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Mendelian Randomization Study of Causal Relationship between Inflammatory Factors and Vascular Dementia and Chinese Herbal Medicines Screening for Prevention and Treatment

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Abstract

Objective: This study aims to examine the causal relationship between inflammatory factors and the probability of developing vascular dementia (VD) using Mendelian Randomization (MR) and Chinese herbal medicine prediction method, and to screen potential Chinese herbal medicines for the prevention and treatment of VD. **Methods:** Single nucleotide polymorphisms (SNPs) that exhibit a strong association with vascular dementia (VD) were identified as instrumental variables from the summary statistics of genome-wide association studies (GWAS). The primary analytical method employed was inverse variance weighting (IVW), while auxiliary analyses included the MR-Egger method, weighted median method, simple model, and weighted model. A two-way Mendelian randomization analysis was conducted to assess the causal relationship between inflammatory factors and the risk of VD, thereby identifying the key inflammatory factors involved. The MR-Egger intercept test and Cochran's Q test were employed to assess the horizontal polymorphism and heterogeneity of instrumental variables. A sensitivity analysis was conducted by excluding one method at a time. Ultimately, based on key inflammatory factors, predictions for the prevention and treatment using traditional Chinese medicine were made, along with the screening of homologous herbal remedies. **Results:** Based on the results of the forward MR, the probability of developing

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VD was elevated when the inflammatory factors CXCL10 and CXCL5 were expressed at higher levels, whereas the probability of developing VD decreased as the expression levels of IL-13 and IL-20RA increased. These findings were supported by the assessment of pleiotropy, heterogeneity, and sensitivity. The results of the reverse MR analysis showed that there was no causal relationship between VD, as an exposure dataset, and these four inflammatory factors. According to the key inflammatory factors, 37 Chinese herbal medicines such as Siraitia *grosvenorii* were selected. Their characteristics including four natures, five flavors, channel tropism and treatment efficiency were cold, warm, neutral, pungent, sweet, bitter, lung meridian, spleen meridian, liver meridian, kidney meridian and clearing heat. Among them, *Siraitia grosvenorii*, Poria with hostwood, *Perilla frutescens*, and Radix Platycodi were all medicine and food homologous Chinese herbal medicines. **Conclusions:** The increase of CXCL10 and CXCL5 expression levels can increase the risk of VD, and the increase of IL-13 and IL-20 RA expression levels can reduce the risk of VD. *Siraitia grosvenorii* and other Chinese herbal medicines might be potential sources of therapeutic drugs for the treatment of VD. Medicine and food homologous Chinese herbal medicines, such as *Siraitia grosvenorii*, Poria with hostwood, *Perilla frutescens*, and Radix Platycodi, may help the elderly population with corresponding Traditional Chinese Medicine (TCM) constitutions to prevent VD.

Keywords

Inflammatory Factors, Vascular Dementia, Mendelian Randomization Study, Causal Association, Chinese Medicine Prediction, Medicine and Food Homology

1. Introduction

Vascular dementia (VD) is a state of cognitive impairment characterized by pathological alterations in various brain regions as a result of insufficient cerebral perfusion caused by cardiovascular diseases [1]. The second most prevalent subtype of dementia is vascular dementia (VD), which accounts for over 20% of all dementia cases [2]. As the societal population ages, an increasing number of individuals are affected. This not only reduces the quality of life for individuals with VD, but it also imposes a major financial burden on families and society [3]. Currently, the majority of conventional western medicine used to treat VD has limitations. Hence, it is crucial to actively investigate the molecular mechanism underlying the pathogenesis of VD and its therapeutic approaches via the use of Traditional Chinese Medicine (TCM).

The pathogenesis of VD is a complex process that involves several pathogenic processes, with neuroinflammation being a significant factor [4]. Increasing data indicates that inflammatory factors are widely involved in the pathological damage process of VD [5] [6]. However, the initiation of VD may also result in alterations in the levels of inflammatory factors. There has been no research into the causal relationship between inflammatory factors and the probability of developing

VD. Therefore, investigating the causal relationship between specific inflammatory factors and the probability of developing VD is beneficial for the exploration of more effective approaches to prevent and treat VD.

In recent years, Chinese medicine in the prevention and treatment of VD research has made more achievements. The homology of medicine and food is studied in the exploration and treatment of VD. "Medicine food homology" (MFH) refers to the fact that a lot of traditional natural products have both culinary and therapeutic benefits [7]. Mendelian randomization (MR) analysis is a dependent method in epidemiological research. Single nucleotide polymorphisms (SNPs) are employed as genetic tools in MR analysis to assess the influence of relevant exposure factors on outcomes. This approach helps to mitigate biases arising from potential confounding factors, reverse causality, and the inherent limitations of small sample sizes in observational studies [8]. This study used MR analysis and Chinese herbal medicine prediction method to investigate the causal relationship between inflammatory factors and the probability of developing VD, and to identify potential preventative and therapeutic Chinese herbal medicine. Furthermore, it offered a valuable resource for the use of MR analysis in the realm of TCM.

2. Methods

2.1. Data Sources and Instrumental Variables

The references were used to acquire the genome-wide association studies (GWAS) statistics data for 91 inflammatory factors [9]. The Finnish database (https://www.finngen.fi/en) was utilized to acquire the GWAS data for VD, including 2717 VD patients and 393,024 control participants. All of the data originated from the Finnish population. All data used in the paper was obtained from publicly available sources and could be freely downloaded. Each GWAS involved in the paper has obtained ethical approval from its respective institution.

In order to obtain more comprehensive results, SNPs that are closely associated with inflammatory factors or VD ($P < 5.0 \times 10^{-6}$, as determined based on the constraint of sample size) were chosen as instrumental variables (IVs) [7]. The genomic sample data was used to conduct a linkage disequilibrium (LD) analysis, with the operation parameters set as $r^2 < 0.001$ and kb = 100.00. The strength of the IVs was evaluated by calculating the F statistic value. A value of $F > 10$ indicates the absence of weak IV bias, and the IVs with $F < 10$ were excluded.

2.2. MR Analysis

Initially, a forward MR analysis was conducted, with inflammatory factors as the exposure and VD as the outcome. This study used the inverse variance weighted (IVW), weighted median, MR-Egger regression, simple mode, and weighted mode, to perform a two-sample MR analysis in order to deduce causal relationships [10] [11]. The main method used to evaluate the overall effect size was IVW. IVW combined the MR effect estimator of each SNP to obtain the overall weighted estimator of the potential causal effect. When IVs did not exhibit horizontal

pleiotropy, the IVW results were the most reliable [12]. MR analysis was performed using the Two Sample MR software R package.

Finally, a reverse MR analysis was carried out, with VD as the exposure and inflammatory factors as the outcome to evaluate the reverse causal relationship. As previously indicated, the same GWAS data were employed in these reverse MR analyses. R software version 4.3.0 was employed to conduct all statistical analyses.

The study used Cochran's Q to assess the heterogeneity among SNPs [13]. A fixed-effects model was implemented when there was no significant heterogeneity ($p > 0.05$). Otherwise, a random-effects model was utilized. We used the MR-Egger intercept (intercept $p < 0.05$) as an index to evaluate horizontal pleiotropy [14]. The "leave-one-out" method was used simultaneously to conduct sensitivity analysis on the data, aiming to quantify the impact of each individual SNP on the causal relationship. A sensitivity analysis was conducted utilizing the leave-one-out method, where SNPs were individually eliminated and the causal effects of the remaining SNPs were compared with the MR analysis findings of all SNPSs retained. This was done to ascertain whether the observed causal relationship was only attributable to a single IV.

2.3. Screening of Chinese Herbal Medicines for Key Inflammatory Factors

Taking the inflammatory factors that had a causal relationship with VD as the prediction targets, we identified the top 20 Chinese herbal medicines that had biological effects on each prediction target using the Coremine Medical database. The screening was based on a significance level of $p < 0.05$. Furthermore, we conducted an analysis of the four natures, five flavors, and channel tropism of these Chinese herbal medicines.

2.4. Comparison of Medicine and Food Homologous Chinese Herbal Medicines

The predicted Chinese herbal medicines were further screened as medicine and food homologous Chinese herbal medicines based on *Both Food and Pharmaceutical Items List* issued by National Health Commission (Ministry of Health announcement of No. 51 [2002]).

3. Results

3.1. Causal Effects of Inflammatory Factors on VD

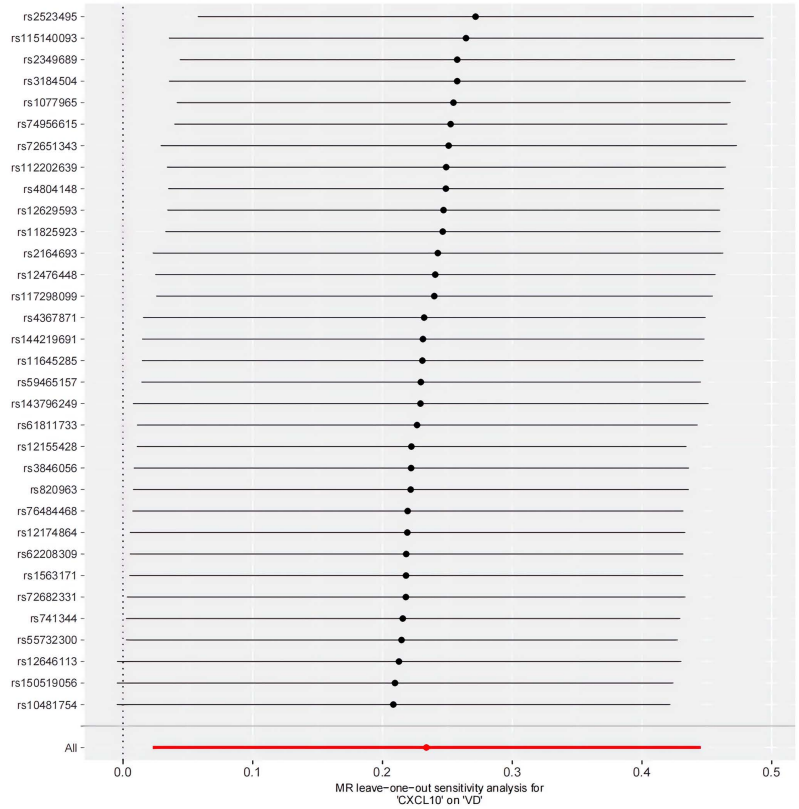
The results of the forward MR analysis indicated that taking inflammatory factors as the exposure dataset, an increase in the expression levels of C-X-C Motif Chemokine Ligand 10 (CXCL10) (IVW: $p = 0.022$, OR = 1.263, 95% CI = 1.023 - 1.560) and C-X-C Motif Chemokine Ligand 5 (CXCL5) (IVW: $p = 0.022$, OR = 1.265, 95% CI = 1.034 - 1.547) elevated the probability of developing VD. Conversely, an increase in the expression levels of Interleukin 13 (IL13) (IVW: $p = 0.002$, OR = 0.788, 95% CI = 0.676 - 0.919) and Interleukin 20 Receptor Subunit Alpha

(IL20RA) (IVW: p = 0.032, OR = 0.682, 95% CI = 0.481 - 0.967) decreased the probability of developing VD.

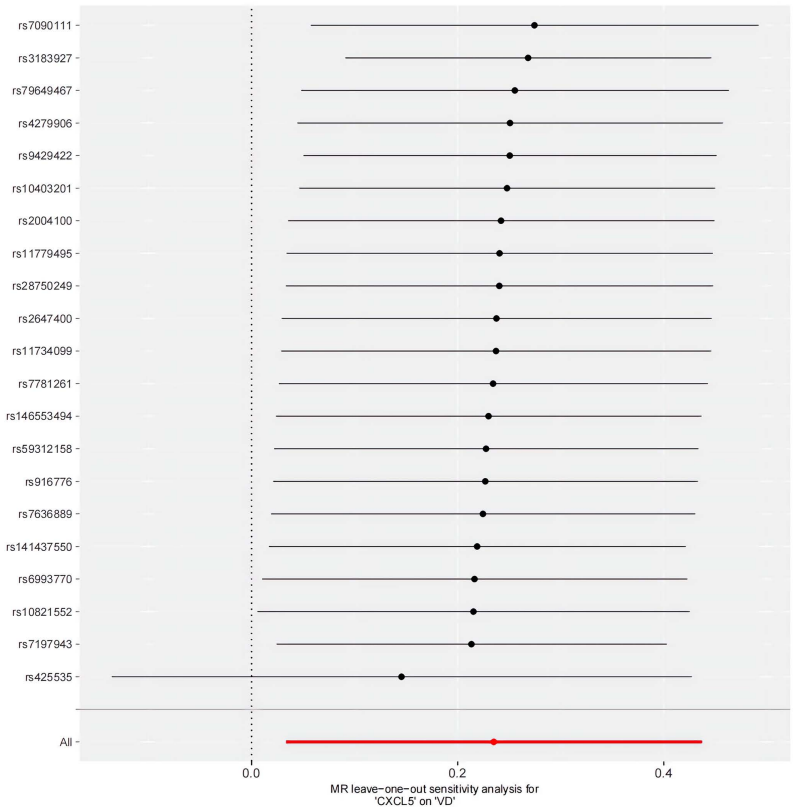
Meanwhile, the MR-Egger intercept test for CXCL10, CXCL5, IL-13, and IL-20RA did not exhibit horizontal pleiotropy. The results of the heterogeneity test showed that there was no substantial heterogeneity among the selected IVs. The results of the sensitivity analysis validated the robustness of the data obtained from the MR study. Furthermore, the pleiotropy test conducted on the inflammatory factor Fibroblast Growth Factor 5 (FGF-5) (IVW: p = 0.024, OR = 1.153, 95% CI = 1.019 - 1.305) ($p < 0.05$) did not meet the criteria, indicating that there was no causal relationship between FGF-5 and VD (Refer to Figure 1 and Table 1).

Table 1. The results of forward MR pleiotropy and heterogeneity.

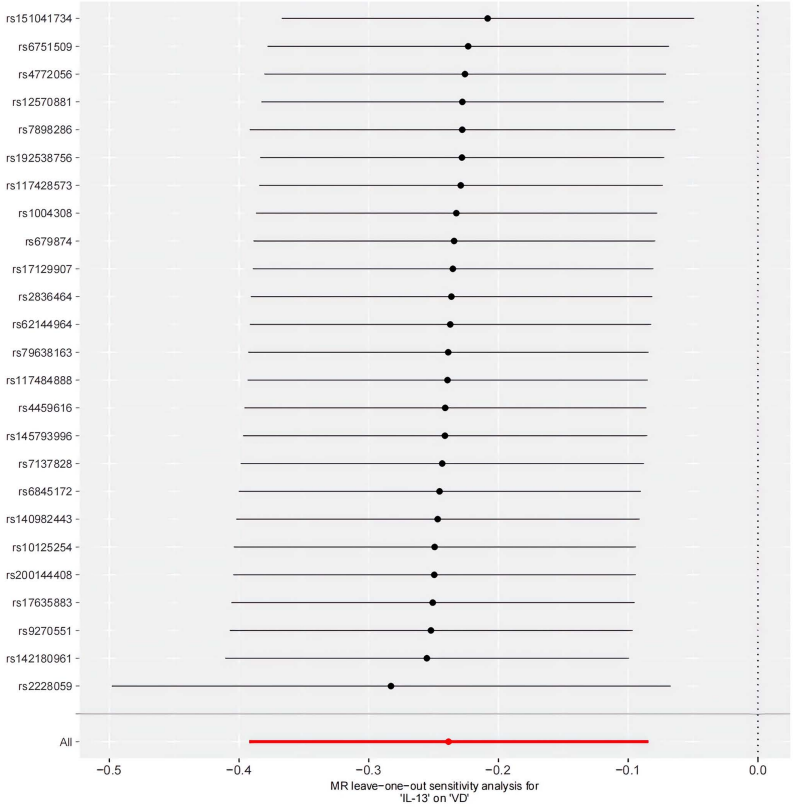
(Exposure dataset) inflammatory factor	MR-Egger intercept		MR Egger			Inverse variance weighted		
	Egger intercept	*p*-value	Q	Q_df	Q_pval	Q	Q_df	Q_pval
CXCL10	0.019	0.320	30.934	31.000	0.470	31.954	32.000	0.469
CXCL5	−0.014	0.536	25.754	19.000	0.137	26.291	20.000	0.156
FGF-5	−0.039	0.029	26.593	30.000	0.645	31.874	31.000	0.423
IL-13	0.001	0.972	19.867	23.000	0.650	19.868	24.000	0.704
IL-20RA	−0.002	0.966	27.374	18.000	0.072	27.376	19.000	0.096



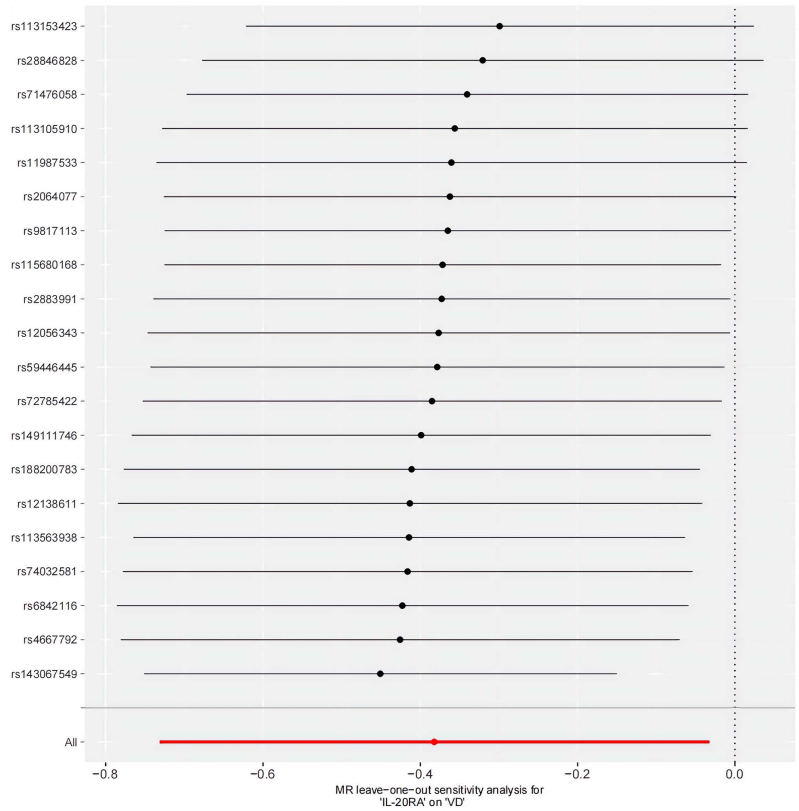
(A) MR leave-one-out sensitivity analysis for "CXCL10" on "VD"



(B) MR leave-one-out sensitivity analysis for "CXCL5" on "VD"



(C) MR leave-one-out sensitivity analysis for "IL-13" on "VD"



(D) MR leave-one-out sensitivity analysis for "IL-20RA" on "VD"

Figure 1. The results of the sensitivity analysis of CXCL10, CXCL5, IL-13, and IL-20RA.

3.2. Causal Effects of VD on Inflammatory Factors

There was no causal relationship between the five inflammatory factors B, E, F, G, H, L2, O, S, and Z acquired in 2.1 and the exposure dataset, VD, according to the findings of the reverse MR analysis ($p > 0.05$), as shown in **Table 2**.

Table 2. The results of reverse MR analysis.

(Outcome data) inflammatory factors	MR Egger		Weighted median		Inverse variance weighted		Simple mode		Weighted mode	
	b	*p*-value	b	*p*-value	b	*p*_value	b	*p*-value	b	*p*-value
CXCL10	−0.018	0.511	−0.034	0.067	−0.020	0.136	−0.023	0.446	−0.036	0.080
CXCL5	0.017	0.522	0.016	0.360	0.015	0.254	0.021	0.430	0.015	0.440
FGF-5	0.028	0.483	0.023	0.256	0.003	0.895	0.005	0.879	0.015	0.498
IL-13	−0.027	0.342	−0.016	0.431	0.000	0.982	−0.031	0.370	−0.018	0.358
IL-20RA	0.020	0.559	0.024	0.252	0.011	0.513	0.016	0.665	0.038	0.099

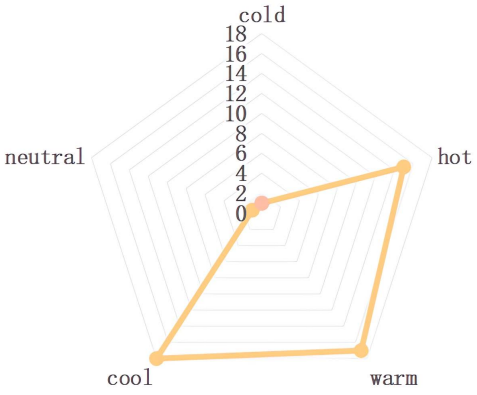
3.3. Chinese Herbal Medicine Prediction of Key Inflammatory Factors

A total of 37 Chinese herbal medicines were obtained. The analysis results of the four natures, five flavors, channel tropism, and treatment efficiency of the Chinese

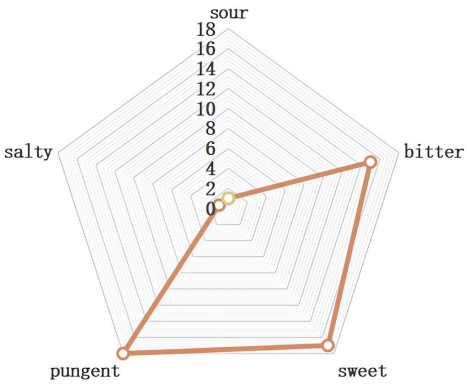
herbal medicines revealed that herbs were categorized into three main natures: cold, warm, and neutral. Similarly, the five flavors were predominantly pungent, sweet, and bitter. The herbs influence the meridians associated with the lung, spleen, liver, and kidney. Furthermore, the herbs were mainly effective in clearing heat. Refer to Table 3 and Figure 2.

Table 3. Chinese herbal medicine prediction results of key inflammatory factors.

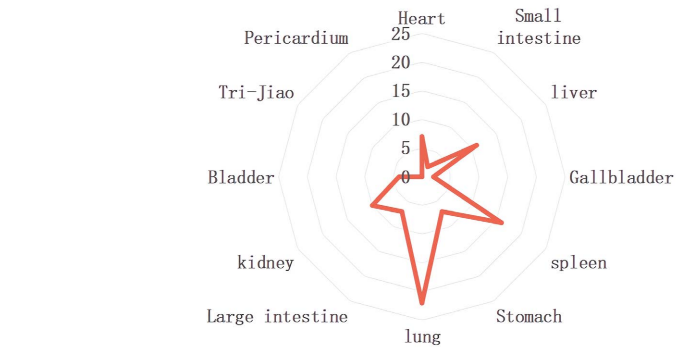
Gene name	Chinese herbal medicines
CXCL10	Herbal Laggerae, Radix Stephaniae Cepharantha, Rhizoma cimicifugae heracleifoliae, Radix Ilicis Asprellae, Alpinia galangal, Rhizoma et Radix Baphicacanthis Cusiae, Fructus Terminaliae Billericae, Radix Isatidis, *Ganoderma applanatum*, Poria with hostwood, Herba Ecliptae, Radix Polygoni Multiflori.
CXCL5	Flos Albiziae, Santalum album, Radix Platycodi, Radix Rehmanniae Recen, Radix Rehmanniae, *Humulus japonicus*.
IL-13	Fructus Xanthii, Herba Centipeda, Artemisia vulgaris, Radix Saposhnikoviae, *Asarum sieboldii*, *Perilla frutescens* L. Britt, Perilla root, Caulis Perillae, Apamin, Rhizoma Saururi, Herba Lysimachiae, *Perilla frutescens*, Radix Kansui, Semen Nigellae, *Urtica fissa*, *Siraitia grosvenorii*, Angelica decursiva, Radix Scutellariae, *Betula platyphylla* Suk. bark.
IL-20RA	N/A



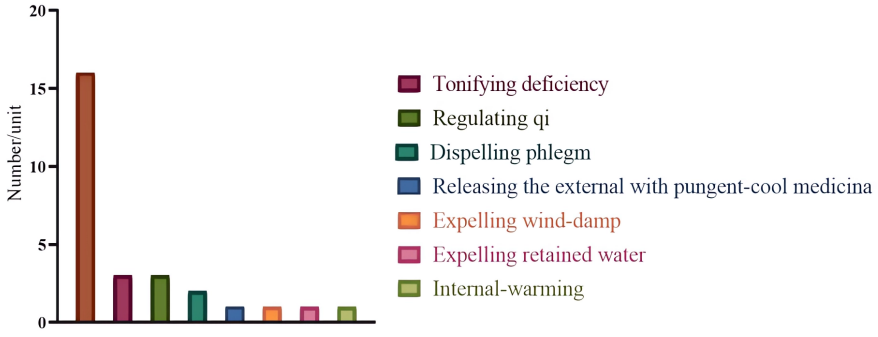
(A)



(B)



(C)



(D)

(A) Radar chart of four natures; (B) Radar chart of five flavors; (C) Radar chart of channel tropism; (D) Bar chart of treatment efficiency, Clearing heat, Tonifying deficiency, Regulating qi, Dispelling phlegm, Releasing the external with pungent-cool medicinal, Expelling wind-damp, Expelling retained water, Internal-warming.

Figure 2. Results of Chinese herbal medicine prediction and analysis.

3.4. Comparison of Medicine and Food Homologous Chinese Herbal Medicines

Four medicine and food homologous Chinese herbal medicines, namely *Siraitia grosvenorii*, Poria with hostwood, *Perilla frutescens*, and Radix Platycodi, were acquired.

4. Discussion

The fundamental pathophysiological mechanism underlying VD is the insufficient supply of essential nutrients, including oxygen, glucose, and amino acids, due to a persistent low perfusion blood flow in the brain. This leads to tissue damage or necrosis in the central nervous system and can contribute to the initiation and progression of neuroinflammation [15]. In fact, VD patients exhibit an inflammatory condition in the hippocampus, which is defined by elevated levels of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), transforming growth factor-β (TGF-β), and inducible nitric oxide synthase (iNOS) [16]. Neuroinflammation, in turn, causes harm to neurons, resulting in the death of cells by apoptosis and pyroptosis, which further hampers learning and cognitive functions [17] [18]. Consequently, a harmful cycle is

established, favoring the gradual advancement of VD. It is evident that neuroinflammation has a dual role in VD, acting as both a catalyst for the disease's pathological process and a consequence of its advancement. Inflammatory factors actively contribute to the process of neuroinflammation. The function of neuroinflammation in the pathophysiology of VD is still uncertain, since it is not obvious whether it acts as a cause or an effect. The purpose of this study is to elucidate the causal relationship between certain inflammatory factors and the probability of developing VD. It also seeks to identify key inflammatory factors and forecast potential Chinese herbal medicines for the prevention and treatment of VD.

In this study, based on the MR analysis of large samples in GWAS, we used genetic tools to systematically analyze the causal relationship between 91 different inflammatory factors and the probability of developing VD for the first time. By combining the results from both forward and reverse MR analysis, we have shown that higher levels of expression of the inflammatory factors CXCL10 and CXCL5 elevated the probability of developing VD. Conversely, increasing expression levels of IL-13 and IL-20RA decreased the probability of developing VD. The reverse MR analysis revealed that VD, as an exposure dataset, did not exhibit any causal relationship with these four inflammatory factors. The finding was further supported by pleiotropy, heterogeneity, and sensitivity analysis, which enhanced its dependability.

CXCL10 is a cytokine with pro-inflammatory properties that plays a crucial function in controlling many biological processes such as chemotaxis, differentiation, activation of peripheral immune cells, and cell proliferation [19]. It has the ability to stimulate microglia, which are macrophages in the central nervous system, and guide them to the lesion site [20]. RNA sequencing analysis showed that CXCL10 is one of the genes with the most significant upregulated expression in the cerebral cortex of mice with cerebral ischemia [21]. CXCL5 belongs to the CXC subfamily of chemokines. According to reports, when mice underwent bilateral carotid artery stenosis to imitate chronic cerebral ischemia, the increased expression of CXCL5 in astrocytes worsened white matter damage and cognitive impairment in mice [22]. IL13 is an immunoregulatory cytokine that can down-regulate macrophage activity, therefore inhibiting the production of pro-inflammatory cytokines and chemokines. A study examining cytokine levels in the brain of individuals with Alzheimer's disease revealed that inadequate cerebral cortical perfusion worsened with the rise of IL-13, tumor necrosis factor-alpha, and other factors [23]. Another separated experimental investigation demonstrated that the secretion of inflammatory factors such as IL13 contributed to ameliorate the impairment of the cerebral ischemia cells [24]. IL20RA is a member of the type II cytokine receptor family. According to reports, glial cells reduce neuroinflammation following trauma or infection in the central nervous system by quickly producing the inflammatory factors IL-19 and IL20RA, while also down-regulating the production of pro-inflammatory cytokines [25]. The results of this study support the notion that CXCL10, CXCL5, IL-13, and IL-20RA have significant implications as both risk factors and protective factors for nervous system diseases, respectively.

The previously mentioned inflammatory factors are supported by reliable evidence regarding their involvement in neuroinflammation. However, we have not found any studies on the regulation of VD neuroinflammation by CXCL10, IL-13, and IL-20RA, and the relevant literature on CXCL5 and VD neuroinflammation is also limited. In conjunction with the results of reverse MR in this study, VD as exposure did not exhibit a causal relationship with the four inflammatory factors. This suggests that CXCL10, CXCL5, IL-13, and IL-20RA are more likely to exacerbate the pathological process of VD as causes by mediating neuroinflammation, rather than as consequences of its pathological process. This further indicates that these four inflammatory factors have significant research potential in the pathogenesis of VD. Potential directions for the effective prevention and treatment of VD may be provided by drugs that target and modulate the inflammatory factors CXCL10, CXCL5, IL-13, and IL-20RA.

In TCM, VD is classified as a "dementia disease." The five zang vacuities detriment and insufficiency of qi and blood are the fundamental pathogenesis, which leads to the brain's lack of nourishment or pathogenic factors disrupting the upper orifices. Currently, there is a lack of research studies that have investigated the integration of MR with TCM. Therefore, this study conducts traditional Chinese medicine prediction and screening on inflammatory factors that have a causal relationship with VD. It revealed that the four natures of the predicted Chinese herbal medicines primarily fell into the categories of cold, warm, and neutral, the five flavors were predominantly pungent, sweet, and bitter, the channel tropism were mainly concentrated in the lung, spleen, liver, and kidney meridians, and their treatment efficiency was primarily associated with clearing heat. From the perspective of the four natures and five flavors, the bitter and cold nature of predicted Chinese herbal medicines are used to eliminate pathogenic factors and excess, while the warm, neutral, and sweet nature can tonify deficiency. This approach aligns with the pathogenesis of dementia, which involves deficiency in origin and excesses in manifestation. According to channel tropism, the predicted Chinese herbal medicines are mostly focused on the lung meridian. This aligns with the views of some experts who suggest treating dementia by targeting the lung [26]. In the therapeutic application of TCM, dementia can be categorized into many syndromes, including qi-blood deficiency syndrome, syndrome of phlegm-turbidity obstructing the orifices, and syndrome of internal exuberance of heat-fire [27]. In terms of treatment efficiency, the predicted Chinese herbal medicines were mostly focused on clearing heat. This suggests that when managing the syndrome of internal exuberance of heat-fire in dementia in clinics, it may be beneficial to consider using Chinese herbal medicines such as Radix Ilicis Asprellae, Radix Scutellariae, and *Siraitia grosvenorii*.

At present, the prevention and treatment of VD has become a great challenge in clinics. As one of the unique preventive treatment of disease methods in China, dietary therapy has played an indispensable role in disease prevention and healthcare. Based on Mendelian randomization analysis, this study screened out four Chinese herbal medicines of the same origin as both food and medicine,

namely *Siraitia grosvenorii*, Poria with hostwood, *Perilla frutescens*, and Radix Platycodi by comparing the predicted Chinese herbal medicines with the Both Food and Pharmaceutical Items List. Therefore, it is very probable that *Siraitia grosvenorii*, Poria with hostwood, *Perilla frutescens*, and Radix Platycodi have the potential to be efficacious drugs for the prevention of VD. It has been reported that the majority of individuals over the age of 65 have constitutions characterized by phlegm-dampness, Yin-Yang balance, damp-heat, yang-deficiency, or blood-stasis [28] [29]. After analyzing the treatment efficiency, four natures, and five flavors, it recommends that elderly individuals with a phlegm-dampness constitution should consume diets containing Poria with hostwood, *Perilla frutescens*, and Radix Platycodi. Elderly individuals with a damp-heat constitution should consume diets containing *Siraitia grosvenorii*, and Poria with hostwood. Elderly individuals with a balanced constitution should consume diets containing Poria with hostwood, as this may help lower their probability of developing VD in the future.

It is imperative to keep in mind that this study is subject to certain limitations. Firstly, all the study data was derived exclusively from the Finnish population. Further verification is necessary to determine the applicability of our results to different populations. Future research will increasingly prioritize MR analyses across diverse racial and regional contexts to improve the generalizability and global applicability of findings. Furthermore, the efficiency of Chinese herbal medicines screened out using MR analysis and Chinese herbal medicine prediction in decreasing the probability of developing VD still has to be confirmed through future clinical or experimental validation.

In summary, our study employed the MR analysis to identify the causal relationship between inflammatory factors and the probability of developing VD. Additionally, this study predicted the Chinese herbal medicines related to the inflammatory factors that have a causal relationship with VD. Finally, this study originally explored the capacity of the elderly population to prevent VD using Chinese herbal medicines of the same origin as both food and medicine. This study could serve as a guide for the prevention and treatment of VD and the use of MR in the realm of TCM.

Author Contributions

manuscript, LW, JZ, WC, CY and GZ; Formal analysis, JZ and MS; Funding acquisition, ZZ and FL; Investigation, YF and XC; Methodology, JZ, MS, BY and XZ; Writing—original draft, JZ; Writing—review & editing, JZ and LW. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest.

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