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Research Article

Identification of Biological Risk Genes and Candidate Drugs for Psoriasis Vulgaris by Utilizing the Genomic Information

Lisza Niarisessa [1]
Anisa Nova Puspitaningrum [1]
Arief Rahman Afief [1]
Dyah Aryani Perwitasari [1]
Wirawan Adikusuma [2,3]
Rocky Cheung [4]
Abdi Wira Septama [5]
Lalu Muhammad Irham [1,5*]

[1] Department of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Special Region of Yogyakarta, Indonesia

[2] Department of Pharmacy, Universitas Muhammadiyah Mataram, Mataram, West Nusa Tenggara, Indonesia

[3] Research Center for Vaccine and Drugs, National Research and Innovation Agency Republic of Indonesia, South Tangerang, Banten, Indonesia

[4] Department of Chemistry and Biochemistry, University of California, Los Angeles, Los Angeles, California, United States

[5] Research Centre for Pharmaceutical Ingredients and Traditional Medicine, National Research and Innovation Agency Republic of Indonesia, South Tangerang, Banten, Indonesia

*email: lalu.irham@pharm.uad.ac.id

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Abstract

Psoriasis is an autoimmune disease that causes inflammation on the skin's surface, characterized by the appearance of pink plaques covered with white scales. Currently, the availability of psoriasis vulgaris therapy is still limited. Therefore, considering the discovery of new drug candidates by utilizing genetic variations, such as single nucleotide polymorphisms (SNP) through drug repurposing, is a profitable method. The SNP associated with psoriasis was obtained from Genome-Wide Association Studies (GWAS) and Phenome-Wide Association Studies (PheWAS) databases. We identified 245 SNPs associated with psoriasis vulgaris with criteria of r^2 >0.8. To prioritize the candidate of a gene associated with psoriasis, we used five criteria of functional annotation (missense/nonsense, cis-eQTL, PPI, KEGG, and KO mice) where if there were more than two criteria of assessment, they were defined as the risk gene of psoriasis vulgaris. Fifty-two genes were identified as the risk gene of psoriasis vulgaris, then expanded using the STRING database to obtain more gene candidates of drug targets. The result is 104 genes candidates for drug targets, of which 24 overlapped with 96 drugs, according to DrugBank. Of the 96 drugs that have been approved for other indications, we found that five drugs (ustekinumab, tildrakizumab, risankizumab, guselkumab, and etanercept) are currently in clinical trials for the treatment of psoriasis that target two genes (*IL23A* and *TNF*). We argue that these two genes are the most promising targets based on their high target scores on functional annotations. This research explains the potential that utilizing genomic variation can contribute to drug discovery.

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INTRODUCTION

Psoriasis is an autoimmune disease that can cause inflammation on the skin surface[1]. Psoriasis vulgaris disease is characterized by erythematous plaques such as scaly localized or scattered all over the skin surface[2]. Areas of skin that often occur lesions are the elbows, knees, and the skin surface of the head. Psoriasis is classified into eight, including Plaque Psoriasis (Psoriasis Vulgaris), Guttate Psoriasis, Pustular Psoriasis, Generalized Pustular Psoriasis, Palmoplantar Pustulosis, Acrodermatitis Continua of Hallopeau, Erythrodermic Psoriasis, Inverse Psoriasis[3]. Of the many types of psoriasis vulgaris described above, psoriasis is the most widely reported species. Psoriasis vulgaris is characterized by red or pink plaques covered with white or gray scales, large or small plaques, thick or thin, with clear boundaries. Psoriasis vulgaris affects about 2% of the population in North America and Europe. Women are more likely to experience psoriasis vulgaris than men, with a ratio of 9 : 1[4]. Psoriasis vulgaris is experienced by sufferers starting from the age of 33 years, with 75% of cases occurring before 46 years of age[5].

The pathogenesis of psoriasis vulgaris involves inflammatory mechanisms, especially the pathway of T-helper cell pathway[6]. In the pathogenesis of psoriasis vulgaris, the genetic factor becomes an essential part of developing psoriasis itself. Therefore, the genetic factor plays a vital role in developing psoriasis vulgaris. Several studies have described successfulness in identifying locus susceptibility of psoriasis vulgaris[7-9]. In addition to the genetic factor, other studies explain involvement in other things, such as smokers with an incidence rate of 95% more affected by psoriasis vulgaris than non-smokers[1].

Treatment options for psoriasis include topical corticosteroids, vitamin D analogs, calcineurin inhibitors, keratolytic, and phototherapy[10]. There are several barriers to the treatment of psoriasis, and resistance can occur due to several factors, such as depression and psychological anxiety, that can worsen the severity level of psoriasis and duration of clinical symptoms[11]. In addition, ineffective dosing and poor adherence, such as severe psoriasis requiring multiple drugs, be a factor in resistance[12,13]. Therefore, it is necessary to find an alternative drug that has the potential for the treatment of psoriasis vulgaris. The development of new drugs is generally long-term, which not only costs much money but also requires research both clinically and preclinically[14]. Recently, many methods have been applied to accelerate the discovery and development of new drugs. One of these methods is the drug repurposing approach. The concept of drug repurposing utilizes old drugs (orphan drugs) for new indications[15]. The development of current health technology based on bioinformatics and big data in the health sector has become an advantage to integrate into the drug repurposing for psoriasis vulgaris disease. In several previous studies, the concept of drug repurposing has been used for the development of new drugs in tuberculosis[16], chronic hepatitis B, asthma, depression, colorectal cancer[17], and atopic dermatitis[18], with a system of score assessment and to find the candidate of drug repurposing. Our research aims to utilize a genomic database with a drug-repurposing approach for psoriasis vulgaris. Our methodology is based on utilizing a genomic database and genomic variant drive drug repurposing.

MATERIALS AND METHODS

Materials

The database used includes Genome-Wide Association Studies (GWAS; https://www.ebi.ac.uk/gwas/), Phenome-Wide Association Studies (PheWAS; https://phewascatalog.org/), HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php), Drugbank (https://go.drugbank.com/), and ClinicalTrial.gov (https://clinicaltrials.gov/).

Methods

Psoriasis vulgaris risk genes

Analysis of psoriasis vulgaris disease used GWAS[19] (accessed on February 3rd, 2022) with total 49 single nucleotide polymorphisms (SNP) and PheWAS[20] (accessed on February 3rd, 2022) with total 196 SNP. We obtained SNP associated with psoriasis vulgaris using these two databases. Furthermore, SNP obtained from GWAS and PheWAS Catalog were developed with HaploReg v4.1 (accessed on February 3rd, 2022). Single nucleotide polymorphisms associated with psoriasis vulgaris were identified with significance criteria of $<10^{-8}$ for the GWAS Catalog and a significance of <0.05 for the PheWAS Catalog (**Figure 1**).

Biological psoriasis vulgaris risk genes

The genes obtained were prioritized using five functional annotations: Missense, Cis-eQTL, KEGG, Komice, and PPI. Genes that have been prioritized and according to significance were given one point. Each gene was assigned a point based on matching criteria, and the score ranged from 0-5[21,22] (**Figure 1**).

Candidate drugs for psoriasis vulgaris

The genes were mapped based on the Drugbank (accessed on March 19th, 2022) to find a candidate drug for psoriasis vulgaris. The Drugbank database provides information about drugs and gene targets for discovering new drugs. Drugbank is a data source that provides detailed information on drug action with comprehensive drug targets. Drugbank is often used in education to find drug targets, drug design, drug screening, drug metabolism prediction, and drug interactions prediction[23]. Drugbank has detailed information about 1467 drugs approved by Food Drug Association (FDA) that have been matched with 28.447 brand names and synonyms. Furthermore, all drug data was confirmed to ClinicalTrial.gov (accessed on March 19th, 2022). ClinicalTrial.gov is a web-based resource that provides easy access for a person, both the general public, patients, family members of patients, researchers to obtain information regarding clinical studies of various diseases and conditions[24] (**Figure 1**).

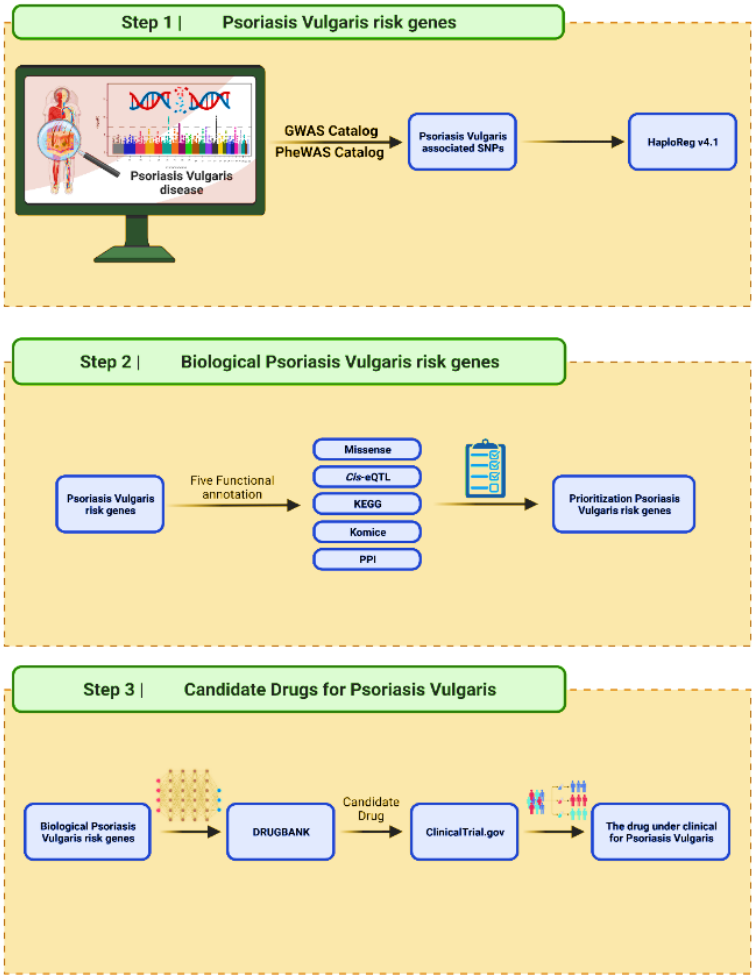

Figure 1. Schematic of drug repurposing by utilizing the database of the genome for psoriasis vulgaris

RESULTS AND DISCUSSION

We systematically identified 245 SNP associated with psoriasis vulgaris, retrieved from GWAS and PheWAS. We set the criteria from the GWAS catalog database with inclusion criteria $<10^{-8}$ and the PheWAS catalog with inclusion criteria <0.05, developed with HaploReg V4.1. We further expanded the SNP based on the criterion of LD >0.8, in this step, we identified 245 SNP.

Functional annotation of the risk gene of psoriasis vulgaris

Five functional biological annotations were prioritized for the risk gene of psoriasis vulgaris. One point is assigned for each functional annotation. Assessment of each of the 359 genes used the following five criteria: genes with risk variant of psoriasis vulgaris missense (n=8); genes of cis-eQTL (n=20); genes involved in the KEGG pathway (n=36); genes in the knockout/KO mice phenotype (n=14); and genes involved in GO terms used for PPI application (n=40) (**Table I**). After the data is collected, the next step is to determine the biological score. Genes with a score of 0 have 0 genes, genes with a score of 1 have 0 genes, genes with a score of 2 has 39 genes, genes with a score of 3 has 12 genes, and genes with a score of 4 has one gene. The calculated genes with a score >2 are 52 genes (**Figure 2**). One risk gene of the top biological psoriasis vulgaris is *Cluster of Differentiation 247* (*CD247*), with a gene score 4 with muromonab drug candidate data.

Table I. Assessment of genes for the risk gene of psoriasis vulgaris

Genes code name	Missense	Cis-eQTL	KEGG	KO mice	PPI	Total Score
CD247	0	1	1	1	1	4
CDK6	0	0	1	1	1	3
CXCR2	0	1	1	0	1	3
DDX58	0	0	1	1	1	3
HLA-DQB1	0	1	1	1	0	3
NFKBIA	0	0	1	1	1	3
NFKBIZ	0	1	1	0	1	3
PLCL2	0	1	1	0	1	3
RFTN1	0	1	1	0	1	3
RUNX3	0	0	1	1	1	3
SH2B3	1	1	0	0	1	3
TNF	0	0	1	1	1	3
TNFAIP3	0	0	1	1	1	3
ADIPOQ	0	0	1	0	1	2
BAK1	0	1	0	1	0	2
C4B	1	0	0	0	1	2
C6orf57	1	1	0	0	0	2
CCDC88B	0	0	1	0	1	2
CCND3	0	0	0	1	1	2
DENND1B	0	0	1	0	1	2
EDC4	0	1	0	0	1	2
ELMO1	0	0	1	0	1	2
EOMES	0	1	0	0	1	2
ERAP1	0	1	1	0	0	2
ESR1	0	0	1	0	1	2
ETS1	0	0	1	0	1	2
GP1BA	1	0	1	0	0	2
HCLS1	0	0	1	0	1	2
HLA-DRA	0	0	1	1	0	2
HRG	0	0	1	0	1	2
HSPA1L	1	1	0	0	0	2
IFIH1	0	0	1	0	1	2
IL13	0	0	1	0	1	2
IL23A	0	0	1	0	1	2
IL23R	0	0	1	0	1	2
IRF4	0	0	1	0	1	2
IRF8	0	1	0	0	1	2
LDLR	0	0	1	0	1	2
MAP3K14	0	0	0	1	1	2
MICB	0	1	1	0	0	2
PIK3R2	0	0	1	1	0	2
PPT2	1	0	0	0	1	2
PSMB10	1	0	0	0	1	2
PSMB8	1	1	0	0	0	2
PSMB9	0	1	0	0	1	2
REL	0	1	0	0	1	2
STAT2	0	0	0	1	1	2
TNIP1	0	0	1	0	1	2
TRAF3IP2	0	0	1	0	1	2
TRIM38	0	1	1	0	0	2
TSLP	0	0	1	0	1	2
UBASH3B	0	1	1	0	0	2
Total	**8**	**20**	**36**	**14**	**40**	

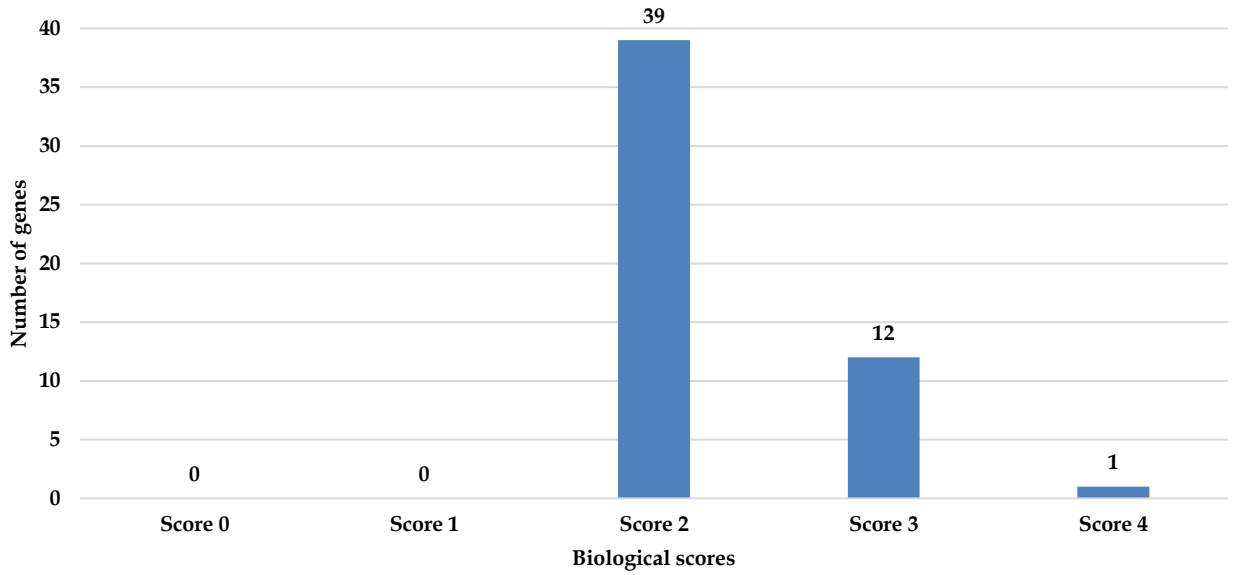

Figure 2. The number of genes (*y*-axis) that fulfill each of the five biological criteria (*x*-axis) for drug priority. The genes with a score of 0 and 1 are 0, while genes with a score of 2 and more (39 + 12 + 1 = 52 genes) are described as the risk gene of biological psoriasis vulgaris.

Expanding the risk list of biological psoriasis vulgaris

This study uses the STRING database. There are 104 genes listed in this study. These genes are a list of genes for new drug candidates that are used for further analysis in psoriasis vulgaris.

Discovery of psoriasis vulgaris drug target

New drug candidates for psoriasis vulgaris were mapped to the Drugbank to find candidates for psoriasis vulgaris drugs. From the search results in the Drugbank, by entering 24 genes and 96 drug targets, it was found that two genes were used for psoriasis. Those that have been approved for psoriasis vulgaris disease have been clinically approved are the *Interleukin-23A* (*IL23A*) gene, and the drug targets consist of ustekinumab, tridakilzumab, risankizumab, and guselkumab (**Figure 3**).

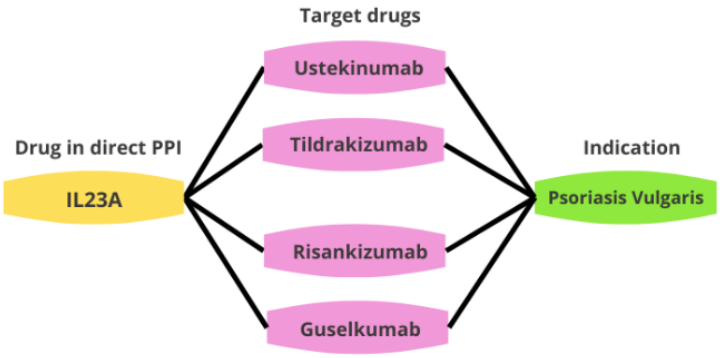

Figure 3. Relationship between psoriasis vulgaris risk genes and available drugs for psoriasis vulgaris.

In this study, two genes of the drug target were found that bind for each gene with two drugs that are approved for other diseases and currently under clinical investigation for psoriasis vulgaris, including guselkumab, tildrakizumab, etanercept, and infliximab. These drugs are likely used to treat psoriasis vulgaris (**Table II**). This study focuses on finding new drugs for psoriasis vulgaris based on candidates of genes identified from the catalog of GWAS and PheWAS. This study also prioritizes genes at risk for psoriasis vulgaris with an assessment that uses five functional annotations to predict new drug candidates. This research found 24 genes target that bind to 96 drug targets, of which two genes bind to drug targets related to psoriasis vulgaris, including the *IL23A* and the *Tumor Necrosis Factor* (*TNF*) genes. The *IL23A* is the drug target of guselkumab, ustekinumab, tildrakizumab, and risankizumab. At the same time, the *TNF* is a drug target of etanercept.

Table II. The drug in clinical investigation for psoriasis vulgaris

Drugs	Target	Mecanism in psoriasis vulgaris	Original indication	Development status	Identifier (ClinicalTrial.gov)	Recruitment status
Guselkumab	*IL23A*	Blocking the signal of cascade inflammation, which elevates abnormally, drives epidermal abnormalities, including keratinocyte hyperproliferation and psoriatic plaque formation	Plaque psoriasis	Phase 4	NCT04080648	Recruiting
Ustekinumab	*IL23A*	Interferes with the actions of proteins, interleukin 12 (IL12) and interleukin 23 (IL23), which reduces inflammation (swelling) in the skin	Plaque psoriasis	Phase 2	NCT01999868	Completed
Tildrakizumab	*IL23A*	IL23 is a natural cytokine involved in inflammatory responses and immune. Tildrakizumab inhibits the release of cytokines and proinflammatory chemokines	Plaque psoriasis	Phase 4	NCT05683015	Recruiting
Risankizumab	*IL23A*	Binds to the P19 IL-23 subunit to prevent the cytokine from binding to its receptor. IL23 is involved in peripheral inflammation, particularly in T-cell responses, so this inhibition aims to reduce psoriatic skin lesions	Plaque psoriasis	Phase 4	NCT05685940	Recruiting
Etanercept	*TNF*	TNF is a natural cytokine involved in inflammatory responses and normal immunity. The elevated level of TNF is found in the network and fluid of those who experience rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and plaque psoriasis	Rheumatoid arthritis	Phase 4	NCT00640393	Completed

Interleukin-23 is a member of the *Interleukin-12* (*IL12*) family of cytokines with pro-inflammatory properties[25]. Both *IL12* and *IL23* have different immunological pathways and have separate functions but complete each other. *Interleukin-12* is required for antimicrobial response against intracellular pathogens, whereas *IL23* is essential for the recruitment and activation of various inflammatory cells required to induce chronic inflammation and granuloma formation. These two cytokines regulate the cellular immune response necessary for host defense and tumor suppression[26]. *Interleukin-23* is secreted by activated macrophages and dendritic cells (DCs) in peripheral tissues (skin, intestinal mucosa, and lungs). The *IL23* receptor has therapeutic potential for autoimmune diseases, including psoriasis vulgaris, inflammatory bowel disease, rheumatoid arthritis, and multiple sclerosis[27]. Based on our study, it was found that *IL23* is the drug target of tildrakizumab and guselkumab for psoriasis vulgaris. Tildrakizumab is a humanized IgG1 monoclonal antibody that targets *IL23* p19, and it is approved for use in moderate to severe psoriasis vulgaris[28]. Meanwhile, guselkumab is a specific inhibitor of *IL23* through binding to the *IL23* p19 subunit, significantly improving psoriasis vulgaris signs and symptoms[29].

Tumor Necrosis Factor is a multifunctional cytokine that plays a vital role in cellular events such as cell survival, proliferation, differentiation, and death. *Tumor Necrosis Factor* is also a pro-inflammatory cytokine, so *TNF* is secreted by inflammatory cells that may be involved in carcinogenesis related to inflamation[30]. Currently, *TNF* plays a role in the pathogenesis of several inflammatory conditions, which has led to increased use of target therapies with *TNF* to treat inflammatory bowel disease (IBD), rheumatoid arthritis, psoriasis vulgaris, and psoriatic arthritis[31]. Currently, five *TNF* inhibitors are approved by the Food and Drug Administration (FDA), including etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab[32]. This is in line with the research that we have done, in which of the 115 drug targets found, a *TNF* gene binds to the target associated with psoriasis vulgaris, i.e., etanercept and infliximab.

Etanercept is a fully human *TNF* receptor that reduces the inflammatory response by inhibiting the interaction between *TNF* and receptors of *TNF* on the cell surface[33]. The working mechanism of etanercept is inhibiting *TNF* activation and binding it competitively, resulting in antagonistic interactions with receptors on the cell surface and preventing inflammatory activation[34]. The average half-life of etanercept is about 4.3 days (70-100 hours) and peaks at 48-60 hours with a bioavailability of 58%[35]. Infliximab is a murine-human IgG1 monoclonal antibody that binds to the transmembrane precursor *TNF*[36]. The

mechanism of infliximab is by binding specificity, affinity, and avidity to *TNF*, and through its inhibition, neutralizing and cytotoxic activity, it interferes with the pathology of psoriasis vulgaris and other inflammatory diseases characterized by overproduction of *TNF*[37]. Infliximab is effective in the induction and treatment phase of psoriasis vulgaris. Infliximab not only clears skin lesions but also significantly improves the quality of life that is related to health. The work concept of infliximab is shorter at 3.5 weeks than other biologic drugs such as adalimumab, etanercept, and alefacept[38]. Efficacy rates of infliximab were significantly higher up to week 24 than etanercept[39].

The advantage of drug repurposing by utilizing a gene variation from the GWAS and PheWas catalog database is finding potential ways to use new drug candidates for psoriasis vulgaris. However, this approach has limitations, in which not all identified gene targets have pharmacological activity, and these genes can potentially miss the drug target. Therefore, further investigation is needed to determine the effect of drugs candidate in clinical applications.

CONCLUSION

In this research, 52 genes were identified as biological risk genes of psoriasis vulgaris and obtained one gene with the highest score of 4: *CD247*, with candidate data of muromonab drug. In this case, the involvement of genes in drug discovery against psoriasis vulgaris is likely to be very significant, so further research is needed.

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AUTHORS' CONTRIBUTION

LN and **LMI** conceived and designed the study. **LN** and **LMI** performed the computational analysis. **LN** wrote the manuscript. **LN**, **ANP**, **ARA**, **DAP**, **WA**, **RC**, and **LMI** revised the manuscript. **LMI** and **WA** supervised and coordinated this study. All authors have read and approved the manuscript and made significant contributions to this study.

DATA AVAILABILITY

The data presented in this study are available in supplementary material by contacting the corresponding author.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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