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Pharmacovigilance-Based Identification and Mechanistic Exploration of Periodontitis-Related Drugs

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ABSTRACT

Background: Periodontitis is a common chronic inflammatory disease. However, drug-related risks and underlying molecular mechanisms remain underexplored from large real-world data.

Methods: We first mined the US Food and Drug Administration Adverse Event Reporting System (FAERS) database to identify drugs disproportionately associated with periodontitis, using four signal detection algorithms and logistic regression for confounder adjustment. Identified drugs were then mapped to their protein targets via DrugBank, followed by pathway enrichment and protein–protein interaction (PPI) network analysis to explore biological relevance. To assess potential causality, we conducted Mendelian randomisation (MR) using cis-pQTLs from UKB-PPP and deCODE cohorts. Finally, we used single-cell RNA sequencing (scRNA-seq) data from gingival tissue and peripheral blood of periodontitis patients to evaluate cell type-specific expression of candidate causal genes.

Results: Five drugs (actonel, aclasta, aredia, amlodipine and avastin) were significantly positively associated with periodontitis based on FAERS. *VEGFA* showed an association with disease risk (OR = 1.043, $p = 0.049$) after meta-analysis of two cohorts. scRNA-seq data identified high *VEGFA* expression in monocytes in both gingival and blood samples of periodontitis patients.

Conclusion: This study uncovered the association between drug and periodontitis and highlighted *VEGFA* as a potential molecular mediator. Further studies are needed to confirm causality.

1 | Introduction

Periodontitis is a chronic inflammatory disease of the periodontal supporting tissues that can cause gum recession, alveolar bone loss and tooth loss (Heitz-Mayfield 2024). It affects

approximately 10%–15% of the global population and is associated with systemic diseases such as diabetes, cardiovascular disease and rheumatoid arthritis (Linden and Herzberg 2013; Hajishengallis 2022). Despite ongoing advances in treatment, the molecular mechanisms underlying drug-related

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periodontitis are largely unexplored. No studies have yet systematically examined this issue using large-scale real-world data (Rosa et al. 2021; Zhang et al. 2022).

The US Food and Drug Administration Adverse Event Reporting System (FAERS) is an important source of data for identifying drug-related adverse reactions (Sakaeda et al. 2013). Through signal mining, it can be used to preliminarily screen for drugs that may be associated with periodontitis. However, this method is mainly used for population-level correlation analysis and cannot reveal the potential molecular mechanisms and causal relationships between drugs and periodontitis. To overcome this, Mendelian randomisation (MR) was applied to infer causality, and single-cell RNA sequencing (scRNA-seq) was used to explore the cellular mechanisms underlying these associations of potential molecular mechanisms.

This study aims to integrate real-world drug adverse reaction data at the population level with molecular target information at the molecular level to construct a 'drug-gene-periodontitis association' mechanistic network. First, a disproportionality analysis was conducted based on the FAERS database to identify suspected drug signals significantly associated with periodontitis. Second, time-to-onset (TTO) analysis was performed to evaluate the temporal relationship between drug exposure and the occurrence of periodontitis. Third, the DrugBank database was integrated to obtain the known target sites of these drugs (Knox et al. 2024). Additionally, we combined gene functional enrichment analysis and protein-protein interaction (PPI) analysis to reveal the biological pathways and the involved key targets. Further, using publicly available genome-wide association study (GWAS) data, we applied the summary data-based MR (SMR) and two-sample MR analysis to investigate the identified drug-related targets with a significant positive association with periodontitis (Sanderson et al. 2022). Finally, scRNA-seq data were systematically analysed for exploring their cell type-specific expression characteristics in periodontal tissues and peripheral blood. This not only facilitates the systematic identification of high-risk drugs associated with periodontitis but also holds promise for elucidating their potential mechanisms of action and cellular origins.

2 | Methods

2.1 | Study Design

The workflow chart is presented in Figure 1. In population-level data mining, we first used the FAERS database to identify drugs potentially associated with periodontitis by applying signal detection methods, including the reporting odds ratio (ROR), proportional reporting ratio (PRR), information component (IC), empirical Bayes geometric mean (EBGM) and the p -value from Fisher's exact test after false discovery rate (FDR) correction (Glickman et al. 2014). These methods are widely used in pharmacovigilance signal detection by regulatory agencies such as the WHO-UMC and FDA (Szarfman et al. 2002; Bate and Evans 2009). A summary of their formulas, signal detection criteria and corresponding references is provided in Table S1. Drugs with positive signals were further evaluated using multivariable logistic regression, adjusting for age, gender, weight

group, reporter type, country and reporting year. Drugs that showed positive signals across all disproportionality metrics and achieved statistically significant associations ($p_{\text{FDR}} < 0.05$) in both multivariate logistic regression and Fisher's exact test were selected for further TTO analysis. This combined strategy has been previously applied to improve the robustness of pharmacovigilance signal detection (Harpaz et al. 2012).

In molecular-level mechanism analysis, molecular targets of these drugs were obtained from DrugBank. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed to explore their biological functions. PPI network analysis was conducted using STRING to identify key hub genes. To validate genetic relevance, we performed a meta-analysis of SMR results from the deCODE and UK Biobank Pharma Proteomics Project (UKB-PPP) cohorts, identifying shared genes related to periodontitis. Building on these findings, we subsequently applied two-sample MR analysis to evaluate the potential causal effect of drug-related targets on periodontitis risk. Finally, single-cell RNA-seq data from gingival tissues and peripheral blood of periodontitis patients were analysed. A summary of data sources used in this study is presented in Table S2.

Detailed descriptions of statistical methods, preprocessing pipelines, software versions and parameters used are provided in [Supplementary Methods](#).

3 | Results

3.1 | Population-Level Analysis

3.1.1 | Baseline Characteristics

A total of 38,129,121 adverse event reports were analysed, among which 5938 (0.016%) involved periodontitis (Table 1). Compared to the non-periodontitis group, the periodontitis group had a higher proportion of females (57.3% vs. 51.6%), healthcare professional reports (65.6% vs. 39.3%) and patients aged 18–85 years (72.9% vs. 52.8%) (all $p < 0.001$). They also had more reports from non-US regions (77.2% vs. 42.5%) and more individuals weighing < 50 kg (6.9% vs. 2.4%) ($p < 0.001$). A greater proportion of periodontitis cases were reported during 2004–2012 (21.1%), although the overall reporting increased over time, possibly reflecting changes in reporting patterns or terminology.

3.1.2 | Signal Detection of Periodontitis-Related Drugs From FAERS

In this study, multiple statistically significant positive signal drugs were jointly screened based on a variety of adverse reaction signal determination indices, including ROR, PRR, IC, EBGM and Fisher's exact test corrected by FDR (Table S3). Disproportionality analysis results of negative control drugs (statins and antihistamines) for periodontitis in the FAERS database are presented in Table S4.

The results of the analysis showed that a variety of bone metabolism-related drugs, such as fosamax, alendronate sodium,

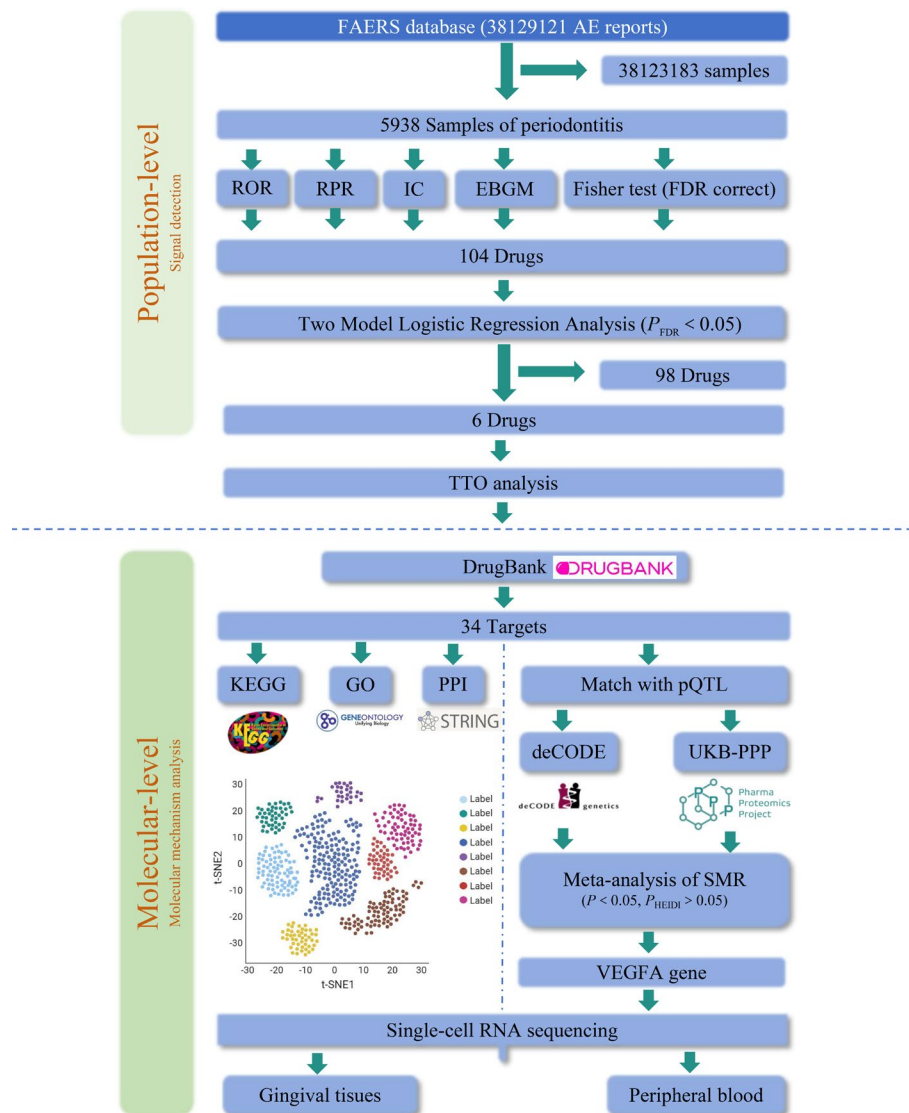


FIGURE 1 | Workflow chart of this study. EBGM, empirical Bayes geometric mean; GO, gene ontology; IC, information component; KEGG, Kyoto Encyclopedia of Genes and Genomes; PPI, protein–protein interaction; PRR, proportional reporting ratio; ROR, reporting odds ratio.

boniva, aclasta, denosumab, pamidronate disodium, ranmark and actonel, exhibited significant positive signals in the five indicators, suggesting a possible close association between them and periodontitis.

Meanwhile, some antineoplastic drugs also showed significant signals, including ado-trastuzumab emtansine, aflibercept, cabozantinib, bortezomib, pembrolizumab (keytruda), ribociclib, vidaza, venetoclax, incb018424 (ruxolitinib), isatuximab, nivolumab, paclitaxel, cytarabine, folotyn and pertuzumab, which may trigger specific adverse events through immunological or metabolic mechanisms and are worthy of attention in clinical application.

In addition, some cardiovascular drugs such as amlodipine, nifedipine, valsartan, briliq, trombyl and phenprocoumon have been identified as potential signal-positive drugs, suggesting that there is a certain risk of these drugs in specific populations.

It is worth noting that several drugs belonging to other classes also showed strong positive signals, such as ranitidin series preparations, neomallermin tr, infliximab-dyyb, tavegil, gabapentine and granisetron. Some of these drugs have 10 times more signal strengths (e.g., ROR or EBGM value), which is worthy of further investigation.

3.1.3 | Logistic Regression Analysis

Logistic regression analysis identified multiple medications that were significantly associated with the reporting risk of periodontitis (Figure 2). After adjusting for age, gender, weight group, reporting source, country and year of reporting, several drugs remained positively associated with periodontitis in the frequentist model, including aclasta (OR = 38.06, 95% CI: 29.88–48.47, $p < 0.001$), actonel (OR = 81.88, 95% CI: 68.76–97.52, $p < 0.001$), aredia (OR = 147.62, 95% CI: 115.10–189.31, $p < 0.001$) and avastin (OR = 9.65, 95% CI: 8.29–11.23,

TABLE 1 | Baseline characteristics (periodontitis vs. non-periodontitis).

Characteristics	Group level	No periodontitis	Periodontitis	<i>p</i>
Gender	Total	38,124,183	5938	< 0.001
	Male	13,461,110 (35.3%)	2046 (34.5%)	
	Female	19,667,951 (51.6%)	3402 (57.3%)	
	Missing	4,995,122 (13.1%)	490 (8.3%)	
Age group	< 18	1,436,143 (3.8%)	67 (1.1%)	< 0.001
	18–64	13,116,444 (34.4%)	2680 (45.1%)	
	65–85	7,000,442 (18.4%)	1650 (27.8%)	
	> 85	752,669 (2.0%)	47 (0.8%)	
	Missing	15,818,485 (41.5%)	1494 (25.2%)	
Weight group	< 50	905,254 (2.4%)	411 (6.9%)	< 0.001
	50–100	6,347,307 (16.6%)	2352 (39.6%)	
	> 100	952,303 (2.5%)	150 (2.5%)	
	Missing	29,919,319 (78.5%)	3025 (50.9%)	
Reporter	Consumer	14,510,264 (38.1%)	1023 (17.2%)	< 0.001
	Health professional	14,976,825 (39.3%)	3898 (65.6%)	
	Others	7,189,791 (18.9%)	779 (13.1%)	
	Missing	1,447,303 (3.8%)	238 (4.0%)	
Country	Non-US	16,193,766 (42.5%)	4584 (77.2%)	< 0.001
	United States	21,853,671 (57.3%)	1351 (22.8%)	
	Missing	76,746 (0.2%)	3 (0.1%)	
Report year group	2022–2024	11,151,954 (29.3%)	1503 (25.3%)	< 0.001
	2019–2021	10,467,073 (27.5%)	1398 (23.5%)	
	2016–2018	7,193,417 (18.9%)	849 (14.3%)	
	2013–2015	4,681,961 (12.3%)	934 (15.7%)	
	2004–2012	4,629,328 (12.1%)	1254 (21.1%)	
	Missing	450 (0.0%)	0 (0.0%)	

$p < 0.001$). To further validate the robustness of these associations, we performed Bayesian logistic regression, which yielded more conservative yet still significant effect sizes (e.g., aclasta: OR = 7.68, 95% CI: 5.39–10.94; actonel: OR = 49.49, 95% CI: 37.18–65.87; aredia: OR = 277.20, 95% CI: 233.59–328.97; and avastin: OR = 4.66, 95% CI: 3.55–6.13), supporting the reliability of the findings even under weakly informative priors.

Interestingly, amlodipine showed a statistically significant negative association with periodontitis in the frequentist model (OR = 0.49, 95% CI: 0.29–0.84, $p = 0.009$), despite showing a positive signal in prior disproportionality analyses. However, the Bayesian model suggested a contrary trend with an OR of 11.19 (95% CI: 9.00–13.90), raising the possibility of model instability, confounding bias or prior signal overestimation. For other drugs such as aflibercept and amn107, the risk estimates were non-significant ($p > 0.05$) with wide confidence intervals, possibly due to small sample sizes or reporting bias. These findings

highlight the value of incorporating both multivariate adjustment and Bayesian modelling for more robust signal validation, thereby helping to distinguish potential causal relationships from spurious associations and providing guidance for future mechanistic and clinical investigations.

3.1.4 | TTO Analysis

In Table 2, among the analysed drugs, avastin showed the shortest median TTO of 3.5 days, indicating that adverse events often occurred shortly after drug initiation; however, its mean TTO was higher (44.8 days), suggesting variability in onset timing. Amlodipine exhibited a consistent TTO distribution with a median of 167 days and a narrow interquartile range. Aclasta presented a longer median TTO of 252 days. In contrast, actonel and aredia showed earlier onsets with median TTOs of 65.5 and 64 days, respectively.

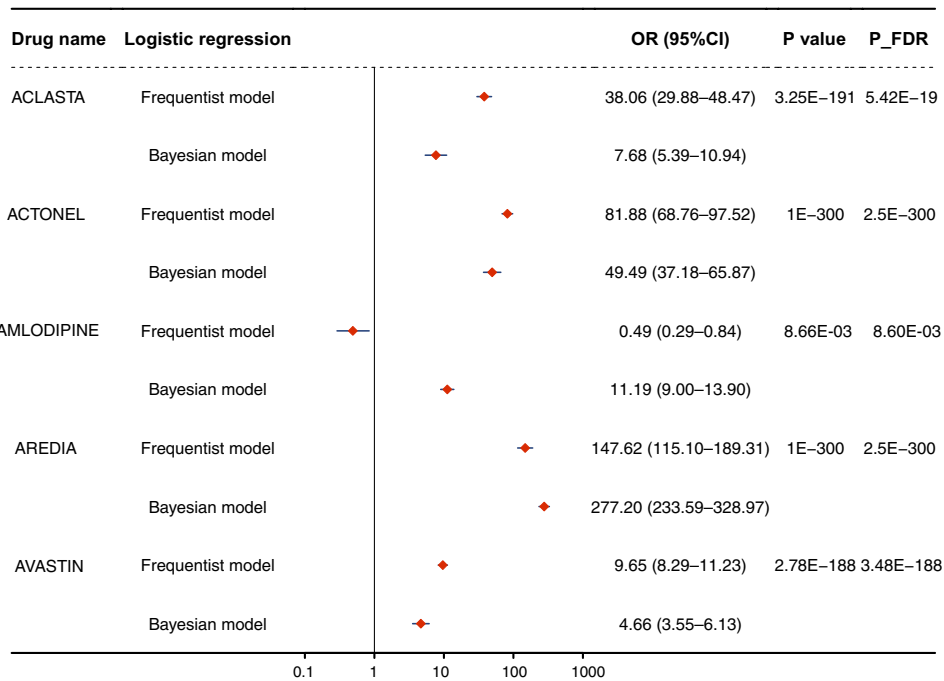


FIGURE 2 | Forest plot of identified periodontitis-related drugs after ROR, PRR, IC, EBGM, *p*-value from Fisher's exact test and logistic regression analysis. CI, confidence interval; OR, odds ratio.

TABLE 2 | Time-to-onset (TTO) summary for five selected drugs associated with periodontitis.

Drug name	Count	Mean	Median	Q1	Q3
Aclasta	3	216	252	171	279
Actonel	2	65.5	65.5	48.2	82.8
Amlodipine	10	165	167	167	167
Aredia	5	93.8	64	20	150
Avastin	24	44.8	3.5	2	44.5

Note: Count, total number of reports related to periodontitis for the drug; Mean, average time (in days) from drug initiation to periodontitis onset; Median, the middle value of time to onset, with half of the reports before and half after; Q1 (first quartile), time when 25% of reports occur, representing the lower range; Q3 (third quartile), time when 75% of reports occur, representing the upper range. For amlodipine (*n* = 10), Q1, median and Q3 are all 167 days because most events occurred at similar times, and rounding to the nearest day results in identical values.

3.2 | Molecular-Level Target Analysis

A total of 34 drug targets were retrieved from the DrugBank database (Table S5). GO enrichment analysis revealed that these targets were predominantly involved in metabolic and immune-related BP levels, including xenobiotic catabolic and metabolic processes, terpenoid and isoprenoid metabolism, arachidonic acid metabolism, long-chain fatty acid metabolism and oxidative demethylation (Figure 3A). At the CC level, enriched terms included voltage-gated calcium channel complexes, cation channel complexes, transmembrane transporter complexes and the sarcolemma. In the MF category, significant enrichment was observed in oxidoreductase activity, aromatase activity, haeme binding, steroid hydroxylase activity and voltage-gated calcium channel activity, suggesting key roles in detoxification,

redox regulation and signal transduction. KEGG pathway enrichment analysis showed that these genes were significantly involved in multiple pathways associated with inflammation and metabolism, such as drug metabolism—cytochrome P450, metabolism of xenobiotics by cytochrome P450, arachidonic acid metabolism, retinol metabolism, MAPK signalling pathway and linoleic acid metabolism—underscoring their relevance to inflammatory processes and metabolic adaptation in disease contexts (Figure 3B). Detailed enrichment analysis is presented in Tables S6 and S7.

PPI analysis via STRING revealed a highly connected network of 32 nodes and 101 edges (expected = 14), with a highly significant PPI enrichment *p*-value of $<1.0 \times 10^{-16}$, indicating that these proteins functionally interact more than what would be expected by chance (Figure 3C). The top hub genes identified included *PTGS2*, *CYP1A1*, *CYP3A4*, *CYP2C9*, *CYP2C19*, *CYP3A5*, *CYP2D6*, *ABCB1*, *CYP2B6*, *CYP2C8* and *ABCC1*, many of which are central players in drug metabolism and immune modulation.

To further investigate genetic associations, we integrated SMR results from both the deCODE and UKB-PPP cohorts (Tables S8 and S9). Only six targets (*VEGFA*, *FCGR2A*, *FCGR2B*, *SMPD1*, *CASP3* and *CA1*) were consistently identified across both datasets. Meta-analysis of SMR results highlighted *VEGFA* as the only gene reaching nominal statistical significance (OR = 1.043, 95% CI: 1.000–1.089, *p* = 0.049; not corrected for multiple testing; Table S10), suggesting that increased expression of *VEGFA* may be associated with a higher risk of periodontitis. To further evaluate the robustness of the SMR-derived association between circulating *VEGFA* levels and periodontitis risk, we performed two-sample MR analyses using data from both the UKB-PPP and deCODE pQTL datasets. In the inverse variance weighted (IVW) models using periodontitis GWAS data from the FinnGen cohort, higher *VEGFA* levels were significantly

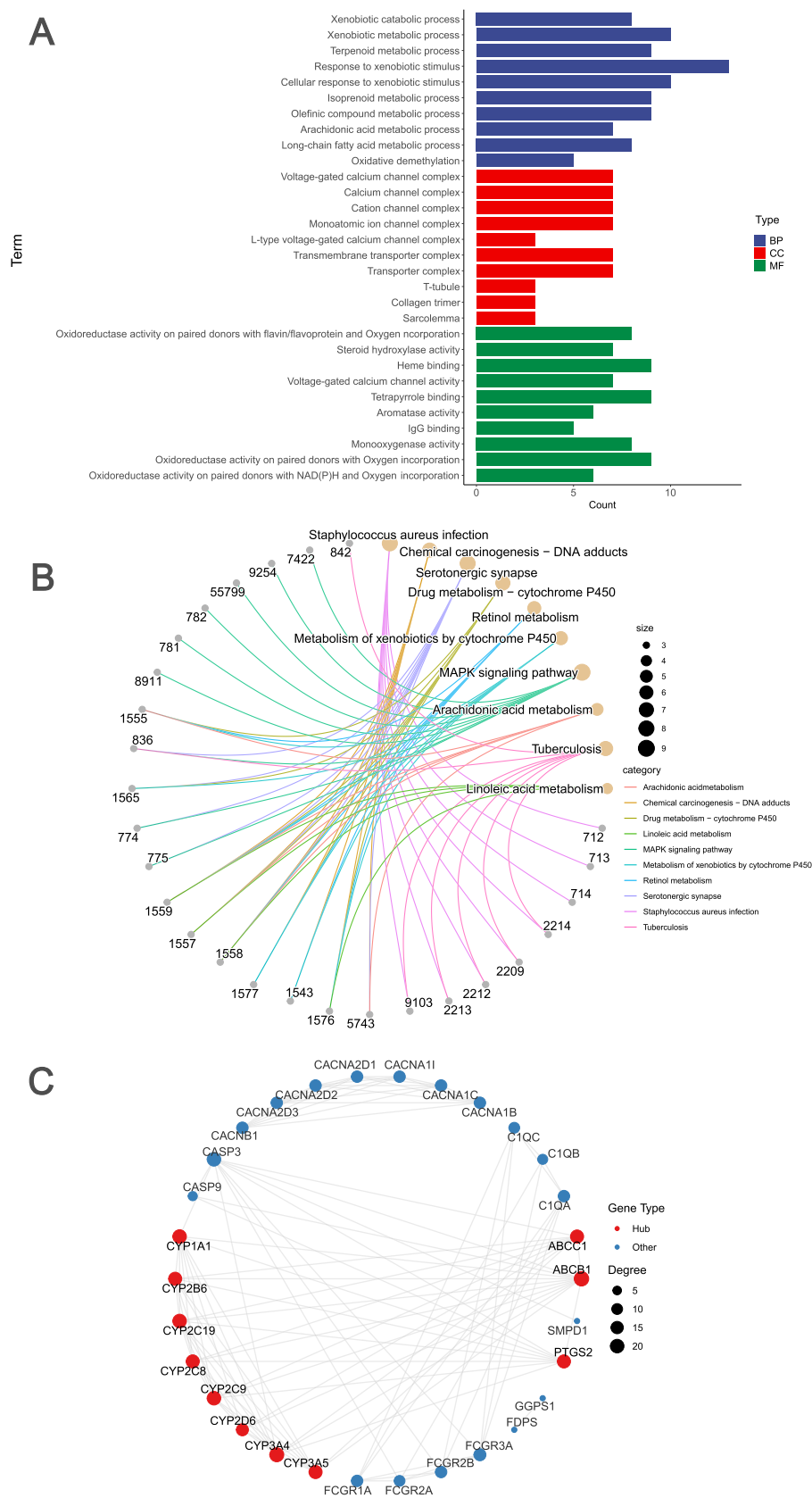


FIGURE 3 | Results of enrichment and PPI analysis. (A) GO result of identified target genes from BP, CC and MF levels. (B) KEGG result of identified target genes. (C) PPI network of identified target genes. The genes with red circles are hub genes.

associated with increased periodontitis risk, with an OR of 1.04 (95% CI: 1.033–1.048, $p=2.30\times 10^{-27}$) in the UKB-PPP dataset and OR=1.04 (95% CI: 1.032–1.050, $p=3.59\times 10^{-19}$) in the deCODE dataset (Table S11). The association remained consistent across MR-Egger and weighted median approaches. No evidence of directional pleiotropy was observed based on MR-Egger intercept tests (UKB-PPP: $p=0.067$; deCODE: $p=0.205$), and heterogeneity tests indicated no significant variation across instruments ($p=1.00$). In the IVW models using periodontitis GWAS data from the Gene–Lifestyle Interactions in Dental Endpoints (GLIDE) cohort, higher *VEGFA* levels were significantly associated with increased periodontitis risk, with an OR of 1.02 (95% CI: 1.01–1.03, $p=1.92\times 10^{-11}$) in the UKB-PPP dataset and an OR of 1.01 (95% CI: 1.00–1.01, $p=9.41\times 10^{-3}$) in the deCODE dataset (Table S12). After integrating the IVW MR results from the two protein cohorts, using periodontitis GWAS data from the GLIDE cohort as the outcome, a random-effects model was used because of heterogeneity, yielding an OR of 1.01 (95% CI: 1.00–1.03, $p=1.77\times 10^{-2}$), which further supports a positive association between *VEGFA* levels and periodontitis risk (Table S13).

Single-cell RNA sequencing of peripheral blood identified immune subsets such as naive CD4⁺ T cells, CD4⁺ T cells, CD8⁺ T cells, naive B cells, naive CD8⁺ T cells, B cells, NK cells, mDC, $\gamma\delta$ T cells (gdT), plasmacytoid dendritic cells (pDC) and plasma cells (Figure 4A). *VEGFA* expression was predominantly detected in monocytes and mDCs, further supporting its immunoregulatory role in systemic compartments (Figure 4B,C). In parallel, scRNA-seq of gingival tissues from periodontitis patients revealed multiple immune and stromal cell types, including B cells, CD4⁺ T cells, CD8⁺ T cells, monocytes, dendritic cells (mDC), fibroblasts, mast cells, epithelial cells and endothelial cells (Figure 4D). Among these, *VEGFA* expression was notably enriched in monocytes and highly expressed in fibroblasts, mast cells and epithelial cells, indicating its potential involvement in tissue inflammation and remodelling (Figure 4E,F).

4 | Discussion

In this study, we applied pharmacovigilance signal mining, logistic regression analysis and proteomics in an integrated manner to systematically explore the potential association between drug use and periodontitis risk from large-scale real-world FAERS adverse event report data, and further revealed the relevant molecular mechanisms by target functional enrichment, protein interaction network, SMR analysis and single-cell transcriptome analysis. These results may offer useful insights for drug safety evaluation, periodontitis mechanism research and the identification of potential targets.

The results of the signalling assay showed a variety of bone metabolism-related drugs (actonel, aclasta and aredia) as risk factors, indicating a potential role in periodontitis development. Most of these drugs are bisphosphonates or RANKL inhibitors, and their mechanism of action is mainly through the inhibition of osteoclast function, thus affecting the process of bone reconstruction (Yoshimoto et al. 2022; Wu et al. 2024). As periodontal tissues belong to a highly dynamic osteoimmunology (Gruber 2019), inhibition of bone metabolism may interfere with

alveolar bone repair and homeostasis, increasing the risk of periodontal tissue destruction (Tsukasaki 2021; Chen et al. 2022). In addition, avastin, an anti-tumour drug, shows strong positive signals. It has a profound effect on the inflammatory microenvironment and tissue repair by inhibiting angiogenesis or modulating immune checkpoints, and may exacerbate inflammatory damage in periodontal tissues through mechanisms such as immune activation and vascular barrier disruption (Ponzetti et al. 2016; Gujral et al. 2008). Interestingly, amlodipine showed a significant negative association with periodontitis in the frequentist multivariate logistic regression, despite demonstrating positive signals in signal detection analyses and a positive association in the Bayesian regression. This inconsistency may suggest a potential protective effect after adjusting for confounders or, alternatively, reflect limitations of the frequentist model such as over-adjustment or residual confounding. Further investigation is warranted to clarify this relationship. Previous studies have suggested that amlodipine induced gingival overgrowth (Rajkarnikar et al. 2023; Seymour et al. 1994). This result emphasises the importance of signal mining in conjunction with regression correction to help improve the reliability of adverse drug reaction association determination.

These periodontitis-related drugs were significantly enriched in metabolic classes and inflammation-related biological processes (e.g., exogenous substance metabolism, arachidonic acid metabolism, MAPK pathway, etc.), and molecular functions were enriched in cytochrome P450-related oxidoreductase activity and voltage-gated calcium channel activity. These pathways are closely associated with inflammatory responses, oxidative stress and immune regulation, providing a potential molecular basis for drug-induced periodontitis. Significant functional interactions exist among these targets, with *PTGS2*, *CYP1A1*, *CYP3A4* and *ABCB1* as key central hub genes, all of which are closely related to drug metabolism, redox regulation and immune function, suggesting that these genes may play a central role in drug-induced inflammation in periodontal tissues. *VEGFA* suggested that its high expression may be correlated with an elevated risk of periodontitis. *VEGFA* is a key factor in angiogenesis (Oltra et al. 2020), which has been widely studied in tumours and cardiovascular diseases (Claesson-Welsh and Welsh 2013; Hiller-Vallina et al. 2024), but in recent years it has also been found to be closely related to periodontal vascular permeability and inflammatory cell migration (Teles et al. 2025, 2024; Morland et al. 2017), which may exacerbate periodontal tissue injury by enhancing neovascularisation at the site of inflammation and promoting inflammatory cell infiltration. In single-cell transcriptome analysis, *VEGFA* was abundantly expressed in monocytes, fibroblasts, mast cells and epithelial cells in gingival tissues, suggesting that *VEGFA* may play an important role in the regulation of local inflammatory microenvironment and tissue remodelling. In the annotation of peripheral blood immune cells, *VEGFA* was highly expressed in monocytes and mDC, further supporting its potential function in systemic immunomodulation.

The present study has several strengths. First, by relying on the adverse event reports in the FAERS database, it has a large sample size and covers a wide range of populations, which is highly representative and statistically efficacious. Second, in the signal detection stage, multiple adverse event signal mining indicators

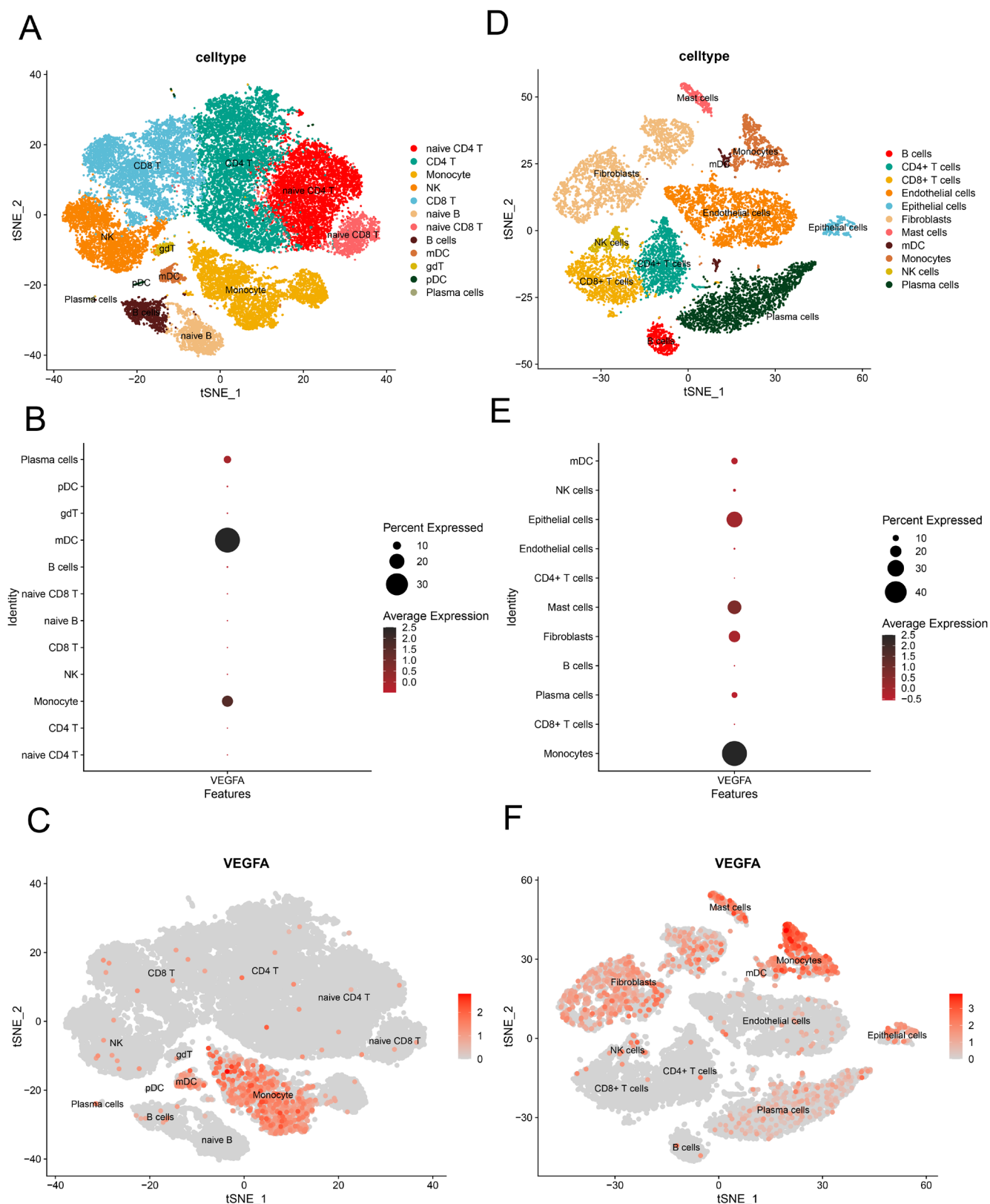


FIGURE 4 | Single-cell transcriptomic analysis of *VEGFA* expression in peripheral blood and gingival tissue. (A) Identified immune cell populations from single-cell RNA sequencing (scRNA-seq) of peripheral blood. (B, C) *VEGFA* expression levels across different cell clusters in peripheral blood. (D) Identified cell populations from scRNA-seq of gingival tissue. (E, F) *VEGFA* expression levels across different cell clusters in gingival tissue.

were used and combined with FDR correction to achieve a multi-dimensional, multi-method joint screening, which improved the stability and credibility of the positive signals. In terms of statistical modelling, the study further introduced logistic regression models to adjust for potential confounders such as age, gender, weight grouping, reporting source, country and reporting time, which resulted in a more accurate risk estimation of drug–periodontitis association while minimising confounding bias as much as possible given the available data. In addition, the study also integrated drug target information and used multiple bioinformatics tools to explore the potential mechanisms from molecular function and biological pathway perspectives.

Despite the integration of large-scale real-world data and proteomics analyses in this study, certain limitations still exist. First, the FAERS data suffer from spontaneous reporting bias, missing information and ambiguous event classification. Additionally, all disproportionality analyses are based on FAERS (US data), which may not be generalisable to other pharmacovigilance systems. Second, the low reporting rate of periodontitis may lead to underreporting or selection bias. Furthermore, while SMR, MR and scRNA-seq provided mechanistic insights, the correlative nature of these data and the lack of multiple testing correction in the SMR analysis—due to the limited number of matched pQTLs—represent important limitations that warrant cautious interpretation of these findings. Further functional studies are needed to establish causal relationships. In addition, it is important to recognise that FAERS is a spontaneous reporting system which inherently lacks the capacity to establish causality (Chen et al. 2025). Confounding by indication remains a key limitation. For instance, patients receiving anti-resorptive therapy often have osteoporosis, a condition that itself predisposes to periodontal bone loss (Tilotta et al. 2025), so whether these are due to the medication or the condition with periodontitis is hard to know. However, a dose–response analysis was not feasible in this study because dosing information in the FAERS database (e.g., DOSE_VBM fields) is frequently missing or inconsistently reported. We attempted age- and sex-stratified analyses; however, these analyses were underpowered because of limited sample sizes, and therefore specific stratified results are not presented. This limitation should be considered when interpreting the findings.

Taken together, our findings are intended to generate hypotheses for future causal investigations rather than draw confirmatory conclusions. To further explore the mechanistic basis of our findings, future studies could implement targeted functional validation experiments. These may include gene knockout or knockdown studies to directly assess gene function, in vitro cell-based assays to examine cellular responses and molecular pathways and animal models to evaluate in vivo effects. Such approaches would help confirm the causal role of the identified genes and guide subsequent translational research. Notably, drugs such as actonel and aredia showed unusually high ORs in the multivariate analysis. As these are commonly used to treat conditions such as osteoporosis or bone metastases—both of which may predispose to periodontitis—the findings may reflect indication bias. Given the limited clinical detail in the FAERS database, such as comorbidities and treatment indications, residual confounding cannot be fully ruled out. Caution is therefore warranted in interpreting these associations, and

further validation using datasets with richer clinical information is recommended.

5 | Conclusion

These results underscore the critical importance of monitoring periodontal health in patients undergoing treatment with actonel, aclasta, aredia, amlodipine and avastin, while also emphasising the urgent need for early screening and intervention to address periodontal issues. Our integrative analysis identifies *VEGFA* as a potential molecular mediator in the pathogenesis of periodontitis. However, owing to the observational and exploratory nature of this study, these findings should be interpreted with prudence. Further validation through in vitro cell experiments and animal models is important to elucidate the specific roles of *VEGFA* and the aforementioned drugs.

Author Contributions

Wuda Huoshen, Heng Wang and Junkai Xiong participated in study design, data analysis, result interpretation, and manuscript drafting. Ge Shuai participated in data preprocessing and visualisation. Xunmi Ma, Panyu Cheng and Xinyu Chen contributed to data curation and literature review. Yi Chen provided methodological support and critically revised the manuscript. Xinyue Zhang, Chen Sun, Chunhui Li and Rui Shi supervised the study, contributed to study conception and design, interpreted the results and critically revised the manuscript. All authors reviewed and approved the final manuscript and agreed to be accountable for all aspects of the work.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** jcpe70040-sup-0001-Supinfo1.docx. **Data S2:** jcpe70040-sup-0002-Tables.xlsx.