to systematically examine the immunomodulatory effects of phytocompounds derived from *P. macrocarpa* in relation to COVID-19 and type 2 diabetes mellitus (T2DM). The study integrates compound identification via LC-HRMS and HPLC with bioinformatic analysis of target proteins, protein-protein interactions, gene ontology, and pathway enrichment, thereby offering a thorough systems-level insight into potential mechanisms of action. We identified six key phytochemical compounds that interact with 27 immune-related targets, emphasizing specific molecular pathways, including the interferon and toll-like receptor signaling pathways, pertinent to hyperinflammation in comorbid conditions. The incorporation of ADME profiling enhances translational relevance, thereby endorsing the viability of selected compounds for subsequent drug development.

The limitations of this study include the reliance on an in-silico network pharmacology approach only, which, although valuable in identifying potential interactions between phytocompounds and immune-related targets, does not validate actual biological activity or efficacy. Validation of the findings through in vitro and in vivo experiments is necessary to confirm the immunomodulatory effects of the key compounds from *P. macrocarpa*, particularly against SARS-CoV-2 infection and type 2 diabetes mellitus (T2DM). This study establishes a crucial basis for further research for drug development from herbal medicine that contains multiple compounds, by pinpointing particular phytochemicals and multiple molecular targets that could affect hyperinflammatory responses. Our study may contribute to understanding the mechanism of drug candidates and improve the drug discovery process for patients with metabolic comorbidities.

5 Conclusion

In conclusion, six bioactive compounds from 24 constituents of *P. macrocarpa* were identified as interacting with 27 protein targets associated with the immune response in COVID-19 patients with type 2 diabetes mellitus (T2DM). These targets play key roles in modulating immune function through pathways such as defense response to virus, interferon-mediated signaling pathway, cellular response to virus, toll-like receptor signaling pathway, and type 1 interferon-mediated signaling pathway.

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Disclosure of Interests. The authors declare no conflicts of interest.

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