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Genetic and therapeutic for oral lichen planus and diabetes mellitus: a comprehensive study

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Background This study employed a bidirectional Mendelian Randomization (MR) approach to explore the causal relationships between Oral Lichen Planus (OLP), diabetes mellitus (DM), and glycemic control. It also aims to identify potential pharmacological and herbal treatments that effectively address both OLP and the metabolic dysfunctions associated with DM.

Methods This study employs a two-way MR approach to investigate the potential causal relationships between diabetes type and glycated hemoglobin (HbA1c) levels, and the risk of OLP. We analyzed differentially expressed genes from the OLP dataset in the Genomics Expression Omnibus (GEO) database, cross-referencing these with HbA1c-related genes for enrichment analysis. Additionally, the Drug-Gene Interaction Database (DGIdb) and Traditional Chinese Medicine Systems Pharmacology Database (TCMSP) were utilized to assess the effectiveness of specific drugs, herbs, and ingredients in treating OLP while managing blood glucose levels.

Results The MR analysis revealed a significant association between Type 1 Diabetes mellitus (T1DM) and an increased risk of OLP, unlike Type 2 Diabetes mellitus (T2DM). This finding indicates a unique immunological interaction in T1DM that may predispose individuals to OLP. The drug prediction analysis focused on core targets linked to OLP and HbA1c, evaluating the therapeutic potential of retinoic acid, prednisone, and thalidomide for treating OLP and regulating blood glucose levels. Additionally, herbal medicines such as *Ecliptae herba*and *Amygdalus communis vas*, along with herbal ingredients like quercetin, luteolin, and 17-beta-estradiol, were identified for their anti-inflammatory properties and potential to mitigate metabolic dysfunction in diabetes.

Conclusion The study highlighted a complex interplay between diabetes and OLP, underscoring the efficacy of integrated therapeutic strategies that target both conditions. The findings suggest that both pharmaceutical and herbal treatments can effectively manage the clinical manifestations of OLP and associated metabolic challenges. This holistic approach to treatment could significantly enhance patient outcomes by addressing the interconnected aspects of these chronic conditions.

Keywords Lichen planus, Oral, Diabetes mellitus, Mendelian randomization analysis, Glycated hemoglobin, Thalidomide, *Amygdalus communis vas*, Quercetin

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Introduction

Oral Lichen Planus (OLP) is a chronic inflammatory condition that affects the mucous membranes inside the mouth, manifesting as symptoms ranging from mild discomfort to severe erosions and ulcers. It is noteworthy that approximately 15% of OLP patients develop skin lesions, 20% experience genital lesions, and about 1% of cases may evolve into oral squamous cell carcinoma, underscoring its potential malignancy [1, 2]. The etiology and progression of OLP are critically important in clinical settings, especially given its association with systemic diseases. Notably, research indicates a higher prevalence of OLP among diabetic patients compared to healthy individuals, which is thought to be linked to systemic factors such as immune status, chronic inflammation, and oxidative stress. This association highlights the complex interplay between metabolic disorders and immune-mediated conditions [3].

Diabetes Mellitus (DM) is a prevalent metabolic disorder characterized by elevated hyperglycemia levels, with approximately 45% of cases globally diagnosed [4]. The disorder is divided into two main types: Type 1 Diabetes Mellitus (T1DM), which results from an autoimmune-induced insulin deficiency, and Type 2 Diabetes Mellitus (T2DM), caused by insulin resistance. Diagnosis for both types involves measuring elevated levels of HbA1c in the blood [5]. Diabetes not only poses significant health burdens globally but also leads to a myriad of complications affecting multiple organ systems [6]. This widespread impact makes it a focal point for in-depth epidemiological and genetic studies.

The intersection of mucosal diseases and metabolic disorders presents a rich area for research due to the systemic nature of these conditions. Observational studies have indicated potential links between metabolic syndromes and oral mucosal diseases [7], yet the causal relationships remain elusive. Mendelian Randomization (MR), which uses genetic variants as instrumental variables, offers a method to estimate the causal effects of an exposure on an outcome, thus mitigating the confounding factors common in observational studies [8]. This study aims to harness the robust framework of MR to delve deeper into the potential connections between diabetes and oral lichen planus. By leveraging genetic data related to both conditions, we specifically aim to investigate whether a genetic predisposition to diabetes could influence the development of oral lichen planus, and vice versa. Based on MR research, we also propose exploring joint effect drug predictions for both diseases to potentially enhance treatment outcomes.

Materials and methods

MR analysis

Data collection

For this study, rigorous statistical analysis was conducted using data from two major databases: FINNGEN and the IEU OpenGWAS database. From the FINNGEN database, detailed data were extracted for oral lichen planus (587 cases and 411,594 control samples), type 1 diabetes (4,320 cases and 335,112 control samples), and type 2 diabetes (65,085 cases and 335,112 control samples). Additionally, the IEU OpenGWAS database provided diabetes data under entry ID GCST90038633, encompassing 24,659 cases and 484,939 controls. The associated biomarker dataset for hemoglobin A1c, crucial for assessing metabolic control in diabetes patients, was accessed under ID GCST90002244, including 146,806 cases and 281,416 controls (Table 1). This comprehensive data collection facilitated a robust assessment of the genetic intersections between DM and OLP.

Analytical strategy

The analytical strategy of this study employed sophisticated statistical models to investigate potential causal pathways linking diabetes, HbA1c, and OLP. MR research adheres to three core assumptions: the correlation hypothesis, the exclusion restriction hypothesis, and the independence hypothesis. With the extensive data available, the study screened for single-nucleotide polymorphisms (SNPs) associated with the exposures, setting the significance threshold at $P<5e\text{-}5$. The statistical analysis primarily utilized MR frameworks, employing genetic variants linked to diabetes and HbA1c as instrumental variables to explore their impact on oral lichen

Table 1 Detailed information of summary statistics used in the analysis

Phenocode	GWAS ID	Databases	Sample size	Number of SNPs	PMID
Oral lichen planus	—	FINNGEN	587	411,594	—
Type 1 diabetes	—	FINNGEN	4,320	33,512	—
Type 2 diabetes	—	FINNGEN	65,085	335,112	—
Diabetes	ebi-a-GCST90038633	IEU	484,598	9,587,836	33,959,723
Glycated hemoglobin levels	ebi-a-GCST90002244	IEU	146,806	30,649,064	34,059,833

planus. An F-value > 10 was set to ensure robust instrument strength. Linkage disequilibrium was controlled by setting conditions to $r2 < 0.001$ and a window of 10,000 KB. Confounding factors were mitigated using the PhenoScanner tool (lifestyle factors, smoking and alcohol consumption, medication use, etc.). Additionally, reverse causation was assessed through reverse validation to strengthen the findings.

Statistical models and analysis

Mendelian Randomization analyses in this study were meticulously executed using various methods to enhance the robustness and validity of the findings. Data were analyzed using R language version 4.3.2, employing primary statistical tools such as the Inverse Variance Weighting (IVW) method and MR-Egger method. Supplementary methods, including MR weighted mode, MR weighted median, and MR simple mode, were also utilized. To assess heterogeneity and the potential for pleiotropy, Q-value tests and tests for directional horizontal pleiotropy were conducted. Each single-nucleotide polymorphism (SNP) was incrementally excluded using the leave-one-out method. This approach allowed for the calculation of the meta-effect of the remaining SNPs and observation of any changes in the results after each SNP exclusion, thereby ensuring the reliability of the findings (Fig. 1).

Gene obtain

Data procurement

Gene expression microarray data for this study were sourced from the GEO database (https://www.ncbi.nlm.nih.gov/geo/), specifically targeting published datasets on OLP. The selected dataset, identified as GSE131567, includes samples from Homo sapiens and was chosen after thorough screening. Published on May 21, 2022, it comprises six oral mucous biopsies from untreated OLP patients and six normal oral mucous tissues from healthy individuals.

The screening of differentially expressed genes (DEGs) was conducted using the GEO2R tool, an online application that facilitates the comparison of gene expression profiles between experimental conditions. Data processing and identification of DEGs between OLP and normal tissues were performed using the GEO2R limma toolkit in R version 3.2.3. The screening threshold for DEGs was set at a p-value of < 0.05 and a log2 fold change (log2FC) greater than 2, ensuring that only statistically significant and biologically relevant genes were considered.

Screening for relevant targets for hba1c and OLP

To identify relevant targets for HbA1c and OLP, target genes for HbA1c were initially downloaded from the GeneCards database (https://www.genecards.org/). These were then cross-referenced with differentially expressed

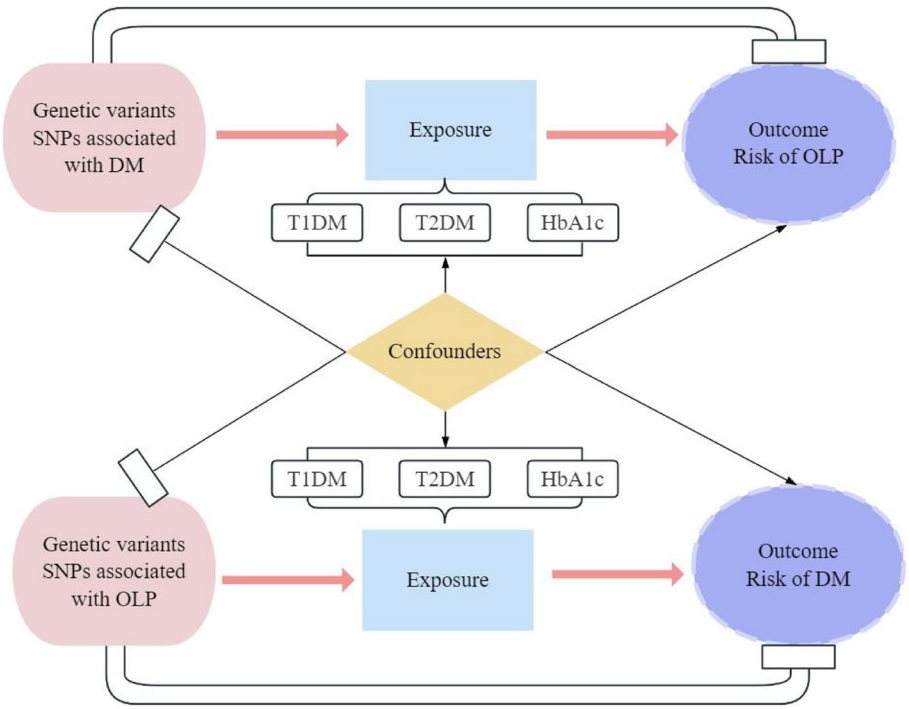

Fig. 1 Diagram of design of bidirectional Mendelian randomization study

genes for OLP obtained from the GEO database. The intersecting targets were selected, and a Venn diagram was constructed to visualize the overlap.

Subsequently, the String database (https://cn.string-db.org/) was used to further analyze the common targets. The search was narrowed to Homo sapiens, with a filter set to exclude disconnected nodes in the network and to ensure a minimum interaction score confidence of greater than 0.700. The resulting protein–protein interaction (PPI) network map was saved in csv format.

This file was then imported into Cytoscape, where the CytoNCA plugin was utilized to analyze the gene interactions based on betweenness centrality (BC), cellular component (CC), and molecular function (MF). This analysis helped visualize the core targets, providing insights into the potential molecular interactions between HbA1c and OLP.

GO and KEGG enrichment analysis

The David database (https://david.ncifcrf.gov/) was utilized. Intersection genes were uploaded to the 'Start Analysis' page for comprehensive data analysis. This process facilitated the extraction of key information on BP, CC, MF, and pathways within the KEGG database. This analysis helped categorize the intersection genes within the context of Gene Ontology, providing valuable insights into the functional and pathway associations relevant to the study.

Drug prediction

Drug screening was conducted using the DGIdb online database (https://www.dgidb.org/). The top 10 key genes identified from the study were input into the database to identify potential therapeutic candidates. Selection criteria for these drugs included the number of drugs matched to each target, their regulatory approval status, and their interaction scores.

Additionally, the TCMSP database (https://old.tcmsp-e.com/) was employed to explore Traditional Chinese Medicine (TCM) and active TCM ingredients. The top 10 key genes were also used to screen for related TCM and active ingredients. Cytoscape software was then utilized to create a network map of these TCM active ingredients. From this network, TCMs and active ingredients showing significant intersections were selected as candidate drugs, providing a dual approach in the search for effective treatments.

Results

MR analytic result

Causal effects of DM on OLP

In our analysis, with DM, T1DM, and T2DM as exposures and oral OLP as the outcome, the results showed no direct causal relationships between DM and OLP or T2DM and OLP. The MR tests across all five algorithms indicated *P*-values greater than 0.05. However, when T1DM was used as the exposure with OLP as the outcome, the MR analysis yielded different results. The Inverse Variance Weighting (IVW) method showed an odds ratio (OR) of 1.331 with a 95% confidence interval (CI) from 1.027 to 1.725 and a *P*-value of 0.031. The MR-Egger method gave an OR of 1.027 (95% CI 0.667–1.583, $P=0.907$), the Weighted Mode an OR of 1.146 (95% CI 0.856–1.534, $P=0.385$), the Simple Median an OR of 1.732 (95% CI 1.147–2.617, $P=0.009$), and the Weighted Median an OR of 1.322 (95% CI 0.987–1.770, $P=0.061$) (Fig. 2A).

In Fig. 2B, the IVW method's red solid line was entirely to the right of zero, suggesting that an increase in T1DM is associated with an increased risk of developing OLP. Moreover, heterogeneity tests (IVW, $Q=11.07$, $P=0.198$) and tests for directional horizontal pleiotropy (Egger intercept $=0.06$, $P=0.198$) supported these findings (Table 2).

Figure 2C illustrated that each data point, representing an SNP site, aligned with the hypothesis that a stronger genetic effect on T1DM correlates with a stronger effect on OLP, indicating a positive causal association. Fig. 2D showed that excluding individual SNPs had little effect on the overall error lines, which consistently remained to the right of zero, demonstrating the reliability of the results. The funnel plot exhibited a symmetric shape, indicating minimal deviation (Fig. 2E). These analyses underscore a potential causal link between T1DM and OLP, while no such link was found between T2DM and OLP.

Impact of hba1c on OLP

Subsequent studies examined HbA1c as a potential risk factor for OLP. In this analysis, HbA1c was considered as an exposure factor, with diabetes as the underlying risk and OLP as the outcome. The results of the MR analysis indicated varied outcomes: the IVW method showed an OR of 5.206 with a 95% CI of 1.273 to 21.288 and a *P*-value of 0.022. The MR-Egger method yielded an OR of 3.396 (95% CI 0.378 to 30.474, $P=0.281$), the Weighted Mode an OR of 5.054 (95% CI 0.561 to 45.494, $P=0.156$), the Simple Median an OR of 0.881 (95% CI 0.020 to 9.835, $P=0.949$), and the Weighted Median an OR of 7.267 (95% CI 1.031 to 51.227, $P=0.047$) as shown in Fig. 3A.

As depicted in Fig. 3B, the IVW red solid line was entirely to the right of zero, suggesting that an increase in HbA1c levels is associated with an increased risk of developing OLP. This pattern suggests a causal relationship between HbA1c levels and OLP. The heterogeneity

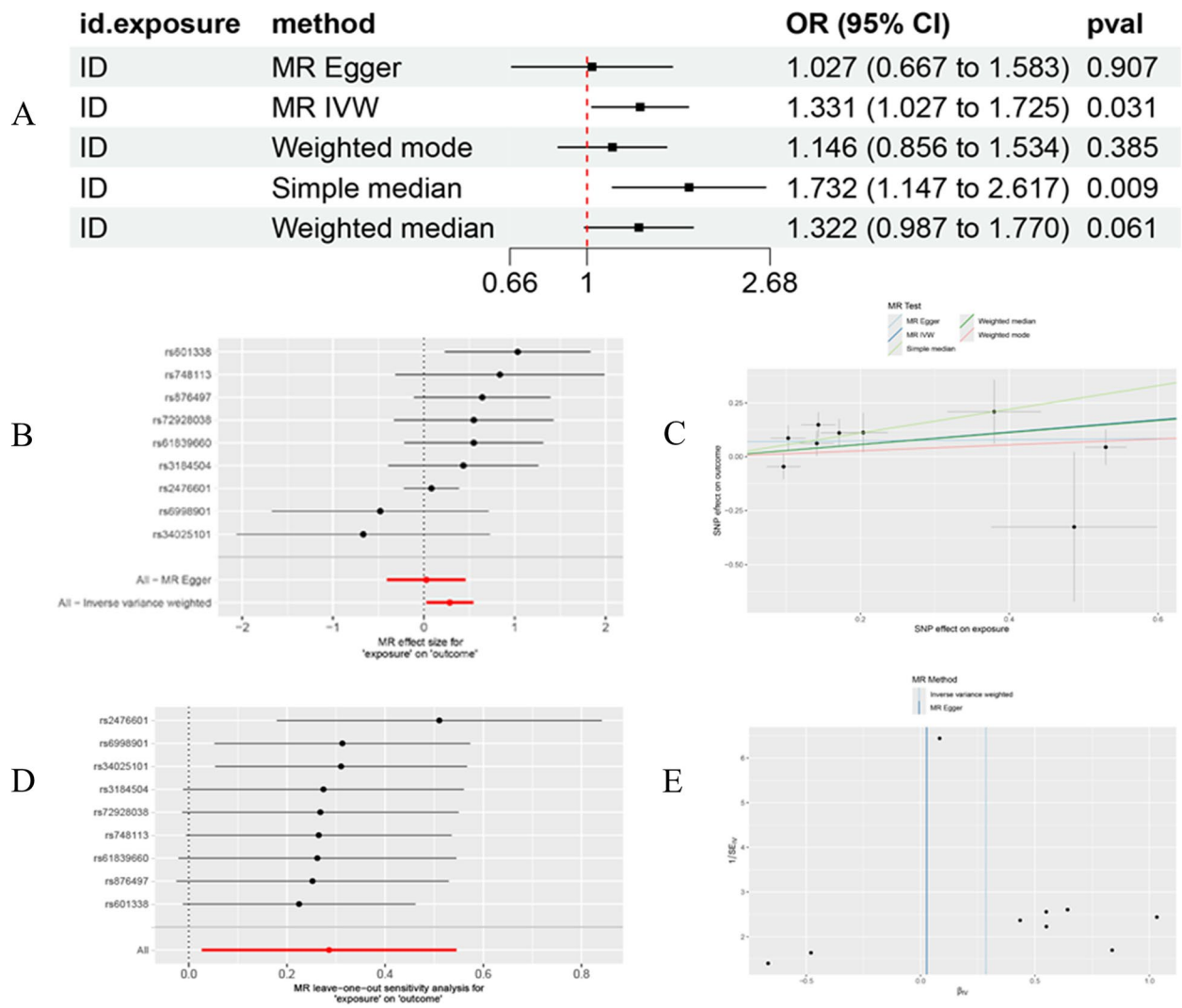

Fig. 2 **A** Comparison of results from different MR methods for T1DM and OLP (Five algorithms). **B** Forest map of the causal relationship between T1DM and OLP (The IVW method's red solid line was entirely to the right of zero, suggesting that an increase in T1DM is associated with an increased risk of developing OLP). **C** Scatter diagram of the causal relationship between T1DM and OLP (Each data point represents an SNP site with an overall upward slope, indicating positive causality). **D** Leave-one-out forest map of the causal relationship between T1DM and OLP (The error line is always kept to the right of zero, indicating the reliability of the results). **E** Funnel diagram of the causal relationship between T1DM and OLP (The funnel plot presents a symmetrical shape, indicating minimal deviation)

Table 2 Sensibility analysis

Exposure	outcome	Heterogeneity tests						Horizontal pleiotropic			MR presso
		MR Egger			IVW			Egger intercept	se	pval	
		Q	Q_df	Q_pval	Q	Q_df	Q_pval				
D1M	OLP	8.58	7	0.284	11.07	8	0.198	0.068	0.048	0.198	0.34
HbA1c	OLP	37.3	40	0.593	37.5	41	0.625	0.008	0.017	0.621	0.84

tests (Q = 37.5, $P = 0.625$) and tests for directional horizontal pleiotropy (Egger intercept = 0.008, $P = 0.621$) supported these findings (Table 2).

Figure 3C illustrated that each data point, representing an SNP site, confirmed that a stronger genetic effect on HbA1c correlates with a stronger effect on OLP,

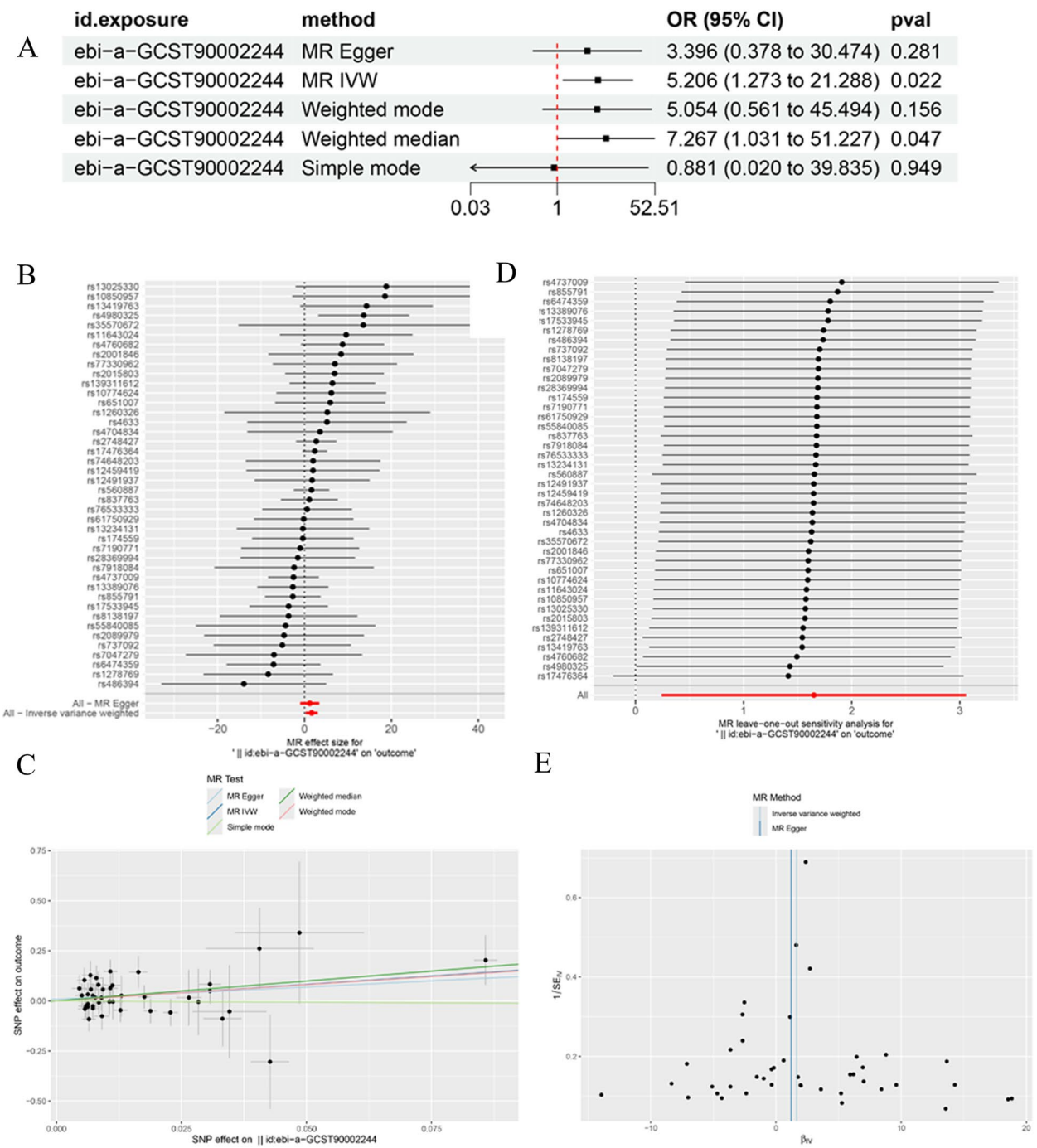

Fig. 3 **A** Comparison of results from different MR methods for HbA1c and OLP (Five algorithms). **B** Forest map of the causal relationship between HbA1c and OLP (the IVW red solid line was entirely to the right of zero, suggesting that an increase in HbA1c levels is associated with an increased risk of developing OLP.). **C** Scatter diagram of the causal relationship between HbA1c and OLP (Each data point represents an SNP site with an overall upward slope, indicating positive causality). **D** Leave-one-out forest map of the causal relationship between HbA1c and OLP (The error line is always kept to the right of zero, indicating the reliability of the results). **E** Funnel diagram of the causal relationship between HbA1c and OLP(The funnel plot presents a symmetrical shape, indicating minimal deviation)

indicating a positive causal association between the two. Fig. 3D showed minimal variation in the overall error lines after excluding individual SNPs (all error bars remained to the right of zero), demonstrating the reliability of these results. The funnel plot exhibited a symmetric shape, indicating minimal deviation (Fig. 3E). However, subsequent analysis revealed direct causal link between HbA1c and OLP, adding a layer of complexity to these findings.

Reverse causality

In a comprehensive analysis, we conducted reverse MR with OLP as the exposure and DM, T1DM, T2DM, and HbA1c as outcomes. The results indicated no inverse causal relationships between OLP and any of the diabetes-related outcomes. Specifically, the analyses showed no reverse causal links between OLP and DM, OLP and T1DM, OLP and T2DM, or OLP and HbA1c. This finding suggests that while OLP may be influenced by these factors, it does not appear to contribute causally to the development of diabetes or variations in HbA1c levels.

Related core targets and enrichment analysis of OLP and hba1c

Screening for relevant targets for hba1c and OLP

A comprehensive dataset of 21,601 OLP-related genes was retrieved from the GEO database, which included 2,353 differentially expressed genes. From the GeneCards

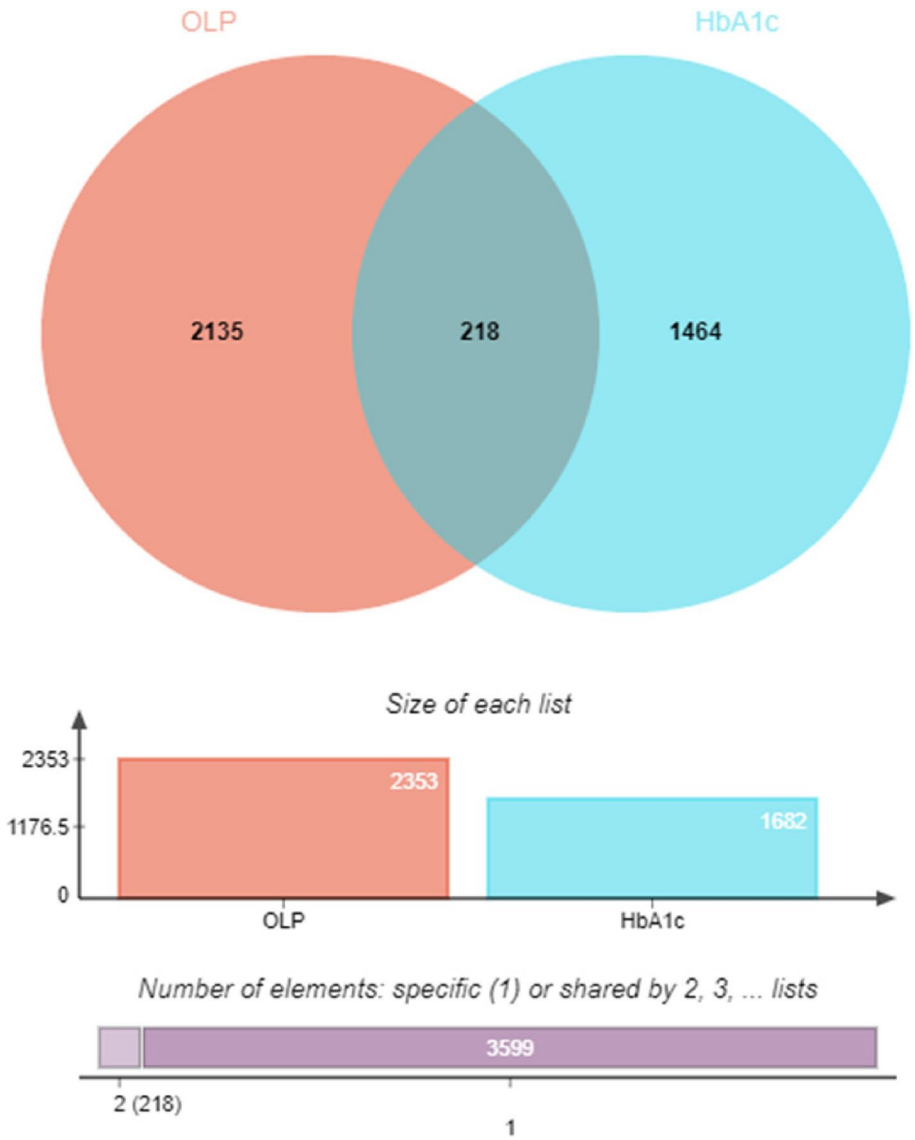

Fig. 4 HbA1c and OLP Intersection Targes

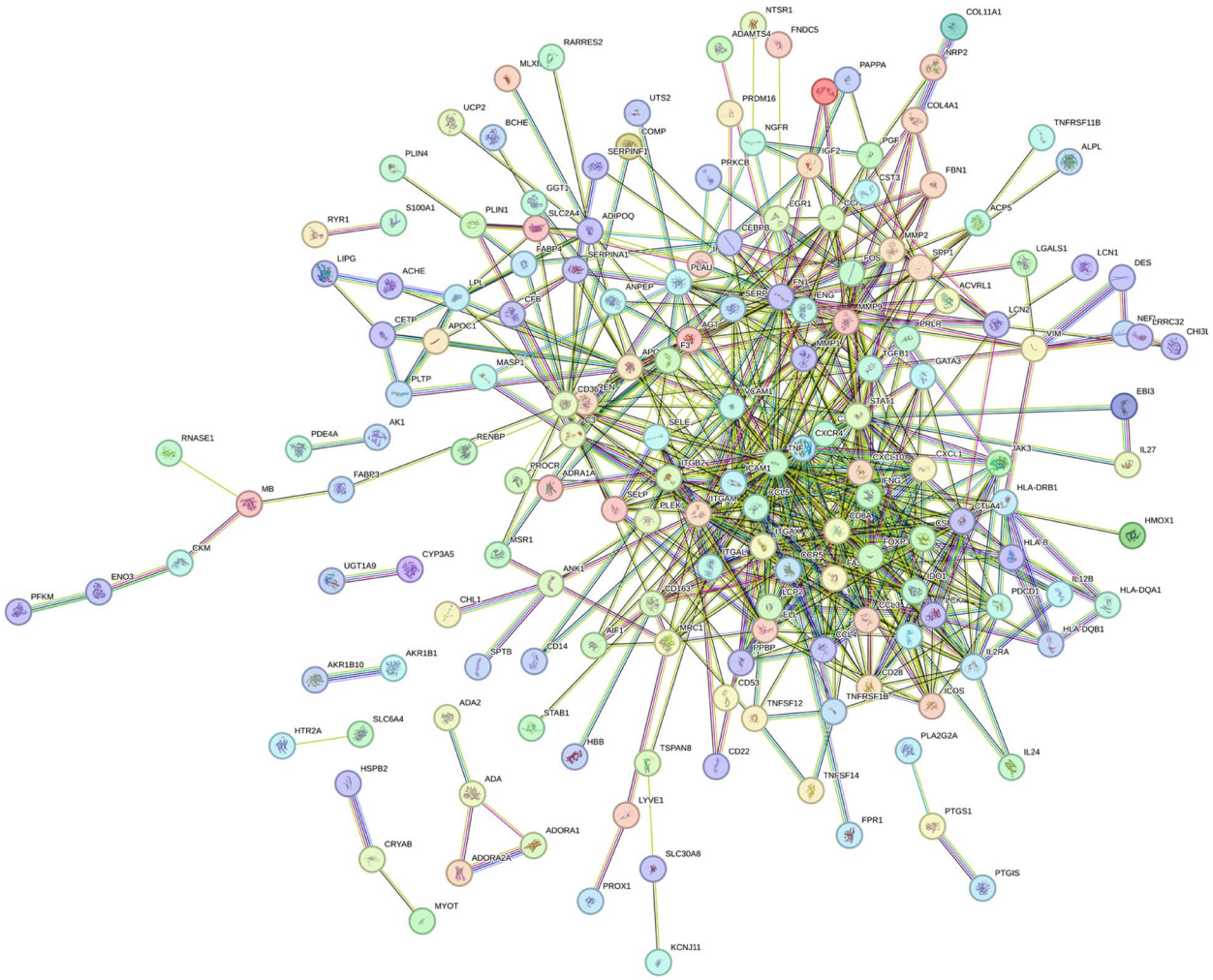

Fig. 5 Protein–protein network construction

database, we identified 1,682 targets related to HbA1c. After cross-referencing these datasets, we isolated 218 intersecting genes between OLP differential genes and HbA1c-related targets, as shown in Fig. 4. Further analysis using the String database revealed a network consisting of 212 nodes and 662 edges, with an average node degree of 6.25 (Fig. 5).

These data were then imported into Cytoscape to analyze the interactions between these genes, resulting in PPI network plots. From this network, the top 15 core targets were identified based on their centrality measures. The core targets included TNF, IFNG, ICAM1, FN1, CD8A, ITGAM, MMP9, STAT1, CXCR4, CCL5, TGFB1, VCAM1, CCR5, APOE, and CTLA4 (Table 3). This analysis highlights the key molecular interactions potentially linked to the pathophysiology of OLP and its association with HbA1c levels (Fig. 6).

Enrichment analysis results

For the GO and KEGG enrichment analysis, the David database was utilized to assess and screen the biological processes, cellular components, and molecular functions associated with the targets, based on the significance of their *P*-values. From the Gene Ontology, we obtained 213 entries for BP, 215 for CC, and 212 for MF. Notably, the predominant BP enrichment entries included inflammatory response, response to hypoxia, immune response, cell adhesion, and positive regulation of inflammatory response, among others. The key CC enrichment entries highlighted areas such as the extracellular space, external side of the plasma membrane, and extracellular exosome. The principal MF entries were cytokine activity, integrin binding, and receptor binding.

The *P*-values for these enrichment results underwent a negative log10 transformation, visually represented in a bubble map. In this map, the transformation's magnitude

Table 3 Core targets

Number	Protein Names	Gene Names	Uniprot ID
1	Tumor necrosis factor	TNF	P01375
2	Interferon gamma	IFNG	P01579
3	Intercellular adhesion molecule 1	ICAM1	P05362
4	Fibronectin	FN1	P02751
5	T-cell surface glycoprotein CD8 alpha chain	CD8A	P01732
6	Integrin alpha-M	ITGAM	P11215
7	Matrix metalloproteinase-9	MMP9	P14780
8	Signal transducer and activator of transcription 1-alpha/beta	STAT1	P42224
9	C-X-C chemokine receptor type 4	CXCR4	P61073
10	C–C motif chemokine 5	CCL5	P13501
11	Transforming growth factor beta-1 proprotein	TGFB1	P01137
12	Vascular cell adhesion protein 1	VCAM1	P19320
13	C–C chemokine receptor type 5	CCR5	P51681
14	Apolipoprotein E	APOE	P02649
15	Cytotoxic T-lymphocyte protein 4	CTLA4	P16410

indicates the significance of the differences, with larger bubbles representing a greater number of genes and thus more significant enrichment (Fig. 7).

Additionally, KEGG pathway analysis of common target genes identified a total of 172 related pathways. Core target pathways were predominantly found in rheumatoid arthritis, cytokine-cytokine receptor interaction, cell adhesion molecules, and AGE-RAGE signaling pathway in diabetic complications, among others. These findings were depicted in a bar chart to illustrate the distribution and significance of these pathways clearly (Fig. 8).

Drug prediction results

In the prediction of potential medications for treating OLP and regulating HbA1c, a search through the DGIdb database using the top 15 key genes identified 208 approved drugs. From these, five key chemicals were selected for final screening: Tretinoin, Prednisone, Dexamethasone, Thalidomide, and Triamcinolone. These drugs have been recognized as potentially effective treatments for OLP and may also influence HbA1c levels.

Additionally, using the top 10 key genes, TCM and TCM components were predicted using the TCMSP database. This analysis revealed that six genes—TNF, IFNG, ICAM1, FN1, ITGAM, CXCR4—were associated with a total of 1,069 related Chinese medicines. From these, eight specific types of Chinese medicine were selected based on their intersections: *Ecliptae herba, Equiseti hiemalis herba, Momordicae fructus, Amygdalus communis vas, Bombyx mori l., Perilla frutescens, Tripterygii radix,* and *Hippophae fructus*. A total of 117 TCM ingredients were visualized using Cytoscape (Fig. 9) (Table 4).

Based on the analyses using the three algorithms—BC, CC, and MF—several key components were identified as particularly relevant. These include 17-beta-estradiol, nicotine, apigenin, genistein, luteolin, progesterone, and quercetin, which may serve as promising components in the treatment of OLP and regulation of HbA1c.

Discussion

OLP is a chronic inflammatory disease characterized by symmetrical bilateral lesions that can cause significant discomfort [9]. The prevalence of OLP varies globally, with a higher incidence in women over 40 years. The etiology of OLP is unclear, though it may involve environmental or genetic factors [10]. While the precise cause of OLP remains uncertain, it is widely regarded as a T-cell-mediated autoimmune disorder. It features elevated intraepithelial lymphocytes and infiltration of subepithelial lymphocytes, with lamina propria lymphocyte CD4 + helper T cells playing a crucial role in activating CD8 + cytotoxic T cells through interaction and cytokine production. This mechanism is implicated in the apoptosis of basal epithelial cells [11, 12]. Approximately 1.43% of OLP cases develop into oral cancer [13]. Current studies suggest that the development of OLP is associated with systemic diseases, where the immune system plays a critical role, including conditions like diabetes mellitus, hypertension, thyroid disease, and hepatitis. This indicates that OLP may not arise independently of other diseases [14–16].

DM represents one of the most significant global public health challenges due to its high and increasing

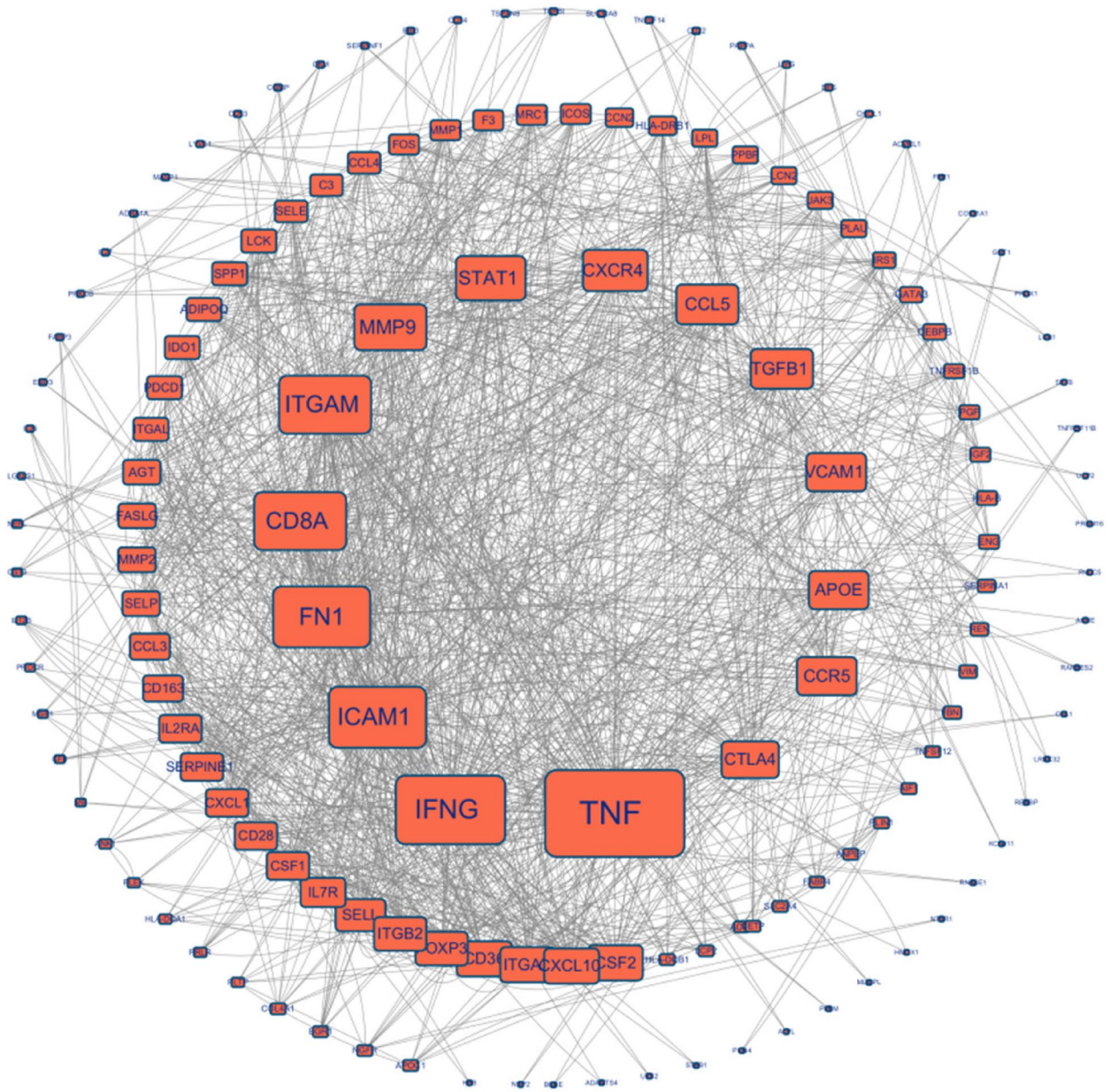

Fig. 6 PPI core target

prevalence and the diverse and extensive morbidity it causes. It affects people of different countries, ages, and genders. As a metabolic disorder characterized by chronic hyperglycemia, diabetes can arise from insulin deficiency or resistance [17]. The prevalence of diabetes is predominantly driven by T2DM, which accounted for over 96% of global diabetes cases in 2021 [18]. HbA1c is the gold standard for assessing glucose control and predicting diabetes prognosis. Elevated HbA1c levels not only reflect poor glycemic control but also indicate an environment of persistent systemic inflammation [19, 20]. T1DM, in particular, exemplifies an autoimmune condition where immune system dysregulation plays a significant role. This condition involves the immune-mediated destruction of insulin-producing beta cells in the pancreas, leading to insulin deficiency and hyperglycemia [21]. The involvement of CD4+and CD8+T cells in this process is a focal point of research [22].

The prevalence of autoimmune diseases and their association with OLP demonstrate a high prevalence and significant link between OLP and DM [23]. Both diseases indicate immune dysregulation, but their potential

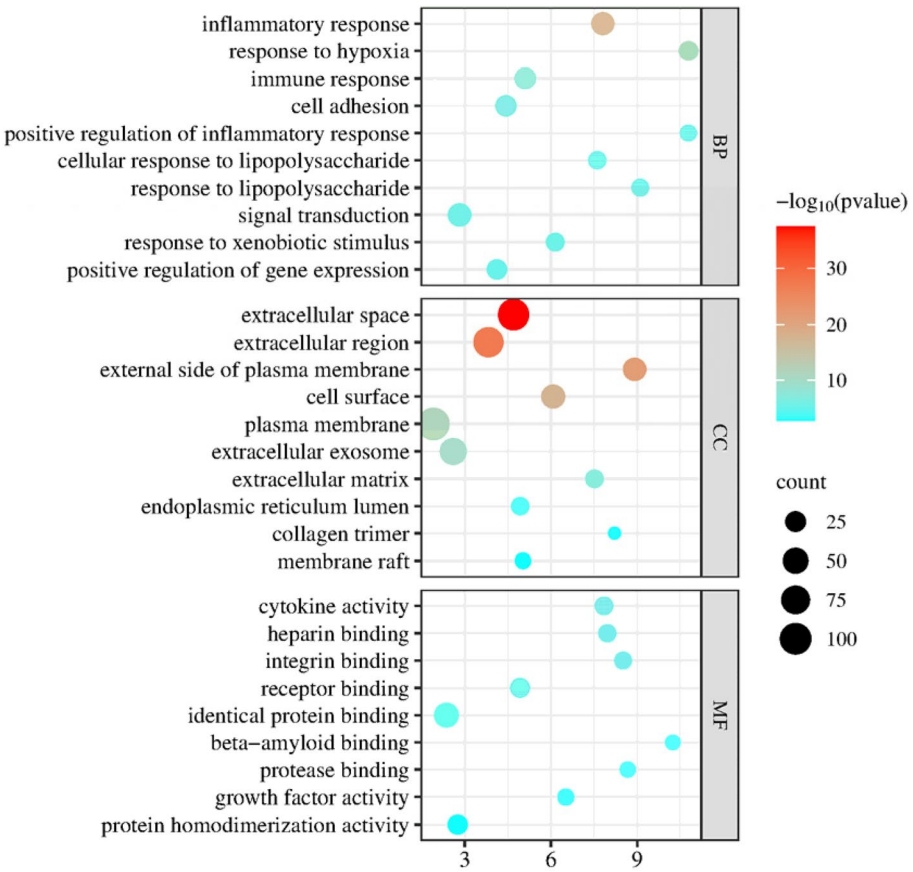

Fig. 7 GO enrichment analysis bubble map. The color of the bubbles indicates the size of the *p* value (the red means the smaller the *p* value), the size of the bubbles means the number of different genes, and the larger the number of bubbles

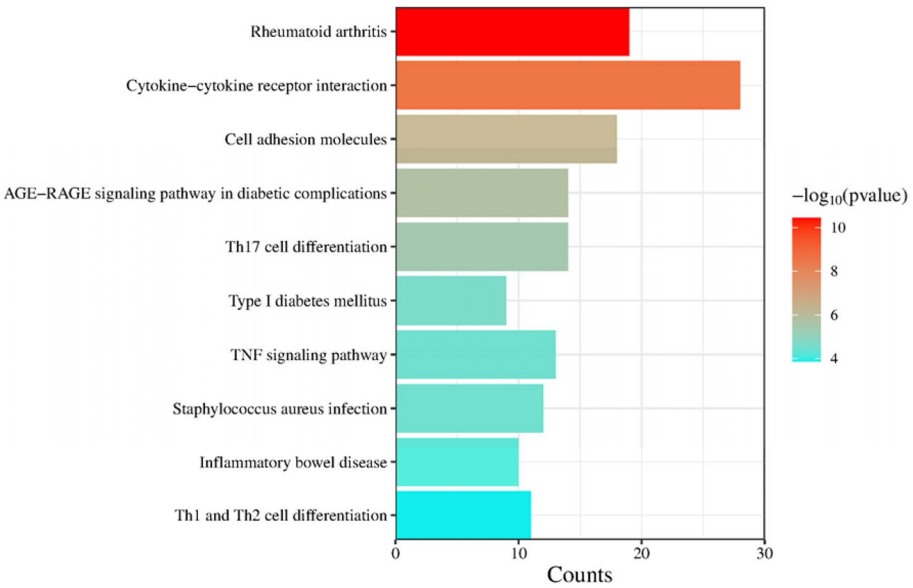

Fig. 8 Bar chart map of KEGG path analysis. The color of the bar indicates the size of*p* value (the more red, the smaller *p* value), the length of the bar indicates the number of different genes, and the longer, the more the number

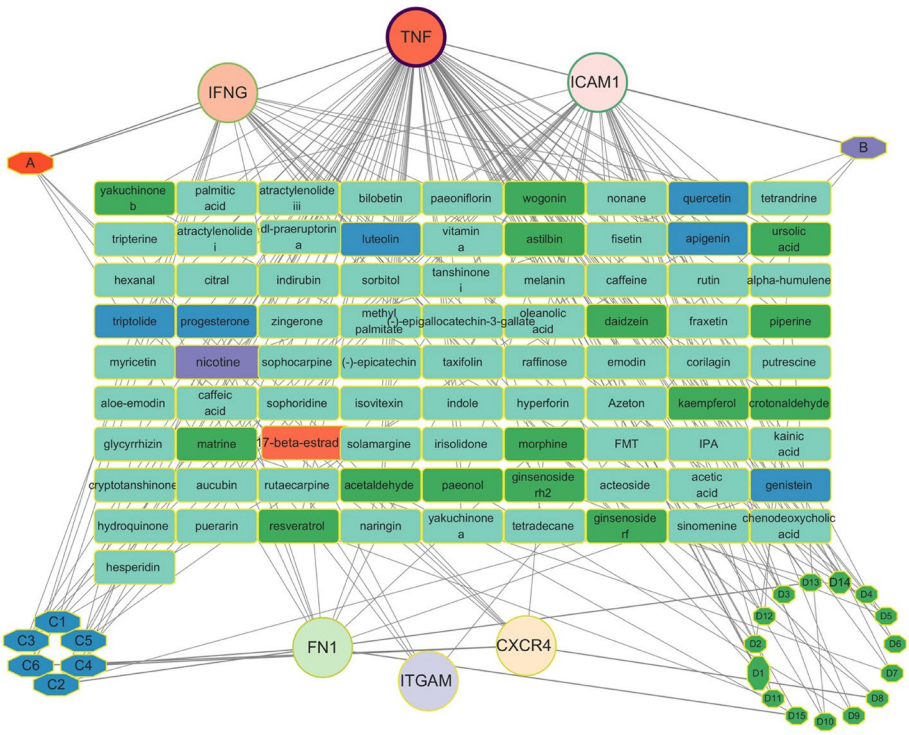

Fig. 9 Disease-target-common target network of active components of TCM. **A** represents17-beta-estradiol, a crucial TCM ingredient, depicted in orange. **B** denotes Nicotine, another key TCM ingredient, which is linked to four related targets, shown in purple. The associated targets for **C** are three, illustrated in dark blue, while **D** is associated with two targets, represented in dark green. For detailed information on the relevant targets, please refer to Table 3

interconnection remains poorly understood and often contested in medical literature. Studies have shown that the prevalence of oral mucosal lesions is higher in diabetic patients, indicating that OLP could be an oral complication of diabetes. Chronic hyperglycemia affects oral health through poor neutrophil function, microangiopathy, neuropathy, reduced collagen synthesis, and decreased collagenase activity [24].Key TNF polymorphisms have been associated with obesity, diabetes mellitus, and other aspects of metabolic syndrome [25]. Elevated TNF levels correlate positively with T2DM, blocking insulin signaling and promoting carbohydrate dysregulation. Similarly, in OLP tissues, TNF significantly affects erosive and reticulate forms, leading to an immune dysregulated state [26]. Additionally, the core target ICAM1 is involved in multiple regulatory functions in keratinocytes within the oral and other mucosal sites [27, 28].

In exploring the correlation between OLP and diabetes mellitus, this study, based on data from the FINNGEN and IEU databases, provided a substantial cohort for examining potential links, particularly with T1DM. Mendelian randomization was employed to estimate the causal effect of exposures on outcomes, minimizing confounding factors often present in observational studies [22]. HbA1c was used as a measure of the risk of developing diabetic complications [29].The identification of diabetes as a risk factor for increased HbA1c levels aligns with well-established medical insights. This study further enhances our understanding by elucidating the genetic underpinnings that contribute to this relationship, providing insights into how a genetic predisposition to diabetes can lead to poorer glycemic control, as evidenced by elevated HbA1c levels. Furthermore, assessing oral lichen planus (OLP) as a risk factor in the context of diabetes, with HbA1c as a marker of long-term glycemic control, suggests that higher HbA1c levels could potentially increase the risk of developing OLP. This association opens a novel area for further research, indicating that poor glucose control and elevated glucose levels in saliva may lead to oral complications. Such systemic effects of long-term high blood sugar may exacerbate or trigger inflammatory responses in mucosal tissues, possibly leading to conditions like OLP [30].

Further enrichment analyses of HbA1c and OLP indicate significant associations with biological processes such as inflammation response, hypoxia response, immune response, cell adhesion, and positive regulation

Table 4 Drug prediction

classification	Drug Name	Drug Target	Number of Matches
chemical medicine	Tretinoin	IFNG, APOB, TGFBI	3
	Prednisone	IFNG, CTLA4	2
	Dexamethasone	VCAM1, CTLA4	2
	Thalidomide	TNF, CTLA4	2
	Triamcinolone	APOB, TGFB1	2
TCM	*Ecliptae herba*	TNF, IFNG, ICAM1, FN1, ITGAM	5
	Equiseti hiemalis herba	TNF, IFNG, ICAM1, FN1, ITGAM	5
	Momordicae fructus	TNF, IFNG, ICAM1, FN1, ITGAM	5
	Amygdalus communis vas	TNF, IFNG, ICAM1, FN1, ITGAM, CXCR4	5
	Bombyx mori l	TNF, IFNG, ICAM1, FN1, ITGAM	5
	Perilla frutescens	TNF, IFNG, ICAM1, CXCR4, FN1	5
	Tripterygii radix	TNF, IFNG, ICAM1, CXCR4, FN1	5
	Hippophae fructus	TNF, ICAM1, CXCR4	3
TCM ingredients	17-beta-estradiol	TNF, IFNG, FN1, ITGAM, CXCR4	5
	Nicotine	TNF, ICAM1, FN1, ITGAM	4
	Apigenin	TNF, IFNG, ICAM1	3
	Genistein	TNF, ICAM1, FN1	3
	Luteolin	TNF, IFNG, ICAM1	3
	Progesterone	TNF, FN1, CXCR4	3
	Quercetin	TNF, IFNG, ICAM1	3
	Triptolide	TNF, IFNG, CXCR4	3

of inflammatory response. These findings are consistent with other studies confirming that both OLP and T1DM are linked to inflammatory and immune responses [31–34]. Lipopolysaccharide (LPS), a primary component of the bacterial cell wall and an endotoxin, is stimulated by keratinocytes in the inflammatory environment of OLP, which can trigger a robust immune response [35]. Additionally, increased levels of LPS may also induce the onset of T1DM and T2DM [36].Core target pathways from KEGG pathway analysis mainly focus on conditions such as rheumatoid arthritis, the AGE-RAGE signaling pathway (which plays roles in diabetic complications), Th17 cell differentiation, T1DM, and the TNF signaling pathway. Th17 cells are identified as stable T cells that can drive disease, suggesting that altering Th17 function could be an effective strategy for combating T1DM [37]. In the immunological landscape of OLP, the predominant cellular component consists of subepithelial dilated CD4+T helper cells, particularly Th17 cells, which are associated with Th17-mediated enhanced mucosal inflammation [38]. This immunological feature underscores the potential for OLP to develop in contexts where systemic inflammation is a factor, further linking it to conditions such as diabetes.

Currently, there is no definitive cure for OLP, particularly for patients with diabetes mellitus. This study has identified potential drugs that might treat OLP while also regulating HbA1c levels. Among the core targets of OLP and HbA1c, chemicals such as Tretinoin, Prednisone, Dexamethasone, Thalidomide, and Triamcinolone have shown potential therapeutic value.Traditional treatment for OLP primarily involves the topical or systemic application of corticosteroids [2], such as Triamcinolone and Dexamethasone, and retinoic acid drugs. Systemic treatments often include immunomodulatory drugs like hydroxychloroquine and immunosuppressives like systemic corticosteroids, particularly Prednisone. However, while effective for short-term symptom relief, long-term use of systemic corticosteroids can lead to significant adverse effects, including hypertension, weight gain, stretch marks, muscle weakness, anemia, sleep disorders, and more critically, hyperglycemia and DM [39, 40].

Oral vitamin A drugs are another option to promote the healing of erosions but must be used cautiously in patients with contraindications such as pregnancy, liver disease, or hyperlipidemia [38, 41]. Thalidomide, known for reducing TNF production and inhibiting NF-κB activity, also increases T-cell inhibition, Th cell activity suppression, and anti-angiogenesis. Its application in OLP

treatment has shown efficacy [42–44], particularly in reducing high glucose-induced ER stress, thereby managing different disease manifestations simultaneously [45, 46].

TCM offers a relatively safer alternative to chemical drugs. For example, *Amygdalus communis vas* contains various phytochemicals with pharmacological activities like anti-cancer, antioxidant, antibacterial, anti-inflammatory, and anti-diabetic properties [47]. Its main component, 17-beta-estradiol (E2), is crucial for regulating energy homeostasis and glucose metabolism, thus potentially preventing or treating metabolic disorders [48].*Ecliptae herba,* another TCM, exhibits pharmacological effects such as lipid-lowering, antioxidant, anti-inflammatory, and immune modulation. Its components like quercetin, apigenin, nicotine, and luteolin have significant therapeutic effects [49]. Quercetin, in particular, is known for its antidiabetic properties, improving blood glucose levels and insulin sensitivity [50]. It also influences the immune response in OLP by affecting the proliferation, apoptosis, and migration of T lymphocytes [51]. Apigenin is notable for its potential in ameliorating metabolic diseases by inhibiting oxidative stress and regulating glucose and lipid metabolism [52]. Combinations of TCM like *Folium mori, Fructus momordicae charantiae, Radix puerariae lobatae,* and *Rhizoma dioscoreae* have shown efficacy in reducing blood sugar levels in diabetic patients [53]. Luteolin enhances insulin sensitivity and is linked to reduced mortality in T2DM patients [54, 55].

OLP-related inflammation, particularly the TNF signaling pathway, is significantly heightened in the erosive form of OLP. Targeting this pathway with agents like quercetin and luteolin, which inhibit TNF [56–58], may not only address the symptoms of OLP but also help manage HbA1c levels, thereby offering a dual therapeutic approach. Anti-inflammatory therapy specifically targeting TNF and addressing the pathogenesis of T2DM could significantly reduce HbA1c levels in patients [59], further highlighting the interconnection between these chronic conditions and the potential of integrated treatment strategies.

Conclusion

The intersection of OLP and diabetes mellitus reveals a complex relationship where immune dysregulation plays a significant role. The study underscores the importance of a multifaceted treatment approach that not only alleviates symptoms of OLP but also addresses underlying systemic conditions such as diabetes. Continued exploration of genetic and immunological factors may enhance our understanding of the pathogenesis of OLP and its association with systemic diseases, potentially leading to targeted therapies that can improve patient outcomes while minimizing adverse effects. This integrated approach promises not only to manage OLP more effectively but also to address the broader health challenges posed by associated conditions.

The study highlights a promising therapeutic approach for treating OLP by simultaneously managing associated metabolic dysfunctions such as diabetes. Drugs including retinoic acid, prednisone, and thalidomide demonstrated potential in treating OLP while regulating blood glucose levels. Furthermore, traditional herbal medicines and key herbal components like quercetin and luteolin were explored for their anti-inflammatory and anti-diabetic properties, providing a comprehensive treatment strategy that addresses both the symptoms of OLP and the complexities of related systemic conditions. This integrated approach could significantly improve patient outcomes by tackling the interrelated aspects of these chronic diseases. To build on these findings, future research should explore how these results could be integrated with other screening methods to better identify OLP. Addressing the study's limitations and exploring these avenues could further refine treatment strategies and improve patient outcomes. This integrated approach not only aims to manage OLP more effectively but also addresses the broader health challenges posed by associated conditions.

Abbreviations

OLP	Oral lichen planus
MR	Mendelian Randomization
DM	Diabetes mellitus
TIDM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
HbA1c	Glycated hemoglobin
GEO	Genomics Expression Omnibus
DGIdb	Drug-Gene Interaction Database
TCMSP	Traditional Chinese Medicine Systems Pharmacology Database
TCM	Traditional Chinese Medicine
IVW	Inverse Variance Weighting
SNP	Single-nucleotide polymorphism
PPI	Protein–protein interaction
BC	Betweenness centrality
CC	Cellular component
MF	Molecular function
OR	Odds ratio
DEG	Differentially expressed genes

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Clinical trial number

Not applicable.

Authors' contributions

MY and YL were responsible for the conception and design of the study. MY conducted the statistical analyses and drafted the initial manuscript. HS, TL, HL, and YX provided critical revisions for important intellectual content. BD performed English language revisions. All authors contributed to the article and approved the final version submitted for publication.

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Availability of data and materials
The datasets analyzed for this study are available in the following public resources: GEO database (https://www.ncbi.nlm.nih.gov/geo/), GWAS database(https://gwas.mrcieu.ac.uk/), GeneCards database (https://www.genecards.org/), David database (https://david.ncifcrf.gov/), DGIdb online database (https://www.dgidb.org/), and TCMSP database (https://old.tcmsp-e.com/).

Declarations

Ethics approval and consent to participate
This study utilized publicly accessible databases; therefore, ethical approval was not required as the research did not involve human participants or personal data.

Competing interests
The authors declare no competing interests.

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